The Science of Paediatrics

MRCPCH Mastercourse

Editor
Dr Tom Lissauer

Deputy editor
Dr Will Carroll

Foreword by
Professor Neena Modi
President Royal College of Paediatrics and Child Health

RCPCH

Royal College of
Paediatrics and Child Health

Leading the way in Children's Health

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Paediatrics
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Editor
Tom Lissauer
MB BChir FRCPCH
Honorary Consultant Paediatrician, Imperial College Healthcare Trust, London, UK

Deputy editor
Will Carroll
MD MRCP MRCPCH BM BCh BA MA(Oxon)
Consultant Paediatrician, University Hospital of the North Midlands, Stoke-on-Trent, UK

Associate editors
Robert Dinwiddie
MB ChB FRCP FRCPCH DCH
Formerly Consultant Paediatrician, Great Ormond Street Hospital for Children, London, UK

Michael Hall
MB ChB FRCP FRCPCH DCH
Consultant Paediatrician, Princess Anne Hospital, Southampton
Senior Clinical Lecturer, University of Southampton, Southampton, UK
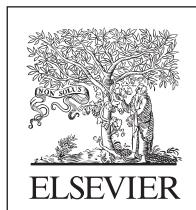
Foreword by
Neena Modi
MB ChB MD FRCP FRCPCH FRCPE
President of the Royal College of Paediatrics and Child Health, UK;
Professor of Neonatal Medicine, Imperial College London, London, UK

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Foreword

This book is a welcome addition to the publications from the Royal College of Paediatrics and Child Health. It provides background material for trainees undertaking the 'Theory and Science' component of the MRCPCH examinations. I hope that it will also be widely read by paediatricians and other health professionals involved in caring for children, as it provides a wealth of information on the scientific basis of clinical paediatrics.

Good medical practice that is effective and safe requires constant nourishment from a pipeline that leads from discovery and evidence generation, through implementation to evaluation. Each of these elements is important; discovery may be targeted (such as international collaboration to crack the human genome) or serendipitous (such as the discovery of penicillin), but without successful implementation, discovery is barren, and without evaluation we cannot be certain that an intervention is effective and safe. Medicine as a science recognizes absolute proof, or truth, to be an illusion and instead focuses attention on reducing uncertainty. Hence the principle of the null hypothesis, and the objective to attempt to reject it that is the basis of scientific rigour. This book offers insight into the building blocks of scientific advancement, as well as the excitement.

I am very pleased to have been involved in the genesis of this book. It is innovative and original in assisting the reader to apply the principles of science to paediatric practice, and in conveying the messages of science to our patients and their parents. It will inform and enlighten, and stimulate you to contribute to the advance of paediatrics.

Professor Neena Modi
President, Royal College of Paediatrics and Child Health

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Preface

Learn from yesterday, live for today, hope for tomorrow. The important thing is not to stop questioning.

Albert Einstein

This book, *The Science of Paediatrics: MRCPCH Mastercourse*, is about the application of science to paediatric clinical practice. It is not about the underlying basic science, such as biochemistry and the structure and action of cells, which is covered in undergraduate medical school. Instead, it is about how we can successfully *apply* that science in everyday paediatric care. The book has been designed to cover the curriculum of the MRCPCH Theory and Science examination. It is the culmination of many requests to provide background preparation for the exam. Our aim is to fill the gap between the basic science of undergraduate medical school and its application to paediatrics.

Some paediatricians have questioned us about the need for in-depth knowledge about science in clinical practice. Yet we believe that in order to achieve and maintain excellence it is essential to adopt a scientific understanding of all that we do, whether it is interpreting clinical signs or investigations, prescribing drugs or identifying the best management for our patients. Indeed, separating science from clinical practice is artificial and often unhelpful, and it is this division that we struggled most with in the preparation of this book.

We all wish to provide the best possible care for our patients. Yet paediatricians have been responsible for advocating practices that have turned out to be harmful, such as the recommendation that babies lie prone when sleeping, which substantially increased the risk of sudden infant death syndrome, or uncontrolled oxygen therapy for preterm babies, causing retinopathy of prematurity. These have resulted from lack of scientific rigour when introducing new practices. But it is not just the profession as a whole or in the past that has been responsible for causing harm to children. We are harming our own patients on a daily basis if we misinterpret results of investigations or do not obtain the most appropriate therapy for them. Paediatricians have often thought that scientific questioning cannot be applied to children because trials or investigations are too difficult to perform involving them. Fortunately, this is rapidly changing, and we hope that this book will stimulate paediatricians to question their clinical practice and seek to discover the latest evidence to answer their questions.

In this book there are chapters on the importance of applied science in paediatrics, epidemiology, clinical research, statistics, evidence-based medicine and ethics, which are particularly informative as they contain many examples of their application to paediatrics. There are also chapters covering all the systems, with a particular emphasis on embryology as this explains the origin of many congenital abnormalities, a brief reminder about the relevant anatomy and physiology as well as a particular focus on understanding the application and interpretation of investigations and of the use and mechanism of action of therapies. Rather than providing didactic details of what clinical practice should be followed, we have tried to provide information about the reasons and evidence base for it, whether it be the assessment of bruises and fractures in child protection, different feeding practices in nutrition or the management of shock in intensive care. There is also a chapter of quality improvement, in view of its importance in providing high-quality care.

Exam-style questions have been embedded in the chapters. Mostly, they come before the relevant section in the chapter, so that readers can check their knowledge and understanding before rather than after

reading about the topic. There are also many case histories and examples of recent advances in science that have been of benefit in the care of children.

Further material to assist with exam preparation, which complements this book, can be found in *Clinical Cases for MRCPCH Theory and Science* (RCPCH). We have assumed that readers will have read an undergraduate textbook of paediatrics, and have tried to avoid replicating their content.

We would like to thank all those who helped bring this ambitious project to fruition. Finally, it is to our families we wish to extend a special thanks for putting up with us retreating to our computers at every spare moment for the last couple of years.

Tom Lissauer
Will Carroll

List of Contributors

Louise Allen
MBBS MD FRCOphth
Consultant Paediatric Ophthalmologist, Ophthalmology Department, Cambridge University NHS Foundation Trust, Cambridge, UK;
Associate Lecturer, University of Cambridge, Cambridge, UK
30. Ophthalmology

Mark Anderson
BSc BMedSci BM BS MRCPCH
Consultant Paediatrician, Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
7. Accidents and poisoning

Alice J Armitage
MBBS BSc
Academic Clinical Fellow in Paediatrics, University College London, London, UK
8. Child protection

Megumi Baba
MBBS MRCPCH PgDip Palliative Medicine
Specialty Registrar in Paediatric Palliative Medicine, Paediatric Palliative Care, The Noah's Ark Children's Hospital for Wales, Cardiff, UK
34. Palliative medicine

Chris Barton
MBCHB(Hons) BSc(Hons)
Speciality Trainee in Paediatric Oncology, Alder Hey Children's Hospital, UK;
Clinical Research Fellow, Institute of Translational Research, University of Liverpool, UK
15. Infection and immunity

Maria Bitner-Glindzicz
BSc MBBS MRCP PhD
Professor of Genetic and Genomic Medicine, University College London Institute of Child Health, London, UK
31. Hearing and balance

Simon Bomken
BMedSci(Hons) MBBS(Hons) PhD
Specialist Registrar, Department of Paediatric and Adolescent Haematology and Oncology, Great North Children's Hospital, Newcastle upon Tyne, UK;
Honorary Clinical Lecturer, Northern Institute of Cancer Research, Newcastle University, Newcastle upon Tyne, UK
37. Clinical research

Mary Brennan
MB BChir MRCPCH
Consultant Paediatric and Adolescent Rheumatologist, Royal Hospital for Sick Children, Edinburgh, UK
27. Musculoskeletal disorders

Joe Brierley
MBChB FRCPCH FFICM MA
Consultant Intensivist, Paediatric Intensive Care Unit, Great Ormond Street Hospital, London, UK
35. Ethics

Steve Byrne
MbChB, MRCP, PhD
Consultant Neonatologist (retired), The James Cook University Hospital, Middlesbrough, UK
10. Perinatal medicine

Daniel Carroll
BM BCh BA MA DM MRCS FRCS(Paed)
Senior Lecturer, Department of Paediatric Surgery, James Cook University, Townsville, QLD, Australia
20. Genital disorders

Will Carroll
MD MRCP MRCPCH BM BCh
BA MA(Oxon)
Consultant Paediatrician,
University Hospital of the North
Midlands, Stoke-on-Trent, UK
*3. History and examination, 17.
Respiratory medicine*

Peter Cartledge
BSc MBChB MRCPCH
PCME MSc
Locum Consultant Paediatrician,
General Paediatrics, Leeds
Children's Hospital, Leeds, UK
39. Evidence-based paediatrics

Nicole Y Z Chiang
MBChB(Hons) MRCP(UK)
Specialist Trainee in Dermatology,
Department of Dermatology,
Salford Royal NHS Hospitals
Trust, Manchester, UK
25. Dermatology

Imti Choonara
MBChB MD FRCPCH
Emeritus Professor, Academic Unit
of Child Health, The Medical
School, University of Nottingham,
Nottingham, UK
36. Pharmacology and therapeutics

Timothy H Clayton
MB ChB MRCPCH FRCP(Edin)
Consultant Paediatric
Dermatologist, Dermatology
Centre, Salford Royal NHS
Foundation Trust, Manchester, UK;
Consultant Paediatric
Dermatologist, Paediatric
Dermatology, Royal Manchester
Children's Hospital, Manchester,
UK
25. Dermatology

Aubrey Cunnington
BMBCh PhD DTM&H FRCPCH
Clinical Senior Lecturer, Section of
Paediatrics, Department of
Medicine, Imperial College
London, London, UK
15. Infection and immunity

Max Davie
MA MB BChir MRCPCH
Consultant Community
Paediatrician, Evelina London
Children's Hospital, St Thomas'
Hospital, London, UK;
Convenor, Paediatric Mental
Health Association, London, UK
*24. Child and adolescent mental
health*

Graham Davies
MA FRCPCH
Consultant Paediatric
Immunologist, Great Ormond
Street Hospital, London, UK;
Honorary Senior Lecturer, Institute
of Child Health, University
College London, London, UK
15. Infection and immunity

Eleanor Dawson
MB ChB MRCPCH
Specialty Trainee in Paediatrics,
Northern Deanery, Great North
Children's Hospital, Newcastle
upon Tyne, UK
7. Accidents and poisoning

Ellie Day
MA MBBS MRCPCH
Consultant Community
Paediatrician, Camden
Community Child Health Team,
London, UK
*40. Quality improvement and the
clinician*

Rachel Dommett
PhD BMBS BMedSci
Consultant Paediatrician in
Haematology/Oncology, Bristol
Royal Hospital for Children;
Honorary Lecturer, University of
Bristol, Department of Paediatric
Haematology, Oncology and Bone
Marrow Transplant, Bristol, UK
22. Oncology

Mary Fewtrell
MA MD FRCPCH
Professor of Paediatric Nutrition,
Childhood Nutrition Research
Centre, UCL Institute of Child
Health, London, UK;
Honorary Consultant
Paediatrician, Great Ormond
Street Hospital NHS Trust,
London, UK
13. Nutrition

Miriam Fine-Goulden
MA MBBS MSc MRCPCH
ST8 Paediatric Intensive Care,
Great Ormond Street Hospital for
Children, London, UK
38. Statistics

Helen Foster
MD MBBS(Hons) FRCPCH FRCP
DCH Cert Clin Ed
Professor Paediatric
Rheumatology, Newcastle
University;
Honorary Consultant in Paediatric
Rheumatology, Great North
Children's Hospital, Newcastle
Hospitals NHS Foundation Trust,
Newcastle upon Tyne, UK
27. Musculoskeletal disorders

Shalabh Garg
MBBS MD FRCPCH
Consultant Neonatologist, The
James Cook University Hospital,
Middlesbrough UK
11. Neonatal medicine

Anu Goenka
BSc MBChB DFSRH DTM&H
MRCGP MRCPCH
MRC/ESPID Clinical Research
Training Fellow, Manchester
Collaborative Centre for
Inflammation Research, University
of Manchester, Manchester, UK
33. Global child health

Victor Grech
MD PhD(Lond) PhD(Malta)
FRCPCH MRCP(UK) DCH
Consultant Paediatrician
(Cardiology) and Associate
Professor of Paediatrics, University
of Malta;
Editor-in-Chief, Images in
Paediatric Cardiology;
Editor, Malta Medical Journal,
Malta
38. Statistics

Jessica Green
MRCPCH
Specialist Registrar in Paediatrics,
Bristol Royal Hospital for
Children, Bristol, UK
18. Cardiology

John W Gregory
MBChB DCH FRCP
FRCPCH MD
Professor in Paediatric
Endocrinology, School of
Medicine, Cardiff University,
Cardiff, UK
12. Growth and puberty,
20. Genital Disorders,
26. Diabetes and endocrinology

Hayley Griffin
MB BS BSc MRCPCH PGDip
Specialty Registrar in Paediatric
Neurodisability, Nottingham
Children's Hospital, Nottingham,
UK
*5. Developmental problems and the
child with special needs*

Joanne Griffiths
MBChB
Consultant in Palliative Care and
Community Paediatrics,
Department of Child Health,
Abertawe Bro Morgannwg Health
Board, Swansea, UK
34. Palliative medicine

Richard D W Hain
MD BS MSc MSt FRCPCH
FRCPE DipPalMed PGCertEd
FHEA
Consultant and Lead Clinician,
Child Health, Children's Hospital,
Heath Park, Wales, UK;
Visiting Professor, University of
South Wales;
Honorary Senior Lecturer, Bangor
University, Bangor, Wales
34. Palliative medicine

Christian Harkensee
MD PhD MSc DLSHTM FRCPCH
Consultant Paediatric Infectious
Diseases, Immunology and
Allergy, University Hospital of
North Tees, Stockton-on-Tees, UK
15. Infection and immunity

Deborah Hodes
BSc MB BS DRCOG FRCPCH
Consultant Paediatrician, Royal
Free London NHS Foundation
Trust and University College
London Hospitals NHS
Foundation Trust, London, UK
8. Child protection

Lee Hudson
MBChB MRCPCH FRACP
Consultant Paediatrician, General
Paediatrics and Adolescent
Medicine and Department of
Child and Adolescent Mental
Health, Great Ormond Street
Hospital for Children;
Honorary Senior Lecturer, UCL
Institute of Child Health, London,
UK
32. Adolescent medicine

David P Inwald
MB BChir FRCPCH PhD
Consultant in Paediatric Intensive
Care, Paediatric Intensive Care
Unit, St Mary's Hospital, London,
UK
*6. Paediatric emergencies and critical
care*

Nadya James
MB BS BSc(Hons) MRCPCH
Consultant in Community
Paediatrics, Nottingham University
Hospitals, Nottingham, UK
4. Normal child development, *5.
Developmental problems and the
child with special needs*, *28.
Neurology*

Elisabeth Jameson
BSc(Hons) MBBCh(Hons) MSc
MRCPCH
Consultant Paediatrician in
Inborn Errors of Metabolism,
Willink Biochemical Genetics
Unit, St Mary's Hospital,
Manchester, UK
29. Metabolic medicine

Sharmila Jandial
MBChB MRCPCH MD
Consultant Paediatric
Rheumatologist, Great North
Children's Hospital, Newcastle
upon Tyne, UK
27. Musculoskeletal disorders

Huw Jenkins
MA MB BChir MD FRCP
FRCPCH
Consultant Paediatric
Gastroenterologist, Child Health,
Children's Hospital for Wales,
Cardiff, UK
14. Gastroenterology

Christine E Jones
BMedSci BMBS MRCPCH
PGCertHBE FHEA PhD
Clinical Lecturer, Paediatric
Infectious Diseases Research
Group, Institute for Infection and
Immunity, St George's University
of London, London, UK
15. Infection and immunity

Deirdre Kelly
FRCPCH FRCP FRCPI MD
Professor of Paediatric Hepatology,
The Liver Unit, Birmingham
Children's Hospital;
University of Birmingham,
Birmingham, UK
21. Hepatology

Peter I Lachman
MD MMed MPH MBBCH BA
FRCP FCP(SA) FRCPI
Deputy Medical Director, Great
Ormond Street Hospital NHS
Foundation Trust, London, UK
*40. Quality improvement and the
clinician*

Mithilesh Kumar Lal
MD MRCP FRCPCH
Consultant, Department of
Neonatal Medicine, The James
Cook University Hospital,
Middlesbrough, UK
10. Perinatal medicine, *11. Neonatal
medicine*

Daniel Langer
MBChB BSc(Hons)
PGDip(Paediatric
Infectious Diseases)
Consultant Paediatrician, Epsom
and St Helier Hospital, Epsom,
UK
15. Infection and immunity

Susie Lapwood
MA(Cantab) BM BCh(Oxon)
MRCGP
Head of Research, Education and
Professional Development and
Senior Specialty Doctor, Helen
and Douglas House Hospices for
Children and Young Adults,
Oxford, UK;
Honorary Clinical Fellow, Oxford
University Hospitals NHS Trust,
Oxford, UK
34. Palliative medicine

Kirsty Le Doare
BA(Hons) MBBS MRCPCH
PGCertHBE
Consultant in Paediatric Infectious
Diseases, Department of
Paediatrics, Imperial College,
London, London, UK
15. Infection and immunity

Warren Lenney
MD DCH MBChB
Professor of Respiratory Child
Health, Keele University, Faculty
of Health, Institute for Science
and Technology in Medicine,
Keele, UK;
Consultant Respiratory
Paediatrician, Royal Stoke
University Hospital, Academic
Department of Child Health,
Stoke-on-Trent, UK
17. Respiratory medicine

Simon Li
MBChB BSc(Hons) MRCPCH
Specialist Registrar in Paediatrics,
Royal Derby Hospital, Derby, UK
3. History and examination

YiFan Liang
BM BCh MA DCH FRCPCH
Consultant in Paediatrics, South
Tees NHS Foundation Trust,
Middlesbrough, UK
34. Palliative medicine

Lynette M Linkson
MB CHB MRCP
Darzi Fellow 2013–2014, Quality
Safety and Transformation, Great
Ormond Street Hospital for
Children NHS Foundation Trust,
London, UK
*40. Quality improvement and the
clinician*

Rajib Lodh
MBChB BMedSci MRCPCH
PGCertMedEd PGDipClinRes
Consultant in Paediatric
Neurorehabilitation, Leeds
Children's Hospital, Leeds
Teaching Hospitals NHS Trust,
Leeds, UK
27. Musculoskeletal disorders

Dan Magnus
BMedSci BMBS MRCPCH MSc
Consultant Paediatric Emergency
Medicine, Bristol Royal Hospital
for Children, Bristol, UK
33. Global child health

Stephen D Marks
MD MSc MRCP DCH FRCPCH
Consultant Paediatric
Nephrologist, Department of
Paediatric Nephrology, Great
Ormond Street Hospital for
Children NHS Foundation Trust,
London, UK
19. Nephrology

Michael Marsh
MBBS FRCP
Medical Director, University
Hospital Southampton and
Consultant Paediatric Intensivist,
University Hospital Southampton,
Southampton, UK
*6. Paediatric emergencies and critical
care*

Katherine Martin
MBChB BSc(Hons) MRCPCH
Consultant Paediatrician, Child
Development Centre, Nottingham
Children's Hospital, Nottingham
University Hospitals NHS Trust,
Nottingham, UK
*5. Developmental problems and the
child with special needs*

Gary McCullagh
MB BCH BAO MRCPCH
Consultant Paediatric Neurologist,
Royal Manchester Children's
Hospital, Manchester, UK
28. Neurology

Janet McDonagh
MB BS MD
Senior Lecturer in Paediatric and
Adolescent Rheumatology, Centre
for Musculoskeletal Research,
University of Manchester,
Manchester, UK
32. Adolescent medicine

Flora McErlane
MBChB MRCPCH MSc
Consultant Paediatric
Rheumatologist, Paediatric
Rheumatology, Great North
Children's Hospital, Newcastle
upon Tyne, UK
27. Musculoskeletal disorders

Anil Mehta
MBBS MSc FRCPCH FRCP
Hon Consultant/Reader, CVS
Diabetes, University of Dundee,
Dundee, UK
1. The role of science and research in paediatrics

Nazakat Merchant
MBBS FRCPCH MD
Consultant Neonatologist, West
Hertfordshire NHS Trust, Watford
Hospital, Watford, UK
10. Perinatal medicine,
11. Neonatal medicine

Lawrence Miall
MB BS BSc MMedSc FRCPCH
Consultant Neonatologist, Leeds
Teaching Hospital, Leeds, UK;
Hon Senior Lecturer, University of
Leeds, Leeds, UK
10. Perinatal medicine

Mike Miller
MRCPCH MRCP MB BS Dip
Pall Med
Consultant, Martin House
Children's Hospice, Wetherby, UK
34. Palliative medicine

Neena Modi
MB ChB MD FRCP FRCPCH
FRCPE
President of the Royal College of
Paediatrics and Child Health,
London, UK;
Professor of Neonatal Medicine,
Imperial College London, London,
UK
1. The role of science and research in paediatrics

Daniel Morgenstern
MB BChir PhD FRPCH
Consultant Paediatric Oncologist,
Great Ormond Street Hospital,
London, UK;
Honorary Senior Lecturer, UCL
Institute of Child Health, London,
UK
22. Oncology

Omendra Narayan
MBBS MSc FRCPCH
Consultant in Paediatric
Respiratory Medicine, Royal
Manchester Children's Hospital,
Manchester, UK
15. Infection and immunity

David O'Connor
MBChB PhD FRCPath
Locum Consultant in Paediatric
Haematology, Department of
Haematology, Great Ormond
Street Hospital, London, UK
23. Haematology

Ian Petransky
MBBS MRCPCH
Paediatric Registrar, Department of
Paediatrics, Chesterfield Royal
Hospital, Chesterfield, UK
3. History and examination

Bob Phillips
BMBCh MA MMedSci PhD
NIHR Post-Doctoral Fellow and
Honorary Consultant in Paediatric
Oncology, Centre for Reviews and
Dissemination, University of York,
York, UK
39. Evidence-based paediatrics

Kaukab Rajput
FRCS FRCP MSc
Consultant Audiovestibular
Physician, Great Ormond Street
Hospital for Sick Children NHS
Foundation Trust, London, UK
31. Hearing and balance

Dipak Ram
MBBS MRCPCH
Paediatric Neurology Specialist
Registrar, Royal Manchester
Children's Hospital, Manchester, UK
28. Neurology

Sarah Rayfield
MB BS MSc MFPH
Specialist Registrar Public Health,
Oxford Deanery, Oxford, UK
2. Epidemiology and public health

Irene A G Roberts
MD FRCPath
Professor of Paediatric
Haematology, Oxford University
Department of Paediatrics,
Children's Hospital and Molecular
Haematology Unit, Weatherall
Institute of Molecular Medicine,
John Radcliffe Hospital, Oxford,
UK
23. Haematology

Kerry Robinson
MA MRCPCH
Consultant Paediatrician,
Whittington Health NHS Trust,
London, UK
8. Child protection

Jane Runnacles
MBBS BSc(Hons) MRCPCH MA
Consultant Paediatrician, Royal
Free Hospital, London, UK
40. Quality improvement and the clinician

Nicola Ruth
MBChB BSc(Hons) PGA(Med
Education) MRCPCH
Clinical Research Fellow in
Paediatric Hepatology, The Liver
Unit, Birmingham Children's
Hospital/University of
Birmingham, Birmingham, UK
21. Hepatology

Manish Sadarangani
BM BCh MRCPCH DPhil
Clinical Lecturer and Honorary
Consultant in Paediatric Infectious
Diseases & Immunology,
University of Oxford, Oxford, UK
15. Infection and immunity

Helen Sammons
MBChB MRCPCH DM
Associate Professor of Child
Health at the University of
Nottingham and Consultant
Paediatrician at the Derbyshire
Children's Hospital, Derby, UK
36. Pharmacology and therapeutics

Nwanneka N Sargant
BM MCPCH DFRSH
Paediatric Specialty Registrar,
University Hospitals Bristol NHS
Trust, Bristol Royal Hospital for
Children, Bristol, UK
32. Adolescent medicine

Richard H Scott
MA MBBS MRCPCH PhD
Consultant in Clinical Genetics,
Department of Clinical Genetics,
North East Thames Regional
Genetics Service, Great Ormond
Street Hospital, London, UK;
Honorary Senior Lecturer,
Genetics and Genomic Medicine
Unit, Institute of Child Health,
London, UK
9. Genetics

Mike Sharland
MD MRCP FRCPCH
Professor of Paediatric Infectious
Diseases, Paediatric Infectious
Diseases Research Group, Institute
for Infection and Immunity, St
George's University of London,
London, UK
15. Infection and immunity

Rajiv Sinha
MD FRCPCH(UK) CCT(UK)
Associate Professor, Paediatric
(Nephrology), Institute of Child
Health, Kolkata, India;
Consultant Paediatric
Nephrologist, Fortis Hospital,
Kolkata, India
19. Nephrology

Sunil K Sinha
MD PhD FRCP FRCPCH
Professor of Paediatrics and
Neonatal Medicine, The James
Cook University Hospital,
University of Durham,
Middlesbrough, UK
10. Perinatal medicine, *11. Neonatal
medicine*

Lynn Sinitsky
BA MBBS MRCPCH MSc
Paediatric Registrar, London
Deanery, London, UK
*6. Paediatric emergencies and critical
care*

Charlotte Slaney
BMBCH BA MA BMBCh
MRCPCH FRCR FRANZCR
Staff Specialist in Radiology,
Queensland X-Ray, Townsville,
Queensland, Australia
20. Genital disorders

Elizabeth Starkey
MRCPCH MBChB
Locum Consultant Paediatrician,
Royal Derby Hospital, Derby, UK
36. Pharmacology and therapeutics

Jacqui Stedmon
BSc PhD BPS DipClinPsy
Associate Professor/Programme
Director, Doctorate Programme in
Clinical Psychology, University of
Plymouth, Plymouth, UK
*24. Child and adolescent mental
health*

Shereen Tadros
BMedSci BMBS MML MRCPCH
Specialist Trainee in Clinical
Genetics, Department of Clinical
Genetics, North East Thames
Regional Genetics Service, Great
Ormond Street Hospital for
Children, London, UK
9. Genetics

Hannah Tobin
BA BM BCh MRCPCH
Trainee in General Paediatrics,
Barnet General Hospital, Royal
Free NHS Trust, London, UK
13. Nutrition

Robert M R Tulloh
BM BCh MA DM(Oxon) Cert Ed
FRCP FRCPCH
Professor, Congenital Cardiology,
University of Bristol, Bristol, UK;
Consultant Paediatric Cardiologist,
Bristol Royal Hospital for
Children, Bristol, UK
18. Cardiology

Paul J Turner
BM BCh FRACP PhD
MRC Clinician Scientist in
Paediatric Allergy & Immunology,
Imperial College London, London,
UK;
Hon Consultant in Paediatric
Allergy & Immunology, Imperial
College Healthcare NHS Trust,
London, UK
16. Allergy

Josef Vormoor
Dr med
Sir James Spence Professor of
Child Health and Director of the
Northern Institute for Cancer
Research, Northern Institute for
Cancer Research, Newcastle
University, Newcastle upon Tyne,
UK;
Honorary Consultant Paediatric
Oncologist, Great North
Children's Hospital, Newcastle
upon Tyne Hospitals NHS
Foundation Trust, Newcastle upon
Tyne, UK
37. Clinical research

John O Warner
OBE MD FRCP FRCPCH
FMedSci
Professor of Paediatrics, Imperial
College London, London, UK;
Honorary Professor, Paediatrics
and Child Health, University of
Cape Town, Cape Town, South
Africa
16. Allergy

Premila Webster
MBBS DA MSc MFPHM FFPH
DLATHE DPhil
Director of Public Health
Education & Training, Nuffield
Department of Population Health,
University of Oxford, Oxford, UK
2. Epidemiology and public health

Lisa Whyte
MBChB MSc
Consultant Paediatric
Gastroenterologist Birmingham
Children's Hospital, Birmingham,
UK
14. Gastroenterology

Bhanu Williams
BMedSci BM BS MRCPCH
DTMH BA MAcadMed
Consultant in Paediatric Infectious
Diseases, London North West
Healthcare NHS Trust, Harrow,
UK
33. Global child health

Toni Williams
MBChB
Paediatric Registrar, University
Hospital of Wales, Cardiff, UK
14. Gastroenterology

Helen Yates
MBChB MRCPCH MMedSci
Locum Consultant Neonatologist,
Hull Royal Infirmary, Hull, UK
10. Perinatal medicine

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Neena Modi, Anil Mehta

The role of science and research in paediatrics

LEARNING OBJECTIVES

By the end of this chapter the reader should know:

- Why science and research are relevant to all paediatricians, not just scientists and academics
- Why children's biomedical research is essential
- The relevance of synthesizing existing evidence and identifying gaps
- How children's research has evolved
- Why contributing to research to reduce uncertainties in care is a clinical obligation
- How to acquire research skills
- How and why we should involve patients, parents and the public

Why science and research are relevant to all paediatricians

The practice of medicine is described as both 'art and science', a helpful phrase that emphasizes that the care a doctor provides encompasses subjective (empathy, sensitivity, understanding, communication) and objective (evidence, factual knowledge, competencies) elements working in harmony. We all need to practise the 'art' of medicine when we explain science and research concepts to patients.

The very best paediatricians are also able to critically evaluate what they are taught, synthesize existing evidence, challenge dogma, identify knowledge gaps and understand how medicine advances through patient-centred research. We hope that this chapter will enable you to appreciate why these are professional obligations for paediatricians, and central, not peripheral, to clinical practice. We also hope that you will find that applying scientific principles to diagnostic and therapeutic problems is fun and rewarding.

The word science is derived from the Latin word for knowledge, 'scientia'. Science is systematic; it builds knowledge incrementally through testing hypotheses. Science is perhaps best defined by the acceptance that there are few absolute truths, only ever diminishing uncertainty with each null hypothesis that is rejected following empirical testing. As we progress through our careers, we have a responsibility not only to test new therapies as they become available, but also to help identify which treatments and clinical practices in current use are harmful or useless, and progressively reduce uncertainties in care.

Try and project yourself thirty years into the future; look back at what you are being taught now; much of this will not have withstood the advance of knowledge and scientific scrutiny. If you think this is an exaggerated argument, consider two salutary lessons from the history of paediatrics (Box 1.1). These examples illustrate two key points: that it is dangerous to assume that an untested practice is harmless and that getting evidence adopted into practice can be problematic. Try and think of examples of treatments or practices that are not evidence based but are widely used. Might these practices be harmful? What studies could be done to resolve these uncertainties? Try also to think of examples where translation of evidence into healthcare policy could be expedited through collaborative

Box 1.1 The danger of assuming untested practice is harmless and delay in getting evidence into practice

Thymic irradiation

In the early part of the last century, the possibility that an enlarged thymus was implicated in sudden infant death led to the practice of irradiation to reduce thymic size. A quote from that time illustrates that part of the argument in favour of irradiation was that even if not beneficial, it was certainly not harmful and that the procedure would at the very least alleviate parental anxiety: 'The obstetrician or pediatrician should accede to the wishes of parents who want neonatal X-rays of their children. It might even be wise to administer therapeutic dosage over the thymus; assurance gained by this apparently harmless and perhaps beneficial procedure will aid in alleviating an anxiety which may become a thymus phobia' (Conti and Patton 1948). The substantially increased risk of cancer following thymic irradiation was subsequently established.

Back to sleep

From the 1940s until the 1980s childcare experts recommended the prone sleeping position for infants. This advice was indirectly supported by the decreased work of breathing in the prone position for neonates with respiratory distress. However, prone sleeping had also been noted as a possible risk for sudden infant death syndrome and by the 1970s there was reliable evidence from observational and epidemiological studies, reinforced by the New Zealand Cot Death Study ending in 1990, that this should be avoided. Systematic preventive efforts did not begin until the early 1990s, largely as a result of a campaign led by a charity, the Foundation for the Study of Infant Deaths, together with strong media interest, which led to the Department of Health issuing a policy statement followed by a national campaign, 'Reduce the risk'. This illustrates the need for clear strategies to avoid delay in translating evidence into practice.

Box 1.2 Danger of assuming adult medicines are safe in children

The introduction of sulphonamides

Sulphonamides were the first mass-produced antimicrobial medications. Prophylactic sulphonamide use in preterm babies began in Sweden in the 1940s and subsequently became widely used therapeutically. When a new antibiotic, oxytetracycline, was suggested as an alternative, a randomized study was conducted which showed increased mortality from kernicterus in sulphonamide-treated infants, which would have gone unrecognized had the clinical trial not been done. The increase in kernicterus was due to displacement of bilirubin from albumin binding sites by sulphonamide. Sulphonamides are generally safe in other age groups, but newborn infants are vulnerable to bilirubin toxicity. This illustrates the necessity of testing medications in the specific population in which they will be used.

Thalidomide

The first placebo-controlled trial of any medication prior to market launch involved thalidomide, which showed thalidomide to be 'effective and safe as a sedative and to alleviate morning sickness in pregnancy'. By the mid-1950s, over a dozen pharmaceutical companies were marketing thalidomide around the world. It was not until the 1960s that thalidomide was acknowledged to cause phocomelia in infants exposed *in utero*, and banned. This tragedy illustrates not only the necessity of testing medications in the specific population in which they will be used, but also of selecting the right outcome measures, in this case not only the impact upon morning sickness in pregnant women, but also the impact upon the fetus.

advocacy by professional bodies, charities and other third sector organizations.

Why children's research is essential

'Children are not little adults.'

Children's research is necessary because the biology of disease in children is not necessarily the same as in adults. Human physiology alters with age, so that the actions of medicines may differ in the fetus, in children, and in adults (see also Chapter 36, Pharmacology and therapeutics). There are some important examples of where this is clearly the case. Aspirin is widely used for pain relief and to reduce fever in adults but is not recommended for use in children because of the risk of a serious condition, Reye's syndrome, which causes liver damage and encephalopathy. Young people with cancer have significantly better survival when treated with protocols developed for children compared with protocols used for adults. The use of treatments designed for adults in children without adequate testing is dangerous and new treatments are not necessarily better than old (Box 1.2). Understanding the science of children's disease can also help develop adult treatments (Box 1.3).

The development of statins

Increased serum cholesterol and low-density lipoprotein (LDL cholesterol) accelerates atherosclerosis and promotes the risk of coronary heart disease. Cholesterol is one of the end products of the mevalonate pathway, in which the rate-limiting step is the conversion of HMG-CoA to mevalonate mediated by HMG-CoA reductase. Statins are structural analogues of HMG-CoA, developed to inhibit HMG-CoA reductase and hence biosynthesis of mevalonate and cholesterol. The development of statins can be traced to studies on research into children with familial hypercholesterolaemia; when LDL cholesterol is added to their fibroblasts, there is no reduction in endogenous cholesterol production rate, but it is reduced 50-fold when added to the fibroblasts of healthy humans. This suggested that an LDL sensor pathway exists, an observation that led to the discovery of the mutations in the LDL receptor that stop signal transduction and cause diseases of lipid homeostasis. This research led to the award of the Nobel Prize to Brown and Goldstein and ultimately to the development of statins.

Children's medicines

There have been international efforts to encourage the pharmaceutical industry to improve the development of medicines for children. Currently, around half of children's medicines and approximately 90% of medicines for newborn babies are prescribed off-licence or off-label, having never been tested in these age groups. This unsatisfactory situation was addressed in United States legislation followed by the European Union Regulation on Medicines for Paediatric Use, which came into force in 2007. This requires pharmaceutical companies to define and obtain approval for a Paediatric Investigation Plan with the European Medicines Agency at an early stage in the development of new medicines. It sets out the studies to be undertaken and marketing authorization is only granted if completed. Although there has been an increase in children's medicine studies following the introduction of the regulation, impact has been small and limitations of the legislation have been highlighted. It remains the case that only a minority of medicine trials in neonates and children are industry sponsored. This emphasizes the importance of public and charitable sector support if infants and children are to have access to evidence-based therapies.

Research involving healthy children, and particularly vulnerable children

There are important reasons for involving healthy children in clinical research. These include observational cohorts where the aim is to study normal development and case-control studies where a healthy child is compared with a child with a particular disease or condition. Regardless of the type of research, careful consideration is required of the risks and burdens of participation, the necessity for the information sought and the rigour of the study design. The increasing involvement of parents and children in recent years in deciding what is acceptable in partnership with researchers is a welcome development.

Children receiving end-of-life care, looked-after children and other vulnerable groups also require their care to be assured by robust research evidence. However, there has often been a reluctance to involve them in research because of a fear of intrusion. A relatively recent development is the growing body of evidence that indicates that research participation in such circumstances is more likely to be beneficial rather than harmful, providing an opportunity to come to terms with illness and the prospect of death and to find meaning and solace through involvement that will benefit others.

Wider relevance of children's research

Another area of children's research which has been stimulated by epidemiological observations is the relationship between indices of poor fetal growth and health in adult life. There has been an explosion over the last two decades in research that demonstrates the effects of exposures during early development on adult well-being. There are strong indications that obesity, cardiovascular disease and stroke, the major causes of death and poor health in adult life, have determinants in early development. Substantial research effort involving interventions in adult life have failed to stem the increase in these lethal non-communicable diseases. These observations provide added justification for increased research in infancy and childhood. Rehabilitative therapies that will gain increasing importance in ageing populations require better understanding of developmental biology, neural plasticity, senescence and tissue regeneration, sciences that are centred upon infant and child research.

Synthesizing research evidence and identifying knowledge gaps

How do we know what is known and not known? How do we identify research that is needed? The approach to identifying the most appropriate evidence is described in Chapter 39, Evidence-based paediatrics. The gold-standard tools for evidence synthesis are systematic review and meta-analysis. The purpose of a systematic review is to identify all available high-quality primary research evidence and summarize the findings in order to address a clearly defined question. Meta-analysis is usually used to refer to statistical methods of combining numeric evidence. These approaches are not limited to medicine but are important wherever there is a need to summarize research findings. The results of a systematic review and meta-analysis may be used to guide clinical practice or, if they identify an important knowledge gap, provide justification to carry out a clinical research study to resolve the uncertainty.

The search for all available evidence must be 'systematic' in order to avoid potentially erroneous conclusions being drawn if the evidence considered is biased, for example if an author selects evidence to emphasize a particular personal view, or includes only publications that are easy to find. Bias can take many other forms and will weaken the reliability of conclusions drawn from a systematic review and meta-analysis. Publication bias arises when only some and not all research results are published. For example, journal editors may favour the publication of positive over negative findings; particular concern arises from the alleged failure of pharmaceutical companies to report all research results. In an attempt to reduce this problem, clinical trials and other types of studies should be registered before commencement; increasingly, this is a mandatory requirement. There are a number of international registries (for example, ClinicalTrials.gov, European Union Clinical Trials Register and others listed in Chapter 37, Clinical research); when conducting a literature review, it is useful to search these to try and identify research that is planned or in progress. This is also important to avoid conducting research studies unnecessarily, and to liaise with other investigators so that results can be pooled.

In order to incorporate new trial data, cumulative meta-analysis is recommended (Box 1.4). This incremental evaluation of evidence helps identify stable conclusions earlier, which in turn should facilitate earlier uptake of effective interventions and expose fewer patients to ineffective treatments or unjustified research.

Box 1.4 Need for cumulative meta-analysis

Antenatal steroids

In 1972, Liggins (a scientist) and Howie (a clinician) reported the results of a randomized controlled trial (RCT) that provided evidence of the efficacy of antenatal corticosteroids for the prevention of respiratory distress syndrome associated with preterm birth. By 1991, seven more trials had been reported, following which a systematic review of RCT was published showing that treatment reduces the odds of babies born preterm dying from the complications of immaturity by 30–50%. However, it was not until the publication of a consensus statement by the US National Institutes of Health in 1994 (22 years and 12 trials later), followed by guidance from the Royal College of Obstetricians and Gynaecologists in 1996 recommending the use of antenatal steroids, that this became a standard of care. The delay in recognizing the benefits resulted in tens of thousands of premature babies suffering and dying unnecessarily. This illustrates the human cost of failure to perform systematic, up-to-date reviews of RCT in healthcare, and the powerful impact of evidence on patient care and outcomes. The original forest plot of RCT of antenatal steroids is enshrined in the Cochrane Collaboration logo and is described in Box 39.6.

An understanding of how to conduct a systematic review and meta-analysis is an important and useful skill for all paediatricians.

Evolution of attitudes to clinical research

Attitudes to clinical research have evolved with time. The Declaration of Helsinki, which sets out the ethical principles that underpin research involving humans, has had two notes of clarification and seven amendments, the most recent in 2013. The current version makes no specific provision for children, confining guidance to a stipulation that special consideration is required for research involving vulnerable populations. Acceptance that children need their care to be assured by good research evidence has been a relatively recent phenomenon. In 1980 the British Paediatric Association, the forerunner of the RCPCH, published guidance in relation to research involving children, stating clearly that 'research involving children is important' and 'should be supported and encouraged'. It was also felt necessary to say that 'research which involves a child and is of no benefit to that child (non-therapeutic research) is not

necessarily either unethical or illegal'. This was because, up to this time, little clinical research involved children and the ethics of including children in research was still a matter of controversy. Updated guidance was issued by the RCPCH in 2014.

The development of a framework for research ethics and regulation has been informed by the history of clinical research. This includes examples of conduct that would be considered unacceptable today, that were found to be fraudulent, and where investigators were wrongly vilified (Box 1.5). These lessons from history illustrate that all is not black and white, but that context is important and that society's attitudes change with time. These issues are considered further in Chapter 35, Ethics.

The regulation of clinical research in the UK is described in Chapter 37. There have been significant changes over the last decade. The ways in which society views the impact and opportunities provided by scientific and technological advances, and wider understanding of research methods, will ensure that processes continue to evolve (Box 1.6).

Not all research involves new or experimental treatments. There are many examples of uncertainties in treatments or practices that, despite inadequate evidence, are in wide and accepted use; for example, whether or not a preterm baby receives fortification of maternal milk, or the chemotherapy regimen received by a young adult with leukaemia. Here patients are exposed to a lottery, where the treatment they receive depends upon the personal preference or bias of the clinician. A strong case can be made that in these circumstances the patient is not only well served by receiving care delivered along a clearly designed, closely monitored pathway that constitutes a research study, but also that randomization is the best means to ensure that every patient has a fair chance of receiving the as yet unknown better option; however, this view is not universally accepted. Current regulatory frameworks make no distinction between randomization to an experimental therapy and randomization to a treatment already in wide use. We encourage you to join the debates discussing whether participation in comparative effectiveness research should be the default recommendation of medical practitioners.

A clinical obligation to reduce uncertainties in care

Children and child health are under-represented in biomedical and health services research despite general acknowledgement that research involving children is necessary; for example, currently approximately 15% of all registered clinical trials are aimed at children,

> **Box 1.5 Lessons from history**
>
> **1700s**: Edward Jenner, a Scottish physician working in London, inoculated James Phipps, the eight-year-old son of his gardener, with pus from cowpox blisters on the hands of a milkmaid. Later, he deliberately injected Phipps with smallpox material to show that he was protected, an action that ultimately led to the global eradication of smallpox in 1979, but would not be considered ethical today.
>
> **1950s**: In research conducted at the Willowbrook State School and approved by the New York Department of Health, Krugman and colleagues administered immunoglobulin therapy to mentally-impaired children and then deliberately infected them with hepatitis A to observe the natural progression of the disease and the response to prophylaxis. These studies contributed to the recognition of hepatitis A and B and stimulated vaccine development, but have been widely criticized for exploiting a vulnerable patient group.
>
> **1990s**: Following the publication of the results of a trial by Southall and colleagues of continuous negative extrathoracic pressure in neonatal respiratory distress syndrome, a group of parents made a series of complaints against the investigators to the General Medical Council. The trial was examined seven times over 11 years until, in 2008, all allegations against the investigators, including the charges that signatures on trial consent forms had been forged, were found to be false, but the trial was instrumental in leading to the introduction of the UK Research Governance Framework.
>
> **2010**: The Lancet retracted a discredited paper by Wakefield and colleagues published in 1998, linking autism to the measles vaccine, a false claim that led to a decline in vaccination rates and outbreaks of measles in England and Wales.
>
> **2013**: The SUPPORT trial, approved by 23 US Institutional Review Boards, was designed to determine whether targeting lower or higher oxygen saturations within the accepted standard of care range for preterm babies reduced retinopathy of prematurity. The trial showed that babies at the higher end of the recommended oxygen saturation range had a greater incidence of retinopathy of prematurity, but, unexpectedly, babies at the lower end, had a higher risk of death. An accusation, initiated by a local newspaper but taken up by the United States Office for Human Research Protections against the investigators for failing to fully inform parents of 'the reasonably foreseeable risks of blindness, neurological damage and death', in other words for failing to foresee an unexpected trial finding and to suggest that babies were at greater risk from randomization even though they continued to receive oxygen within the accepted standard of care limits. This met with a storm of protest from around the world.

Box 1.6 A recent change in research regulation

Formerly, before recruitment to a Clinical Trial of an Investigational Medicinal Product, consent had to be given on behalf of a minor by a person with parental responsibility or an authorized legal representative even in an emergency situation. From 2008 an amendment to the Medicines for Human Use (Clinical Trials) and Blood Safety and Quality Regulations permits minors to be entered into a trial before informed consent is obtained provided that urgent action is essential, it is not practicable to obtain consent, and the intervention is approved by a Research Ethics Committee.

Box 1.7 Examples of training resources

Canadian National Collaborating Centre for Public Health: online training resources (http://www.nccmt.ca/index-eng.html)

Cochrane Library: how to prepare a Cochrane review and other resources (http://www.thecochranelibrary.com; http://training.cochrane.org)

Medical Research Council: resources for researchers (http://www.mrc.ac.uk/research)

National Centre for Research Methods: online training resources (http://www.ncrm.ac.uk)

National Institute for Health Research: training in core research activities such as Good Clinical Practice (http://www.crn.nihr.ac.uk/learning-development)

Standards for Research in Child Health (StaR): a resource to improve children's research design, conduct and reporting (http://starchildhealth.org)

School of Public Health, University of Alabama: instructional modules, each containing slide images and a video clip version of the associated lecture (http://biostatcourse.fiu.edu)

University of Reading: interactive resource for bioscience students (http://www.engageinresearch.ac.uk)

Wellcome Trust: workshops, summer schools and advanced courses (http://www.wellcome.ac.uk/Education-resources/Courses-and-conferences/Advanced-Courses-and-Scientific-Conferences/index.htm)

and only about 5% of the UK annual public and charitable biomedical research expenditure is directed at child health research. The reasons are complex and in part reflect valid concerns such as the need to protect children from the dangers of unethical research, experimental therapies and invasive investigative techniques. The constraints consequent upon these concerns are increasingly being balanced by processes and attitudes that acknowledge that children are able to benefit from research participation and have their healthcare assured by evidence obtained from rigorous research. Clinical research is now governed by a strict regulatory framework designed to protect the well-being and rights of participants, and powerful new post-genomic technologies, *in-vivo* imaging and non-invasive monitoring techniques provide increasing opportunity to involve children without risk.

There is also a disparity between the evidence gaps for children's healthcare and current research effort. For diseases where at least 60% of the disease burden is in children, only around 12% of clinical trials involve them. This situation reflects in part the difficulties in achieving a balance between research commissioned to address knowledge gaps of importance to health, and a strategy that encourages scientists to follow their own ideas. This tension is long-standing, and is reflected in deliberations and reports spanning a century.

The reality is that because considerable medical decision-making is based on insufficient evidence, health professionals sometimes harm patients instead of helping them. It is therefore essential that paediatricians recognize their obligations to help reduce uncertainties in care and base treatment decisions on high-quality research. Paediatricians are close to children and their families and are able to make important contributions at many points in the research pipeline. This might take the form of explaining research, recruiting to studies, being part of a multi-disciplinary research group, attending research meetings and encouraging colleagues to do likewise.

Acquiring research skills

Research skills will stand you in good stead in wider ways. For example, establishing a diagnosis may be viewed as a form of hypothesis testing. You take a history and examine the patient; you then make a tentative diagnosis (formulate a hypothesis) and carry out a series of laboratory tests or other investigations (test the hypothesis). You will also find research skills useful when you evaluate the service you provide, for example in relation to audit, quality improvement, assessment of outcomes, questionnaire design, and development of parent- or patient-reported experiences and outcomes. There are a large number of resources available to help one acquire these skills (Box 1.7). The Royal College of Paediatrics and Child Health has developed criteria for the assessment of research experience and competencies that are expected of all paediatric trainees (Box 1.8) and provides an

example of a research skills log (Box 1.9). Acquiring research skills is much more enjoyable when you have a real problem to solve.

Percipient observations by clinicians have been at the heart of many great advances, as have scientific curiosity and serendipity. However, such insights require other mechanisms to drive research endeavour, and to ensure that new treatments and healthcare innovations are successfully developed and implemented. In the UK, the National Institute for Health Research provides support across the entire clinical research pipeline. Further details about research are described in Chapter 37, Clinical research.

Parents, patients and the public

Public understanding of research is important for trust in science; collaboration between investigators, parents and patients will help define important research questions and resolve uncertainties to bring about improvements in care and outcomes more rapidly. Public pressure can help improve representation; for example, public pressure contributed to improving the enrolment of women into clinical trials and to the establishment by congressional mandate in the United States of the Food and Drug Administration Office of Women's Health to advocate for their participation. Wider involvement of parents, the public and children and young people themselves will help increase research aimed at benefiting the health of infants, children and young people (Box 1.10).

INVOLVE is a national advisory group that supports greater public involvement in the National Health Service, public health and social care research in the UK. The INVOLVE website has useful information on topics such as 'how to write a plain English summary'. Parents and young people with whom you discuss science and research are unlikely to be specialists so practice in explaining science and research concepts to non-specialist audiences can help you to be an effective communicator and a better doctor. The Science Media Centre provides fact sheets for non-specialist audiences on areas of topical science interest, and offers training and advice on discussing science and research with the media. The James Lind Library was established to improve public and professional general knowledge about 'fair tests of treatments' in healthcare, and their history. The website is a growing repository of other related resources, including interactive quizzes, factsheets, videos and cartoons that help understand and explain clinical research.

Further reading

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Premila Webster, Sarah Rayfield

Epidemiology and public health

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Understand how disease and health is measured in populations or groups and be able to use measures of disease incidence and prevalence
- Understand and be able to use measures of effect (e.g. relative risk, absolute risk and number needed to treat)
- Know the main indices of population child health and their significance
- Know the strengths and limitations of different epidemiological studies
- Be able to take into consideration bias, confounding and chance when interpreting epidemiological data and understand the difference between statistical association and causality
- Understand the concept of social determinants of health and wider determinants of health and how it affects the health of children
- Understand what is meant by inequalities
- Understand the concepts, definitions, objectives and uses of public health surveillance
- Understand what a 'health needs assessment' is and why it is undertaken
- Understand the principles of screening

Measures of health and disease and epidemiological studies

What is epidemiology?

The word epidemiology is derived from the Greek 'epi', 'demos' and 'logos' and literally translated means the study (logos) of what is among (epi) the people (demos). It is the study of the occurrence and distribution of health-related states/events in specified populations. Its uses are listed in Box 2.1.

The prevention of sudden infant death syndrome (SIDS) is one of the major success stories in epidemiology (see Box 1.1). Epidemiological studies, culminating in the New Zealand Cot Death Study, a three-year case-control study (1987–1990), identified three modifiable risk factors for SIDS, namely prone sleeping position, maternal smoking and lack of breastfeeding. A prevention programme ('Back to Sleep' campaign) was launched and resulted in a dramatic reduction in SIDS mortality. Australia and then the United Kingdom followed suit and the number of deaths in the UK fell from 1500 to 600 per year by the mid-1990s. The 'Back to Sleep' campaign has been implemented in many countries across the world with similar results.

Measuring health and disease of populations or groups

Certain terms are used when measuring health and disease of groups or populations. It is usually unhelpful to state numbers of events alone. In order to interpret the number, they need to be related to a denominator. For example stating 10 children were diagnosed with pertussis does not give as much

9

information as the statement that 10 out of 20 children who had not been immunized were affected or that 10 children had pertussis out of a total population of 100,000 children.

- The *numerator* is the number of people known to have a specific disease or problem.
- The *denominator* is the total number of people at risk in the population.

If 100 children attended a Christmas party and 10 of them develop vomiting, the numerator is 10 and the denominator is 100.

Three terms are usually used to relate the number of cases of a disease or outcome to the size of the source population in which they occurred:

Ratio

A ratio compares values. A ratio says how much of one thing there is compared to another thing, for example the number of stillbirths per thousand live births.

Proportion

Proportion is a type of ratio where those who are included in the numerator must also be included in the denominator, for example the number of fetal deaths out of the total number of births – here the numerator will be the number of fetal deaths and the denominator the number of fetal deaths plus the live births.

Rate

A rate is defined as a ratio in which there is a distinct relationship between the numerator and denominator and most importantly a measure of time is an intrinsic part of the denominator. For example, the number of colds per 1000 primary school children during a one-month period.

However, in medical literature the term 'rate' is used interchangeably to denote different demographic or epidemiological measures that could be true rates, proportions or ratios.

Main indices of population child health

Infant mortality rate

Infant mortality rate is the number of children who die aged less than one year old per 1000 births. Some key facts are shown in Box 2.2.

In 1911, 130 out of every 1000 children born in England and Wales would die before their first birthday. The decrease in infant deaths between 1911 and 2010 is because of considerable improvements in healthcare, including the control of infectious diseases and public health infrastructure over this time period. For the UK as a whole, infant mortality has been declining and is now only about a quarter of what it was in 1970.

Infant mortality rate is linked to several factors including access to healthcare services for mothers and infants, socio-economic status of the child's parents, the health of the mother, birth weight and the proportion of infants born preterm.

Terms used in child mortality statistics are:

- Stillbirths and perinatal mortality rates – reported per 1000 total births (live and stillbirths)
- Early neonatal, neonatal, postneonatal and infant mortality rates – reported per 1000 live births
- Childhood (1–15 years) mortality rates – reported per 100,000 population of the same age

The precise definitions of these terms relating to newborn infants are included in Chapter 10, Perinatal medicine. Analysis of the data around deaths identifies that the majority of deaths in childhood occur before one year of age; 70% of infant deaths in England and Wales in 2011 were neonatal deaths – deaths at less than 28 days. The most common cause of death, in children as a whole group, is now related to perinatal problems and congenital abnormalities.

Identification of cause of death

In England and Wales, stillbirths and neonatal deaths are registered using a special death certificate that enables reporting of relevant diseases or conditions in both the infant and the mother. The Office for National Statistics (ONS) has developed a hierarchical classification system (also referred to as the ONS cause groups), which allows the death to be assigned to a specific category, based on the likely timing of the damage leading to the death. This produces broad causation groups to enable direct comparison of neonatal and postneonatal deaths. The following are mutually exclusive categories:

Before the onset of labour

- Congenital anomalies
- Antepartum infections
- Immaturity-related conditions

In or shortly after labour

- Asphyxia, anoxia or trauma

Postnatal

- External conditions
- Infections
- Other specific conditions

Linkage of births and deaths

The linkage of birth and infant death records has been conducted since 1975 to obtain information on the social and biological factors relating to the baby and parents; it is collected at birth registration. Death registration gives only a limited amount of information about the parents of the deceased infant; for example, occupation of parent. However, a considerable amount of information is given at birth registration. This includes: age of each parent, number of previous children born (the mother's parity), country of birth of parents, place of birth and whether the baby was a singleton or multiple birth. Linking the infant death record to the birth record improves understanding of the key characteristics of the baby's parents as further information is provided by the birth record. In 2010, 98% of infant deaths in England and Wales were successfully linked to their corresponding birth registration record. The potential use of such data is outlined in Box 2.3.

> **Box 2.3 Why collect mortality and morbidity data?**
>
> Childhood mortality rates are a way of evaluating policies concerning the health and welfare of children, as they give an indication of the quality of support available for both children and families. One example is a review which systematically examined mortality and morbidity in children and young people between 1 and 18 years of age in the UK and linked death certificate data with hospital admissions.
>
> It found there had been an overall reduction in all causes of child mortality since 1980 in all age groups. Injury was the most frequent cause of childhood death (31–48% of deaths in children aged 1–18 years old). The highest rates of death due to injury were found amongst boys aged 15–18 years of age. Mortality rates secondary to injury were three times higher in boys compared to girls. Two-thirds of injury mortality among 10–18 year olds was unintentional, with transport accidents accounting for 77% of this.
>
> Higher mortality rates in both infancy and throughout childhood were seen in children whose mothers were less than 20 years old. This association persisted even after taking birth weight into account. Young maternal age was an ongoing risk factor for child death throughout early childhood.
>
> Approximately two-thirds of childhood deaths take place in hospital (of causes other than injury). Two-thirds of children who died were identified as having a chronic condition, with mental and behavioural conditions being the most common.
>
> From a public health perspective, the report highlighted a number of groups in whom preventative policies could be targeted in order to reduce childhood mortality rates, in particular children born to young mothers, those at risk of injuries or those with an underlying chronic condition. Policies designed to address these risk factors may result in lower childhood mortality.
>
> (Data from Child Health Reviews – UK, 2013. Clinical Outcome Review Programme, commissioned by the Healthcare Quality Improvement Partnership.)

Low birth weight

Birth weight is an important indicator of overall health and is influenced by a number of factors including smoking and drinking during pregnancy, low parental socio-economic status, education levels, low income and inadequate living conditions. In the UK nearly 8% of births are preterm.

In England and Wales, around 700,000 babies were born in 2013 of which approximately 50,000 were low birth weight (<2.5 kg). Of all those babies who were born with a low weight, 62% were preterm.

Under five year mortality

This is collected internationally and allows comparison between countries. In the UK in 2013, the under-five mortality rate was 4.9 per 1000 live births, the highest in western Europe; in Iceland it was 2.4, Sweden 2.7, Spain and Germany 3.6, France and Italy 3.7. It was worse in the UK than many eastern European countries, including Serbia, Estonia and Croatia. This means that 2000 more children die in the UK each year than if they lived in Sweden.

Deaths in later childhood

Data show that more children die in adolescence than in any period other than infancy. The World Health Organization (WHO) classifies deaths into communicable and non-communicable disease (NCD). Deaths due to communicable disease are very low in the UK. However, for NCD deaths, for almost all ages the UK does worse than its comparators. Up to 74% of childhood deaths in the UK occur in children with co-morbidities, i.e. a long-term condition, of which the most common is a neurological or sensory condition.

Measures of health and well-being in children

Well-being is increasingly the focus of policy making and evaluation. It is now largely accepted that what children become in their adult life is largely a product of their experiences in the early stages of their lives. Particularly important are issues of health and safety, material and emotional security, education and socialization.

According to the 2011 Census, there were just over 10.5 million children aged 0 to 15 in England and Wales – about one in five of the population compared with one in three in 1911. Whilst the proportion of children in the population has declined, the proportion of the elderly has risen. Over the same period there has been a change in attitudes to children which

has arguably improved their well-being. For example, all children in the UK are expected to be in compulsory education until they are at least 16 years old; and in England in some form of education or training until 18 years.

Many measures of children's well-being are used in surveys. For effective policy making and evaluation, it would be preferable for a systematic and uniform way of measuring children's well-being to be used so that there could be meaningful comparison both between sources and also over time.

As part of the Measuring National Well-being programme, the Office for National Statistics has worked with other government departments, academics and third sector organizations to examine measures of children's well-being. The aim is to understand the data that already exist to measure children's well-being and evaluate its limitations. A framework has been developed based on responses to the national debate, research findings and expert opinion. From this, the 10 domains proposed to measure national well-being for the UK are 'Individual well-being', 'Our relationships', 'Health', 'What we do', 'Where we live', 'Personal finance', 'Education and skills', 'The economy', 'Governance' and 'The natural environment'. For most of these domains, some of the measures proposed for adults are also appropriate for children, either as listed above (for example the measures in 'The economy' domain) or by analysis specifically for children (for example, individuals living in poverty in the 'Personal finance' domain).

Some specific aspects of these domains for children aged 0 to 15 include circumstances in which they live, what they feel about their relationships, what they do and also decisions that adults make on their behalf. These domains (examples in Box 2.4) measure

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Box 2.4 Some key points from Measuring National Well-being – Children's Well-being 2012

1. 89% of children said that they were relatively happy with their lives overall, 4% reported being relatively unhappy.
2. A much higher percentage reported being completely happy with their friends and family than with their school, their school work or, particularly, their appearance.
3. Boys more often reported being happy with their life overall, their friends and their appearance than girls, while girls more often reported being happy with their school work.

(Source: Measuring National Wellbeing – Children's Wellbeing, 2013. Office for National Statistics. Based on data from 2009–10 Understanding Society, the UK Household Longitudinal Study (UKHLS).

what children think and feel about their lives. They focus on:

- How many children there are in England and Wales
- Children's health
- Poverty and its relationship with parental economic activity
- Education and skills
- Children's relationships and their well-being
- Use of technology and social media
- Where children live

Data from children is collected through the Youth Module of the UK Longitudinal Study, a self-completed questionnaire answered by those aged 11 to 15. The questions, employing a seven-point scale, from completely happy to not at all happy, analyse measures of health and well-being in children, including how they feel about:

- Life as a whole
- Schoolwork
- Appearance
- Family
- Friends
- School

Another measure of health and well-being in children in England is the Good Childhood Index published by The Children's Society. It is also produced using surveys. The main measure of overall subjective well-being consists of five statements to which children are asked to respond on a five-point scale from 'strongly disagree' to 'strongly agree':

- My life is going well
- My life is just right
- I wish I had a different kind of life
- I have a good life
- I have what I want in life

Question 2.1

Disease prevalence

Which of the following BEST describes the prevalence of a disease?

A. That part of the population that are at risk of the disease

B. The incidence in the population divided by the time in years

C. The incidence minus the mortality rate

D. The incidence in the population multiplied by the duration of the disease

E. The number of new cases that occur during a specified period of time in a population

Answer 2.1

D. The incidence in the population multiplied by the duration of the disease.

The prevalence and incidence are often confusing. How these two terms are related is described below.

Children's responses to each question are coded on a scale from zero ('strongly disagree') to four ('strongly agree'), to create an overall scale.

Data on children's subjective well-being was also gathered in the 2013 NatCen study; the relationship between well-being and emotional and behavioural problems are considered in Chapter 24, Emotions and behaviour.

Epidemiological studies

Two key elements are measured in many epidemiological studies:

- *Exposure*: the risk factors that are being investigated, that may or may not be the cause
- *Outcome*: disease, event or health-related state of interest.

Measures of disease frequency

The measures of disease frequency used most often in epidemiology are:

- *Incidence*: the number of new cases that occur during a specified period of time in a defined population
- *Prevalence*: the proportion of the population at risk that have the condition, where:

$$\text{Prevalence} = \frac{\text{number of cases}}{\text{population at risk}}$$

- *Population at risk*: that part of the population which is susceptible to a disease.

For example, to calculate the prevalence of all childhood cancers in the age group 0–4 years in the UK:

- The *numerator* would be the number of children aged 0–4 years living in the UK at that time who were diagnosed with cancer
- The *denominator* would be the number of children aged 0–4 years living in the UK at that time (population at risk). The mid-year population is usually used.

Data on incidence and prevalence becomes more useful if converted into rates. The rates are usually expressed as per 1000, per 10,000, per 100,000, etc.

Example: As childhood cancers are rare (between 2008–2010 there was an average of 1603 new cases of

childhood cancer each year in the UK), 883 (55%) in boys and 720 (45%) in girls, the rates are expressed per million – the crude incidence rate shows that there are 160 new cancer cases for every million boys in the UK, and 137 for every million girls.

Interrelationship between incidence and prevalence (Fig. 2.1)

$$Prevalence = incidence \times duration$$

Several factors can influence prevalence:

- *The number of new cases (incidence)*: if the number of new cases per year is high (high incidence) this will result in the prevalence being higher, e.g. up to 400 children are diagnosed with acute lymphoblastic leukaemia (ALL) every year compared to fewer than 15 children per year with chronic myeloid leukaemia (CML).
- *The severity of the illness*: if many children who develop the disease die, the prevalence rate is low, e.g. the survival rate for children with ALL is around 90% compared to 60% in children diagnosed with CML.
- *The duration of the illness*: if a disease lasts for a short time, its prevalence rate is lower than

if it lasts for a long time, e.g. the duration of chickenpox compared with type I (insulin dependent) diabetes.

Risk

There are three common indices of risk: absolute risk, relative risk and attributable risk. The number needed to treat (NNT) is the inverse of attributable risk. The terms are defined in Box 2.5 and an example is shown in Question 2.2.

Box 2.5 Definition of indices of risk

Absolute risk: Incidence of disease in any defined population. It is the number of events ÷ total population at risk.

Relative risk: Ratio of the incidence rate in the exposed group to the incidence rate in the non-exposed group. It is the risk in the exposed group ÷ risk in the unexposed group

Attributable risk: Difference in the incidence rates in the exposed and non-exposed group. It is the risk in the exposed group minus risk in the non-exposed group

Numbers needed to treat (NNT): Inverse of attributable risk.

Question 2.2

Prevalence

A study on the prevalence of asthma in primary school children was undertaken in two towns (A and B). In town A, a questionnaire was sent to all parents of children in primary schools. In Town B, the same questionnaire was sent to a random sample of parents of children in primary schools. Parents were asked whether doctors had ever diagnosed wheezy bronchitis, asthma or bronchitis in their child. If they answered 'Yes' to either wheezy bronchitis or asthma, they were classified as having asthma. If they answered 'Yes' only to bronchitis, they were classified as having bronchitis.

Based on the data in Table 2.1, which of the following statements are true (T) or false (F)?

Table 2.1 Prevalence data – asthma in primary school children in Towns A and B

	Town A		Town B		
Total sample	1500		8000		
Questionnaire returned	1125 (75%)		6960 (87%)		
	Prevalence	**95% CI**	**Prevalence**	**95% CI**	**p-value**
Asthma	7%	5%–9%	9%	8.5%–10%	NS
Bronchitis	30%	26%–34%	15%	14%–17%	<0.01

A. The prevalence of asthma and bronchitis is significantly higher in Town A.

B. The prevalence of asthma and bronchitis is significantly higher in Town B.

C. There is no significant difference in the prevalence of asthma between Towns A and B.

D. There is no significant difference in the prevalence of bronchitis between Towns A and B.

E. The prevalence of bronchitis in Town A is twice the prevalence in Town B.
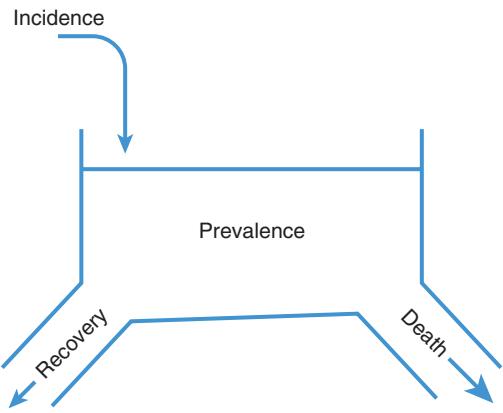
Fig. 2.1 Illustration of the relationship between incidence and prevalence.

Answer 2.2

A. False; B. False; C. True; D. False; E. True.

A. and B. It is tempting but incorrect to add together the prevalences of asthma and bronchitis here. We cannot make assumptions about a composite end point. Therefore, A and B are incorrect (false).

C. This is correct and the information is given in the table. (NS is 'Not significant').

D and E. We do have the data that allows us to conclude that there is a significant difference in the prevalence of bronchitis. It is significantly higher in Town A. It is twice that in Town B.

Types of epidemiological studies

Epidemiologists use the triad of 'when, who and where' to study patterns of health and disease within and between populations. Two main types of epidemiological study are used – observational and experimental (Fig. 2.2).

Observational studies are further subdivided into 'descriptive' and 'analytical', which can be retrospective, use existing data, or prospective with ongoing data collection.

- A *descriptive* observational study is typified by basic population data such as census results and surveys, but can also include case reports and case series. They cannot be used to test any hypothesis, as there is no comparison between different groups.
- An *analytical* observational study attempts to identify subpopulations that differ (for example, presence or absence of a risk factor), and the presence or absence of disease. Examples include cohort and case-control studies.

Fig. 2.2 Types of epidemiological studies.

Experimental studies (also called intervention studies) allocate an exposure of interest (e.g. a drug) to a subgroup, before following them up and assessing outcome. This is typified by randomized controlled trials.

The type of study chosen depends on what question(s) are being addressed, data already available, practicality of design, ethics, and also cost. The main types of study are discussed in more detail in Chapter 37, Clinical research.

Interpreting epidemiological data

An association between an exposure or risk factor and an outcome or disease does not imply that the former causes the latter (Box 2.6). Three possible factors are important when considering whether a causal association really exists:

1. Is this association due to a *chance* occurrence?
2. Is it due to a flaw in the methodology (*bias*)?
3. Is it due to some other factor linked to both exposure and outcome (*confounding*)?

Chance – is the association a chance occurrence?

Chance is mainly determined by sample size – the larger the sample, the smaller the risk that the finding is due to chance alone. This is usually expressed as a 'p-value', usually with 'confidence intervals'. Strictly speaking, the p-value is the likelihood of incorrectly rejecting the null hypothesis. Confidence Intervals (CIs) provide a range within which the true answer will lie at a population level (for more detail, see Chapter 38, Statistics).

Bias – is the association due to a flaw in the methodology?

Bias is a systematic error in the methodology of the study that affects the results. There are several types of bias, such as selection bias, etc., which affect epidemiological studies:

Selection bias

Selection bias occurs when the two groups being compared differ systematically. That is, there are differences in the characteristics between those who are selected for a study and those who are not selected, and where those characteristics are related to either the exposure or outcome under investigation.

Example of selection bias: In Dr Andrew Wakefield's discredited paper on the MMR (measles, mumps, rubella) vaccine, he took 12 children who had behavioural disorders and attempted to link them to vaccines. There was no comparison group employed of children without behavioural disorders to see if their exposure to the MMR vaccine was greater or less.

Information bias

Information bias results from systematic differences in the way data on exposure or outcome are obtained from the various study groups. Types of information bias include:

Observer bias occurs when there are systematic differences in the way information is collected for the groups being studied. Observer bias may occur as a result of the investigator's prior knowledge of the hypothesis under investigation or knowledge of an individual's exposure or disease status. Such information may result in differences in the way information is collected, measured or interpreted by the investigator for each of the study groups.

Example of observer bias: In a trial of a new medication to treat hypertension, if the investigator is aware which treatment arm participants are allocated to, this may influence their blood pressure measurements. Observers may underestimate the blood pressure in those who are being treated, and overestimate it in those in the control group.

Recall bias occurs when a subject with the outcome is more likely to remember the exposure or other events than a subject without the outcome of interest.

Example of recall bias: Data from a study in the 1950s suggested that children who had been exposed to X-rays *in utero* had a 90% increased risk of death from leukaemia or other cancers. However, as exposure status was determined by interviewing mothers of children, it was possible that those whose children died of cancer may be more likely to remember being X-rayed during pregnancy than mothers of healthy children.

Confounding – is it due to some other factor linked to both exposure and outcome?

A confounding factor is:

- A risk factor for the study disease
- Associated with the exposure and independently associated with the outcome.

Example: If an association was observed between coffee drinking and cancer of the pancreas, it may be that coffee actually causes cancer of the pancreas or that the observed association of coffee drinking and pancreatic cancer may be as a result of confounding by cigarette smoking (i.e. the association between coffee drinking and pancreatic cancer is observed because cigarette smoking is a risk factor for pancreatic cancer and coffee drinking is associated with cigarette smoking).

Another example of the relationship between association and causality is shown in Box 2.6.

Child health inequalities

Determinants of health in children

Children live in complex social environments. Figure 2.3 illustrates influences that can impact children's health. They are divided into:

- Prenatal care
- People whom children depend upon and interact with such as caregivers, other adults, and peer groups

- Local structure, such as housing, neighbourhoods, transportation, schools, access to health care, and commercial influences
- The national policy environment that includes policies on health and social programmes and laws that protect the environment where children live.

Some facts and figures relating to children and their health are listed in Box 2.7.

What causes inequalities?

Inequalities in health refer to the marked differences in health outcomes within a given population. Health inequalities can be defined as differences in health status or in the distribution of health determinants between different population groups.

Its causes are complex. Some differences are unavoidable, e.g. genetic make-up, and are considered fixed. Others are not, e.g. undertaking freely chosen activities of high risk, such as certain sports. Most people would not regard these as inequalities in health. The World Health Organization uses the terms 'equity' and 'inequity' to refer to 'differences in health
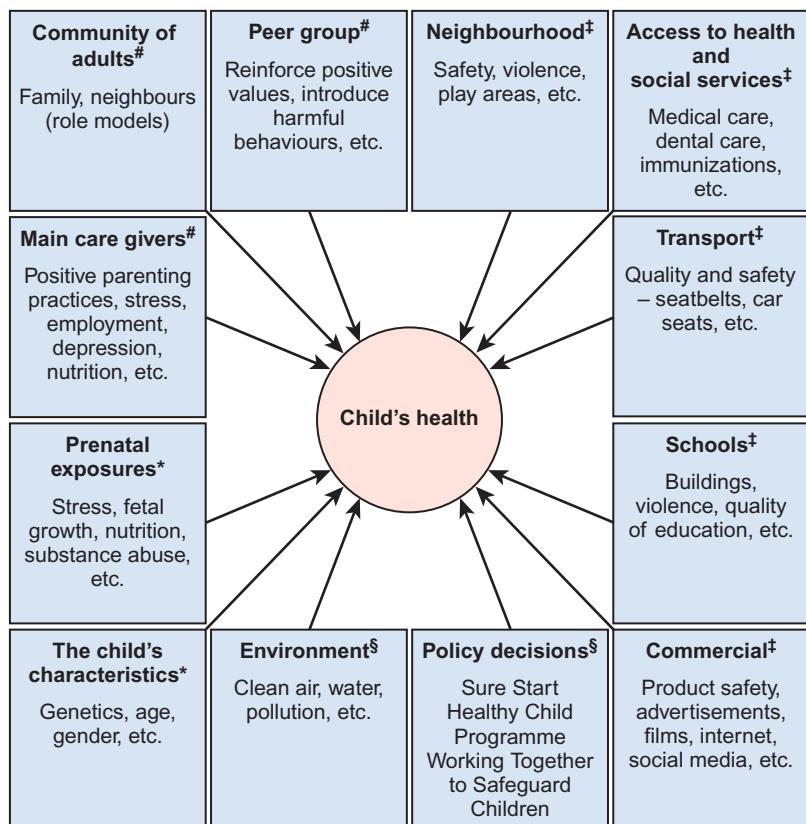
Fig. 2.3 Determinants of health in children. *Prenatal; #People; ‡Local structure; §National structure. *(Adapted from Determinants of Health in Children and the Problem of Early Childhood Caries. Pediatr Dent 2003;25:328–33.)*

that are not only unnecessary and avoidable but, in addition, are considered unfair and unjust'.

Measuring inequalities

Measuring inequalities is important but contentious and challenging, as there are issues regarding definition, technical details and data availability and the selection of appropriate measures. Yet the measuring of inequalities is needed to aid policy development.

Measures of absolute and relative levels of poverty and social deprivation indices, such as the Townsend Index (distinguishes between material and social deprivation) and the Jarman Index (local geographical areas with high demand for primary care services), have been around for several decades and are used and often cited in studies that examine the correlation between deprivation and mortality or morbidity. Reviews reveal a 'social gradient of health' in which the lower a person's socio-economic status, the worse their health. For example, in England, those living in the most deprived areas will, on average, die seven years earlier than those living in the wealthiest areas. In addition, the difference in disability-free life expectancy is 17 years (Marmot Review 2010). Recently there have been substantial attempts to specify, codify, and operationalize the concept of equality using

quantitative data, statistics and indicators. The UK government developed more comprehensive indices that draw on a wide range of routinely collected local data. One such index, the Index of Multiple Deprivation, combines a number of indicators, chosen to cover a range of economic, social and housing issues, into a single deprivation score for each small area in England.

Tackling inequalities in health in children

Infant mortality is seen as a key measure among health outcomes and there is a long-established link between social and health inequalities and infant mortality (see Box 2.3).

Another example, to illustrate some key contributors to health inequality, is childhood obesity (Box 2.8). Data is derived from routine measurement of height and weight at school of children in England

Box 2.8 Some reasons for inequalities contributing to childhood obesity

Early-life factors

Children who were bottle-fed rather than breastfed are at increased risk of obesity in childhood.

Breastfeeding at birth is related to age of mother; 46% among teenage mothers but 78% for mothers aged ≥30 years. Rates also related to age of leaving full-time education: 54% for mothers educated to age 16 or below; 88% for those educated to ≥19 years.

Physical activity

Lifestyle characterized by lack of physical activity and excessive inactivity (particularly television viewing). Greater social support from parents and others correlates strongly with participation in physical activity.

Television advertising could adversely affect dietary patterns – lower socio-economic status is associated with higher levels of television viewing, and exposure to 30-second commercials increases the likelihood that 3–5-year-olds later select an advertised food when presented with options.

Family factors

Parent–child interactions and the home environment can affect behaviours related to risk of obesity. Eating family dinner decreases television viewing and improves diet quality (less saturated and trans fat, less fried food, lower glycaemic load, more fibre, fewer soft drinks, and more fruit and vegetables).

Table 2.2 Pattern of health inequalities in obesity

Overall	Age 4–5 yrs: 23% of children are either overweight or obese Age 10–11 yrs: 34% of children are either overweight or obese
Gender	Both age groups demonstrate a higher prevalence of obesity in boys: Age 4–5 years: 10% of boys and 9% of girls are obese Age 10–11 years: 20% of boys and 17% of girls are obese
Ethnicity	Higher prevalence if 'Black or Black British', 'Asian or Asian British', 'any other ethnic group' and 'mixed'
Location	Parts of south-east England have the lowest obesity prevalence, London the highest, with urban areas higher than rural areas
Socio-economic status	At 4–5yrs, obesity prevalence is 7% among the least deprived children, but rises to 12% amongst the most deprived Overall obesity prevalence amongst the most deprived is twice that of the least deprived Children receiving free school meals have significantly higher rates of obesity

(Data taken from National Child Measurement Programme: England, 2011/12 school year. December 2012. The Health and Social Care Information Centre.)

The surveillance of health in the population and how health needs are assessed

'Surveillance' is defined as the ongoing collection, monitoring and analysis of health-related data required for planning, implementing, and evaluating public health practice. It aims to provide the right information at the right time and in the right place to inform decision-making and action-taking.

It encompasses the processes of data collection, analysis, interpretation and dissemination that are undertaken on an ongoing basis (i.e. there is a defined but not time-limited cycle of processing) and provides measures of population or group health status or determinants of health (hazards, exposures, behaviours) against historical or geographical baselines/comparators.

Health needs assessment (HNA)

This is a systematic method for reviewing the health issues facing a population, leading to agreed priorities and resource allocation that will improve health and reduce inequalities.

There are three main approaches to health needs assessment:

- Epidemiological needs assessment: what data do we have?

aged 4–5 yrs and 10–11 yrs (National Child Measurement Programme). This reveals that the prevalence of obesity varies widely according to gender, ethnic group, geographic location and socio-economic status (Table 2.2). There is a complex interplay between all of these factors. Approximately 70% of the geographical variation in obesity can be explained by socio-economic deprivation. In addition, deprived urban areas in England tend to have a higher proportion of individuals from non-White ethnic groups. The Marmot review in 2010 described a 'social gradient of health' in which the lower a person's socio-economic status, the worse their health. Recognizing the disparities between rates of obesity among different social groups is fundamental to targeting high risk populations with effective interventions.

An aim of the UK Healthy Child Programme is not only to provide medical care including immunizations and developmental checks but also to reduce health inequalities by identifying the most vulnerable children and signposting them to additional assistance available in the community (Box 2.9).

Box 2.9 The Healthy Child Programme

The Healthy Child Programme is an early intervention and prevention public health programme. It is a universal programme offered to all families with a progressive range of services available for those with different levels of need. Integrated services are provided by GPs, midwives, community nurses, health visitors and children's centres. This includes the Sure Start centres, which were set up in the most deprived areas in order to offer more intensive holistic parenting education and support, from antenatal care to early childhood, incorporating specific areas such as fathers' support and ethnic minority inclusion schemes. Through the identification of factors influencing health and well-being and promoting a strong parent–child attachment, the programme aims to reduce health inequalities by focusing on the most vulnerable children and allocating resources where they are most needed.

Generic indicators of children at risk of poorer outcome	Protective factors
Social housing	Authoritative parenting combined with warmth
Young mother or father	Parental involvement in learning
Mother's main language not English	Protective health behaviours, e.g. stopping smoking in pregnancy
Parents are not co-resident	Breastfeeding
One or both parents grew up in care	Psychological resources, e.g. self esteem

A core function of the Healthy Child Programme is the early recognition of disability and developmental delay in order to facilitate support and referral to the appropriate services. Universal health and development reviews provide an opportunity to assess the growth and development of the child. They also give mothers and fathers the opportunity to discuss their concerns and aspirations. The programme aims to provide links with effective interventions which are acceptable to parents, thereby promoting engagement with services in a non-stigmatizing manner.

Opportunities to provide services to children and families	Universal services offered
By the 12th week of pregnancy	Screening tests
Neonatal examination	Immunizations
New baby review (at approx. 14 days old)	Developmental reviews
	Information
Baby's 6–8 week examination	Guidance to support parenting and healthy choices
Between 12–13 months old	
Between 2–2.5 years	

(Adapted from the Healthy Child Programme: pregnancy and the first five years of life. Department of Health Publications, 2009.)

- Comparative needs assessment: what do other areas do?
- Corporate needs assessment: what do stakeholders think?

Why undertake health needs assessment?

Health needs assessment is required to ensure an established health service meets need and provides effective and efficient patient care that is cost-effective. It can also inform local delivery plans, community strategies and commissioning.

Benefits include improved patient care, strengthened community involvement in decision making, improved public and patient participation and improved team and partnership working often across traditional boundaries (e.g. primary and secondary care, health and social care). This, in turn, can lead to improved communication with other agencies and the public and a better use of resources.

It is often challenging to achieve these aims. Challenges include a lack of a shared language between sectors, difficulties in accessing relevant local data and even a difficulty in accessing the target population. This is particularly pertinent to children, who often lack a voice when decisions are made about their healthcare.

An example of assessing specific health care needs of children with diabetes in a specific area is shown in Box 2.10.

Population screening

Definition

Screening is a process of identifying apparently healthy people who may be at increased risk of a disease or condition. They can then be offered information, further tests and appropriate treatment to reduce their risk and/or any complications arising from the disease or condition.

Box 2.10 Health needs assesment (HNA) for insulin pump therapy in children with diabetes

You are a regional specialist in paediatric diabetes. You know there is a body of evidence (as per NICE guidelines) to support the use of continuous insulin pumps in adolescents (age ≥12 years) with either disabling hypoglycaemias or poor HbA1c control. You want to perform a health needs assessment to assess the cost implications of implementing such a proposal.

Critical steps consist of:

1. A clear statement of the population group whose needs are to be assessed.

Adolescents with diabetes and poor control/hypoglycaemias, within each funding region.

2. Identifying subcategories of this population with particular service needs.

Subgroups:
- all children with type 1 diabetes
- disabling hypoglycaemia
- poor HbA1c control

3. Setting out the prevalence and incidence of the subcategories.

How many children with type 1 diabetes live in the area, what proportion are appropriate for pump therapy, and what projections are there for the future? How many are there in each subcategory?

Data will be available from a variety of sources – this could include childhood diabetes registers, health visitors' records, data collected routinely, hospital admission data, ad hoc data collected for research projects, etc.

4. Setting out the current services available (the baseline).

What services are currently provided locally? This should include all services whether in primary care, secondary care, or in the community.

5. Identifying the effectiveness and cost effectiveness of interventions and the associated services.

What evidence is there about effective ways of managing children with diabetes (e.g. community-based versus hospital-based care)?

Identify numbers of hospital admissions for hypoglycaemia and diabetic ketoacidosis. Cost analysis of long-term poor diabetic control.

6. Setting out a model of care that apportions relative priorities.

The needs assessment might result in recommendations for change in service provision to meet the needs of young people with diabetes better. It may introduce a staged implementation (e.g. first use pumps in adolescents with significant hypoglycaemias). Cost analysis may reveal that the region should go beyond NICE standards and implement pump therapy for all adolescents with diabetes. The action taken as a result of needs assessment can be very varied and is not limited to changes in health service provision.

A wide range of stakeholders should be involved to get their perspectives on services and needs. This must include children with diabetes and parents. Other stakeholders could include support groups, policy-makers and teachers. This is vital to enable services to be child-centred and reflect the needs of children.

The WHO has described 10 criteria for population screening:

1. The condition screened for should be an important health problem.
2. The natural history should be well understood.
3. There should be an early detectable stage (latent period).
4. Early treatment is more beneficial than at a late stage.
5. There should be a suitable test for early stage disease.
6. The test should be acceptable to the target population.
7. Intervals for repeat screening should be determined.
8. There should be adequate health service provision for the extra clinical workload resulting from the screen.
9. The risks, both physical and psychological, should be outweighed by the benefits.
10. The costs should be balanced against benefits.

Screening terms

A screening test does not diagnose a particular condition, but merely sorts the population into test positive and test negative groups. These are best described in

terms of sensitivity, specificity, positive and negative predictive values (see below and see Table 2.5).

Sensitivity and specificity

Sensitivity is the proportion of all those with disease who test positive (i.e. the ability of a screening test to detect disease).

A sensitivity of 70% means that for every ten participants with the disease:
- Seven of them will test positive
- The other three will be false negatives.

Poor sensitivity means a large number with the condition will escape detection. They will be falsely reassured, which could possibly delay diagnosis.

Specificity is the proportion of all those who are disease free who receive a negative test result (i.e. the ability of a screening test to rule out disease).

A specificity of 90% means that for every 10 people without disease:
- Nine will get a negative result
- One will be false positive and require further assessment before the possibility of disease can be ruled out.

Poor specificity means large number of false positives, which could result in anxiety and unnecessary further investigations.

Positive and negative predictive values (Box 2.11)

The *positive predictive value* (PPV) of a test is the proportion of those who test positive who actually have the disease. A PPV of 80% means that for every ten participants with a positive test result:
- Eight of them will have the disease
- The other two will be false negatives.

Similar to a low specificity, a poor PPV means a large number of false positives, which could result in anxiety and unnecessary further investigations.

The *negative predictive value* (NPV) is the proportion of those who test negative who are truly disease free. An NPV of 60% means that for every ten participants with a negative test result:
- Six of them will NOT have the disease
- The other four will be false negatives.

Similar to poor sensitivity, a poor NPV means a large number with the condition will escape detection. They will be falsely reassured, which could possibly delay diagnosis.

Accuracy

The *accuracy* of a test is a simplified statistic that combines both sensitivity (all true positives) and specificity (all true negatives) as a proportion of all tests performed. It is a crude measure that is useful for patients. However, a test can be very good at ruling out a disease (i.e. high specificity) but very poor at ruling it in (i.e. high sensitivity) and this will not be reflected in the 'accuracy' of the test.

A hypothetical example of a new screening test for disease X to be added to the blood spot assay to the neonatal biochemical screening (Guthrie) card is shown in Table 2.4. The way in which the sensitivity, specificity and positive and negative predictive values are calculated is shown in Table 2.5.

The relationship between sensitivity, specificity, predictive values and prevalence

There is a complex relationship between sensitivity, specificity and the positive and negative predictive values that is directly influenced by the prevalence of the disease. This is summarized in Table 2.6.

This demonstrates that when a disease is more common (and the sensitivity and specificity remain the same), the positive predictive value increases.

Why is this relationship important in population screening?

The higher the prevalence, the higher the predictive value, so screening is more efficient if it is directed to a high risk population (i.e. the south Asian population in the above example). Screening the general population for a relatively infrequent disease can be very wasteful of resources. However, if a high risk population can be identified and targeted, the screening programme (selective screening) is likely to be more efficient and cost effective.

An ideal screening test should have:

- A high sensitivity (to reduce the number of false negatives)
- A high specificity (in order to reduce the number of false positives).

Table 2.5 Calculation of sensitivity, specificity and positive and negative predictive values and accuracy for our new blood spot test

Term	Definition	Formula	Test for disease X
Sensitivity	Proportion with condition who test positive	$a/(a + c)$	$99/(99 + 1)$ = 99%
Specificity	Proportion without condition who test negative	$d/(b + d)$	$9405/(9405 + 495)$ = 95%
Positive predictive value (PPV)	Proportion with positive test who have the condition	$a/(a + b)$	$99/(99 + 495)$ = 16%
Negative predictive value (NPV)	Proportion with negative test who do not have the condition	$d/(c + d)$	$9405/(9405 + 1)$ = 100%
Accuracy	Proportion of combination of true positives and negatives	$(a + d)/(a + b + c + d)$	= 9504/10,000 = 95%

Table 2.4 A new screening test for disease X

		Disease		
		Present	Absent	Total
Screening test	Positive	99 **(a)**	495 **(b)**	594
	Negative	1 **(c)**	9405 **(d)**	9406
	Totals	100	9900	10,000

Table 2.6 The relationship between sensitivity, specificity, predictive values and prevalence for a new screening test which has 99% sensitivity and 95% specificity in a population of white Caucasians and south Asians

Disease prevalence (hypothetical data)	Test results	Disease present	Disease absent	Total	
1% (in a population of Caucasians) (so 100 per 10,000 have the disease)	Positive Negative	99 1 **Sensitivity = 99%**	495 9405 **Specificity = 95%**	594 9406	**PPV = 16%** **NPV = 100%**
5% (in a population of south Asians) (so 500 per 10,000 have the disease)	Positive Negative	495 5 **Sensitivity = 99%**	475 9025 **Specificity = 95%**	970 9030	**PPV = 51%** **NPV = 100%**

Antenatal, neonatal and child health screening programmes

The current recommendation for child health screening in the UK is to offer:

Antenatal screening

- Sickle cell and thalassaemia
- Fetal anomaly (Down's syndrome and fetal anomaly ultrasound)
- Infectious diseases in pregnancy (hepatitis B, HIV, syphilis and rubella)

Newborn and infant screening

- Newborn and infant physical examination: this includes eyes (for congenital cataracts), heart, hips and testes
- Newborn hearing (Box 2.12)
- Biochemical (Guthrie test) 'heel prick' or 'blood spot' test to check for:
  - Cystic fibrosis
  - Congenital hypothyroidism
  - Phenylketonuria
  - Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)
  - Sickle cell anaemia
  - Maple syrup urine disease (MSUD)
  - Homocystinuria, pyridoxine unresponsive (Hcys)
  - Glutaric aciduria type 1 (GA1)
  - Isovaleric acidaemia (IVA)
- Pulse oximetry screening for critical congenital heart disease, increasingly introduced
- Transcutaneous bilirubin for neonatal jaundice

Screening for children (up to the age of 16):

- Universal checks for height and weight at school entry
- Universal vision and hearing assessment at school entry
- Assessment of health and development as part of the ongoing Healthy Child Programme

Box 2.12 Specific application of the WHO criteria for screening in relation to hearing

1. The condition screened for should be an important health problem

The prevalence of permanent bilateral congenital hearing loss of at least a moderate level is 1.1 per 1000 live births.

2. The natural history should be well understood

Diagnostic delays can significantly impact the acquisition of language and communication skills with a long-term bearing on educational achievement and quality of life.

3. There should be an early detectable stage (latent period)

Neonatal period, prior to spoken language development. The median age of identification of bilateral permanent hearing impairment was 10 weeks with the screening programme, compared to 26 months before the screening programme. Following implementation of the screening programme, median age of fitting hearing aids reduced from 32 months to 16 weeks with very few missed cases.

4. Early treatment is more beneficial than at a late stage

Evidence shows that early identification of hearing loss coupled with early intervention results in significantly better language development. A review of the results of the programme concluded that there was strong evidence in favour of a universal hearing screen to identify bilateral permanent hearing loss of ≥40db. It was shown to have high test specificity (above 90%) with a high sensitivity (80–100%).

5. There should be a suitable test for early stage disease

There are two non-invasive tests available (see Chapter 31, Hearing and balance):
- Automated otoacoustic emission (AOAE)
- Automated auditory brainstem response (AABR)
  These are both graded as either 'clear response' or 'no clear response'. Screening is

undertaken either prior to discharge from the postnatal ward, or at the primary health visitor birth visit (approximately 10 days of age).

6. The test should be acceptable to the target population

Screening is non-invasive and requires informed consent. There were initial concerns that screening could heighten anxiety among new mothers, but evaluation did not substantiate this. It is the parent's right to choose or decline screening for their child (autonomy) and so the mother's written consent is required in order to perform the screening test. Both written and video information about the screen is available. During evaluation in 2004, only 0.3% of parents declined to give consent. Any screening programme requires fairness in the distribution of benefits and equitable access. The initial evaluation showed high scale overall coverage, with 99.6% of mothers of new babies offered screening.

7. Intervals for repeat screening should be determined

Any subsequent testing needed should be completed by 5 weeks of age.

8. There should be adequate health service provision for the extra clinical workload resulting from the screen

All newborns are tested in the NHS by specially trained technicians.

9. The risks, both physical and psychological, should be outweighed by the benefit

This is a non-invasive test. The greatest risk is anxiety in the group of 'no clear response' awaiting repeat screen at 5 weeks. The majority of these cases are unilateral (i.e. one ear) and are 'false positives' due to fluid in the ear canal.

10. The costs should be balanced against benefits

See point 4 above.

Further reading

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Will Carroll, Simon Li, Ian Petransky

History and examination

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Understand the importance of history and examination in securing a diagnosis
- Know where and how history has its limitations
- Understand how the history usually gives important clues to diagnosis
- Know how elements of the history may be used to more effectively target your physical examination
- Understand the value of the clinical examination and the science that underpins some common physical signs

Introduction

The aim of this book as a whole is to provide an understanding of the science that underpins our practice. However, this needs to be set in context. If we were to limit our practice of medicine to what is known and understood, we would soon find it impossible to practise. Therefore, at the outset it is important to set this knowledge within a common framework. Each section of this chapter will start with discussing some of the 'art' of what is done: in history-taking and then examination. This, often considered 'good practice' or 'common sense', is central to best practice. It is reflected in guidelines. It is reflected in the day-to-day practice of paediatrics. It is even reflected within the RCPCH written examinations!

Nonetheless, there is also a huge amount of science that can be applied to history-taking and examination. Some of this will be discussed in the relevant system chapters that follow, but where more general points need to be made they will be discussed here.

The relative value of history, examination and investigation in reaching a diagnosis in children has been examined. Miall and Davies (1992) asked clinicians to propose a diagnosis for children referred to a paediatric outpatient clinic following the history, examination and after any investigations, if any were performed. The initial diagnoses were then compared to the final diagnosis. Following the history alone,

three-quarters of children were given a diagnosis consistent with the final diagnosis. Following examination, the correct diagnosis had been established in more than nine out of ten children. Investigations were requested in fewer than half the consultations, and in more than three-quarters of them the diagnosis remained unchanged. These findings underline the importance of history and examination in paediatric diagnosis and the relatively small contribution of investigations.

The value of history in specific paediatric conditions has also been addressed and is variable. The Dutch study of epilepsy in childhood conducted between 1988 and 1992 included 466 children with epilepsy. The final diagnosis was agreed by three independent paediatric neurologists. History alone was a specific (specificity 89%) but insensitive tool (sensitivity 29%) in establishing the eventual diagnosis.

The art of a good consultation: communication, communication, communication

Training in communication skills increases the diagnostic yield of the consultation. Most importantly, the

consultation itself fulfils a therapeutic need for many families. Parents are most satisfied when they are allowed to express their concerns and expectations early in consultations. Happier and better informed families have better health outcomes with fewer returns to hospital, shorter hospital stays and improved measures of disease control.

Qualitative studies, such as the Children's Voices project have identified that children as young as six years want more involvement in discussions about their illness and an opportunity to have a say about their treatment.

There are three elements of physician–parent–child communication:

- Informativeness
- Interpersonal sensitivity
- Partnership building

During the medical interview, two central issues must be addressed. Patients and parents should have cognitive (need to know and understand) and affective (serving the emotional need to feel known and understood) needs addressed.

Communication skills

These include:
- Introduce yourself to the patient and family
- Clarify understanding
- Establish a rapport
- Show empathy and respect
- Beware of verbal and non-verbal cues
- Speak clearly in plain language
- Discussion about diagnosis often leads to more information sharing

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Something is better than anything

Simple, small alterations to consultation style can have dramatic effects on the value of the consultation. It is widely known that inviting questions at the end of a consultation is helpful. However, there is a

significant decrease (78%) in the proportion of patients reporting unmet concerns at the end of the consultation (odds ratio 0.154, p = 0.001) if general practitioners use the phrase 'Is there something else you want to address in the visit today?' rather than the more commonly used 'Is there anything else you want to address in the visit today?'.

History-taking in children and young people

'Listen to the patient, he is telling you the diagnosis'
Sir William Osler, 1898

The type of history required depends very much upon context. Paediatricians are expected to work in a number of particular environments and the depth and detail required to be successful in a particular setting is a peculiar stress upon doctors new to that environment.

In general, undergraduate teaching stresses the importance of a broad and detailed approach and newly qualified doctors are then understandably confused when they are expected to 'cut corners' in clinical settings. Understanding the context in which you are working and the resources available (in terms of time) are important first steps in being successful. In general, the more acute the illness and the better defined the problem, the less time it should take to conduct a history (Table 3.1).

Sometimes, in very acute settings, little or no history is possible before treatment must begin. This abbreviated approach may also be necessary when time is very short. In general, it takes most skill to adopt the approach of a 'logical strategist'. In this situation, the presenting complaint will define a differential diagnosis that can direct the rest of the history down a narrower path. Subsequent clinical examination and investigation is likewise more focused and this leads to a reduction in the number of unnecessary procedures for the child and reduces the cost of investigations.

There is a good science base that underpins best practice when it comes to history-taking. Interviewing style determines the quantity and quality of information gleaned in a consultation. Whilst we all accept

Table 3.1 Settings for history taking

	Emergency	Acute	Chronic	Life-long
Settings	Emergency department	General paediatric	Outpatients	Community
Examples	Sprained wrist	Bronchiolitis	Recurrent wheeze	Global delay
Time and detail of history	Least (<5 minutes)	Moderate (5–10 minutes)	Thorough	Complete

that the consultation should be a two-way process, studies of clinical practice reveal that it is often dominated by the physician. A US study of general practitioners and internal medicine physicians found that patients spoke, uninterrupted, only for an average of 12 seconds after the doctor entered the room. A quarter of the time, doctors interrupted patients before they finished speaking. The time with patients averaged 11 minutes, with the patient speaking for only about 4 minutes.

Nonetheless, providing information about the eventual diagnosis, its aetiology, prognosis, and prevention is significantly associated with an increase in the amount of information gained overall. Judicious and careful discussion about a proposed diagnosis clearly acts as a useful prompt in clinical practice.

Question 3.1

Interviewing technique

A 17-year-old boy with recurrent headaches attends your clinic. Which interviewer factor has been shown to be MOST important in ensuring that the maximum amount of relevant information is elicited during consultation? Select ONE answer:

A. Clinical expertise
B. Gender
C. Higher ratio of time spent listening : talking
D. Seniority
E. Use of opportunity to provide information for patient

Answer 3.1

E. Use of opportunity to provide information for patient.

All of the factors listed will have an effect on the consultation. However, the evidence is that patient education is the most strongly associated with improving the quality and quantity of information gathered during consultations. In adult patients, an open questioning style, in general, leads to a higher proportion of important information being disclosed. Both open and closed questions lead to an increase in the information gained and a focused, narrow history is sometimes more appropriate in the paediatric setting. Physician seniority is only very weakly correlated with the acquisition of relevant medical facts.

Question 3.2

A child with diarrhoea

A 4-year-old child with diarrhoea has been referred to the paediatric outpatient clinic by their GP. From the following list, which is MOST likely to lead to a diagnosis. Select ONE answer only:

A. Coeliac screen
B. Examination
C. Growth chart
D. History
E. Urine analysis

Answer 3.2

D. History.

There is very little clinical detail, so one can only apply what is known about a general population of children. We know from Miall and Davies (1992) that following the history alone, 76% of children were given a diagnosis consistent with the final diagnosis. Following examination, the correct diagnosis had been established in 91% of children. Investigations were requested in 38% of consultations, but in 79% of cases the diagnosis remained unchanged.

The anatomy of a paediatric history

Whilst it is not essential to stick to a strict order during any given consultation, most paediatricians follow a fairly consistent pattern. This enables information about a history to be shared in an efficient manner as listeners expect a logical ordering of historical details. To the authors' knowledge, there is little or no evidence-base to support this approach and this distinctly remains part of the art of medicine. Nonetheless, it is helpful to break the consultation down into stages:

The introduction

There will be a variable amount of information available prior to seeing each patient. There may be a detailed previous history from a colleague and whenever possible it should be read before seeing the family. Depending upon the age of the child, it is usually helpful to establish how the child likes to be addressed and who any accompanying adults are. For older children and young people, it may be appropriate to conduct the consultation without a parent present.
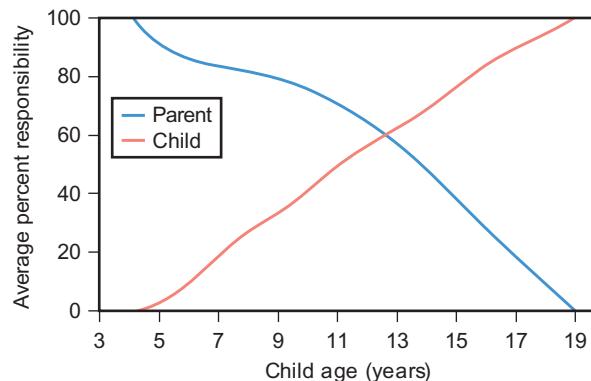
Fig. 3.1 **Change in responsibility for management of chronic illness with age.** *(Adapted from Orell-Valente JK, et al. At what age do children start taking daily asthma medicines on their own? Pediatrics 2008,122:e1186–e1192.)*

Fig. 3.2 **Colour chosen as best match for bile in a baby's vomit.** *(From Walker GM, Neilson A, Young D, Raine PAM. Colour of bile vomiting in intestinal obstruction in the newborn: questionnaire study. BMJ 2006 doi:10.1136/bmj.38859.614352.55.)*

Table 3.2 **Colour chosen as best match for bile**

Group	Green (%)	Yellow (%)
Parents	12 (29)	29 (71)
General practitioners	24 (51)	23 (49)
Special Care Baby Unit nurses	22 (76)	7 (24)
Postnatal midwives	33 (69)	15 (31)

There are no 'hard and fast' rules about when a young person becomes an adult in terms of responsibility for their health. However, there are some useful data from research. In general, the proportion of responsibility for healthcare issues increases as the child gets older. By 13 years of age, the responsibility for taking treatment and disease management in asthma is shared equally (Fig. 3.1). This provides a useful rule of thumb for how to share the consultation in clinical settings. In early childhood, it is necessary to use the parents for much of the consultation, but as the child gets older and increases in confidence, they can come to share and then own the consultation.

The presenting problem

Often this information is available, either as part of the triage information or as a referral letter. However, it is vital to ensure that all parties are in agreement about what the problems actually are. Once all the problems have been identified, it should be possible to start formulating a differential diagnosis and to hone down on the important details of the history.

General enquiry and systems review

These are highly age-dependent questions and should be driven whenever possible by a differential diagnosis. It is only possible to determine a sensitivity and specificity for these questions when they are placed in context and asked at the appropriate time.

For instance, nearly all vomiting is described as 'projectile' by parents. However, this is only a really useful historical clue when the diagnosis of pyloric stenosis is being sought. A 15-month-old child with projectile vomiting does not have pyloric stenosis so

eliciting this history and the distance travelled by vomitus from the child is not helpful outside of this context.

Other symptoms and signs are widely misreported either by parents or healthcare professionals. Whilst there are many possible examples, two of the best described in paediatric practice relate to the lack of specificity seen in the usage of highly informative medical terms. The first is the use of the word 'wheeze' by parents. In a landmark study published in 2000, exactly what parents meant by the term 'wheeze' was unpicked in detail. They found that parents used the term differently from doctors and frequently used it to describe difficulty breathing. When children were directly observed, parents and doctors agreed less than half the time about the presence of wheeze. This study has highlighted the dangers of assuming that families are using specific medical terminology correctly.

However, this phenomenon is not restricted to parents. For example, parents, GPs, SCBU nurses and postnatal midwives were asked to choose the colour of bile from the colour chart shown (Fig. 3.2, Table 3.2). The majority of parents and almost half of the GPs chose a yellow colour (shades 1–4). A quarter of the SCBU nurses and almost a third of the postnatal midwives also selected a yellow colour, whereas the correct answer was a green colour (any shade 5–8).

Past medical history

The past medical history is an important diagnostic clue. However, the relevance of early details, such

as birth history, may become less relevant with time. Nonetheless, it is nearly always important to ask about major events such as birth details, immunizations and past illnesses or hospital admissions. The drug and allergy history often acts as a prompt for 'forgotten' details of previous illnesses. List the child's current medications accurately, including dosage and frequency, and (if possible) when they were commenced.

This is also a useful point at which to ask about developmental status. This is covered in more detail in Chapters 4 and 5. Parents may have brought along the parent-held child record to the interview. This contains details and plots of previous weights and lengths/heights that will allow assessment of the child's physical growth and details of the immunization status. For older children and teenagers, it is important to ask about the onset of puberty (see also Chapter 12, Growth and puberty).

Previous medical history is not always a reliable guide. Whilst previous behaviour is widely purported to be a reasonable guide to future behaviour, this does not always stand up to scrutiny. For instance, in examining paediatric asthma deaths in the eastern region of the UK between 2001 and 2006, only 1 out of 20 children who died had previously been admitted to the paediatric intensive care unit and 40% had never been admitted to hospital previously.

Family and social history

Families will share genetic factors, environmental factors and inevitably many infections. It is therefore vital to take a family history and have an appreciation of some of the recurrence risks of commoner diseases like asthma, diabetes and coeliac disease.

It is usually helpful to record family structure and draw a genetic family tree, including parents, siblings and sometimes grandparents. It is vital to sensitively elicit whether parents are related as this will increase the risk of certain conditions (for more details and some examples of pedigrees, see Chapter 9, Genetics).

Ask about who makes up the household. Details about the size and type of accommodation may be helpful. Occupation of the parents and whether they smoke are covered in this section. Major or psychiatric illness affecting parents can be clarified at this stage. It is worth asking whether there are any financial problems and what benefits the family are currently receiving. It may be relevant to know if the family has any pets. Further details about the child's school, school work and school friends, as well as any problems at school such as bullying or teasing, can also be checked out at this stage.

Examining children

With increasing experience, the correct diagnosis is reached more swiftly by ensuring that both history and examination are goal-orientated and focused. This is particularly helpful with infants and young children, who often have limited patience for doctors, and with adolescents with limited enthusiasm for the entire process.

With adult patients, the length of time a consultation takes is not associated with patient satisfaction. However, patients who are more satisfied *think* that the consultation has lasted longer. The aim should be to use one's experience to become as efficient as possible in using the time available. Patients, and in particular parents, are often highly dissatisfied if an opinion is reached without an examination of the child. In a Dutch study published in 2003, all but 3 of 146 parents presenting with a febrile child expected the doctor to perform a physical examination. Even when examination is likely to add little to the consultation, it remains part of the art of medicine. When examining children, there is science that underpins both normal and abnormal physical signs. An accurate appreciation of the range of normal is also required.

'The first step forward is a step backwards'

It is advisable not to rush into the physical examination of children. Taking a breath, and a step backwards can help remind oneself that a significant amount of information is gained simply by careful observation. Although having a clear technique is useful so that no part of the examination is inadvertently omitted, the order in which it is performed needs to be flexible. Many of the important examination findings can be determined from careful observation whilst the child is playing or sat on the parent's lap whilst one is taking the history. However, with suitable distraction techniques and rapid use of brief opportunities, it is almost always possible to examine infants and young children even if the situation is not ideal.

Based on the history, the relevant aspects of the examination can be targeted and performed rapidly rather than trying to do a complete and thorough physical examination, which will often be thwarted by young children. There are some elements of the clinical examination that are known to be more and others less reliable, e.g. in determining whether a child has congenital heart disease, it has been shown that even amongst experienced examiners, most agree on the presence or absence of digital clubbing but other signs are less reliably determined.

For many observable characteristics, there is a range of normality which exists. This includes simple physiological variables like heart rate and respiratory rate (see below) and more complex characteristics including development. A detailed description of the techniques used to assess development is included in Chapters 4 and 5 and will not be discussed further here.

Rather than discouraging us from undertaking clinical examination, we need to acknowledge its limitations, even in experienced hands. Where technology can assist, especially if non-invasive such as oxygen saturation measurements or ultrasound, we should embrace its use but need to understand the underlying physiology and its limitations. Oxygen saturation monitoring is a particularly good example of how technology can enhance the sensitivity of the clinical exam. By combining pulse oximetry with clinical examination, the sensitivity of screening for congenital heart disease in newborns has been shown to increase from 31% for oximetry alone and 46% for clinical examination alone to 77% using both.

Pulse oximetry

Fig. 3.3 Relative absorbance of red and infrared light by oxygenated and deoxygenated haemoglobin.

Question 3.3

Concerning pulse oximetry

The following will lead to inaccurate measurement of arterial oxygenation using pulse oximetry, true (T) or false (F):

A. A slow heart rate
B. A weak pulse
C. Dim external lighting
D. Swollen peripheries
E. The presence of carboxyhaemoglobin

Answer 3.3

A. False; B. True; C. False; D. True; E. True.

Pulse oximetry is now regarded as one of the most useful elements of the physical examination in children. It forms part of our early warning scores and rightly has a significant role in detecting physiological disturbances. Its discovery was, like many scientific breakthroughs, a chance one. Indeed, the scientists who first developed the technology (Aoyagi and colleagues) were initially attempting to determine cardiac output non-invasively, but their attempts were hampered by the presence of an interfering pulsatile waveform when using a red light source. Although the initial technology was developed in the 1970s, it was not until the 1980s that pulse oximetry entered routine clinical practice.

Oxygen saturation monitors all work using the same principles. These involve the differential absorption of infrared (950-nm wavelength) and red light (650-nm wavelength) of oxygenated and deoxygenated haemoglobin (Fig. 3.3).

Deoxygenated haemoglobin absorbs much more red light and less infrared light. A pulse oximeter works by varying the light source in a pulsatile manner and measuring the transmitted amount of light. This allows small variations in light absorption to be detected. Of course, in any body part (e.g. a finger or ear lobe), arterial blood is not the only thing that will absorb light. However, arterial blood is the only substance that fluctuates significantly and therefore pulse oximeters rely on this 'changing absorbance' to calculate the arterial oxygen saturation. The pulsatile signal is very small though; typically only about 2% of the total signal is pulsatile.

Anything that dampens or disrupts the signal from the arterial blood can lead to an inaccurate reading. Therefore, swollen peripheries, external light sources, electromagnetic signals (diathermy) or movement artefact all will reduce the stability of any signal and the accuracy of any measurement. Poor peripheral perfusion will diminish the arterial supply and lower the proportion of the pulsatile signal. These effects combine to ensure that oxygen saturation monitoring can be difficult in a small, seriously ill child.

Abnormal haemoglobin can affect pulse oximeter readings. Carbon monoxide combines with haemoglobin to form carboxyhaemoglobin. Most pulse oximeters cannot separately detect this and consider carboxyhaemoglobin as normally oxygenated haemoglobin. Thus, following carbon monoxide poisoning, oxygen saturations will appear falsely high. Methaemoglobin, causes the saturation to falsely show readings towards about 85%.

The upside-down and outside-in approach

Of course, it is not possible to conduct a complete physical examination from a distance. Children (and adults) have higher levels of acceptance of physical contact when certain 'rules' are obeyed. The first is that permission is sought, either verbally or non-verbally. Children and parents expect to see that the person conducting the exam has demonstrated that they have performed hand-hygiene either with soap and water or alcohol rub. The physical examination is less daunting and often better tolerated if you adopt the following principles: firstly, that the examiner is level or lower than the child and, secondly, that examination of non-painful areas and peripheries are better tolerated than central areas. Depending on the age of the child, examination of the areas *most* covered by clothing (i.e. breasts, genitals) is most difficult and should be attempted last and only when a degree of trust has been established. Thus, starting at the toes and working upwards and centrally (upside-down and outside-in) is particularly helpful in younger or anxious children.

Determining 'normality' in physical signs

Vital signs

There are many reasons why appreciating the range of normality is important. It is perhaps surprising that a strict approach has only very recently been adopted in identifying what represents normal for the majority of physical signs in children. Historically, normal ranges have been constructed from either small observational studies or expert opinion. One of the key drivers for this research has been the widespread implementation of rapid response systems (RRSs) or paediatric early warning scores (PEWS) over the past decade. This has called attention to the lack of high quality evidence for the reference ranges quoted and led to larger and better controlled studies.

There are two large studies that have given reliable and accurate reference ranges. The first was published in 2012 and describes a meta-analysis of all observational studies of healthy children. The second was a retrospective analysis of hospitalized children in a large paediatric centre in the US and was published in 2013. Unsurprisingly, these give different reference ranges, with ill children having higher heart rates and respiratory rates. It is debatable whether measurements of unwell children can legitimately be described as normal. However, they may be more useful than reference ranges for healthy children in determining cut-off values for early warning score systems, as they do refer

to *all* children seen in hospital settings and therefore allow a sense of 'how abnormal is this measurement?' in the context of a hospitalized child (Figs 3.4, 3.5).

Capillary refill time

Capillary refill time (CRT) is defined as the time taken for colour to return to an external capillary bed after pressure is applied to cause blanching. The physiological principles which determine CRT are complex.

Capillary blood flow is affected by the blood pressure, arteriolar tone and the constituents of the blood. Arteriolar tone depends on the balance between vasoconstrictive (noradrenaline, angiotensin II, vasopressin, endothelin I and thromboxane A) and vasodilatory influences (prostacyclin, nitric oxide and products of local metabolism such as adenosine). The constituents of blood can also impact on capillary blood flow. For example, the size of red blood cells
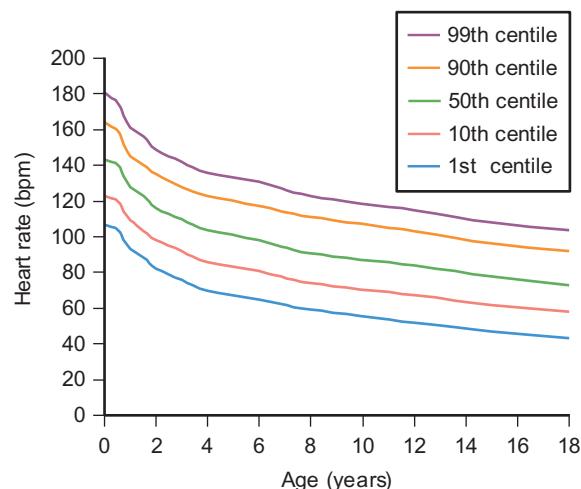
Fig. 3.4 Suggested heart rate cut point based on average predicted values of healthy children.
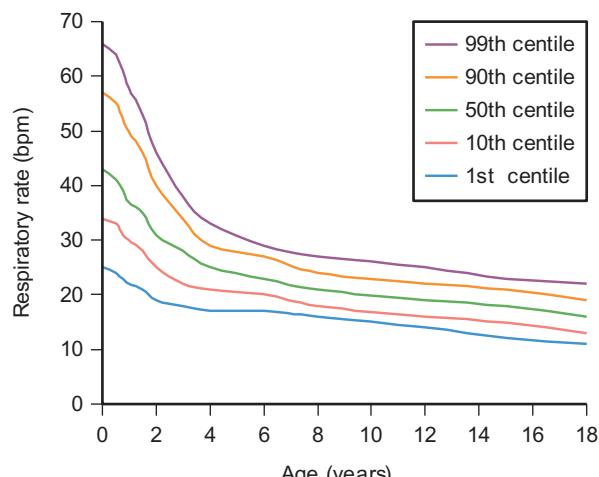
Fig. 3.5 Suggested respiratory rate cut points based on average predicted values of healthy children.

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and plasma viscosity affects flow through narrow capillaries. The other main determinant of capillary perfusion is capillary patency, which is reflected by the functional capillary density or the number of capillaries in a given area, which are filled with flowing red blood cells.

Vasoconstriction is considered an early compensatory mechanism in shock which should reduce distal capillary bed perfusion. It is hypothesized that alterations in capillary bed perfusion will affect the measurement of CRT by altering the time for the external capillaries to become refilled with blood. A prolonged CRT should, therefore, act as an early indicator of shock.

Despite its widespread use in paediatric settings and its adoption into many treatment protocols, there is a great deal of variation in how CRT is performed and its limitations have been somewhat overlooked. It has long been recognized that longer pressing times and lower ambient temperatures will extend the CRT. However, a recent systematic review of the literature (2014) revealed that some common beliefs about CRT are, in fact, incorrect. The best evidence suggests that in children over a week of age the upper limit of normal is approximately 2 seconds when measured on a finger but is considerably longer (4 seconds) when measured on the chest or foot. This belies the commonly held belief that CRT tends to be longer peripherally and shorter centrally (i.e. on the trunk).

Blood pressure

This is considered in detail in Chapter 19, Nephrology.

Fever

Fever is a common reason for medical consultation, perhaps accounting for up to one-third of childhood presentations to health professionals. Indeed, there is much 'fever phobia' amongst parents and health professionals, with antipyretic medications such as paracetamol and ibuprofen being administered to lower their child's temperature as a result of misconceptions rather than for physiological benefit. This is despite a wealth of evidence suggesting that attempts at controlling fever are either futile (for instance, provision of regular antipyretics does not reduce the risk of febrile convulsion) or potentially deleterious (reduction in the immune response to immunization if paracetamol is given routinely following vaccination).

The body's temperature is controlled by the thermoregulatory centre of the hypothalamus by balancing heat production, as a result of metabolic process, against heat loss, via the skin and lungs. Normal body temperature varies with age, with infants and young children generally having a higher body temperature as a result of their greater surface area to body weight ratio and higher metabolic rate. Body temperature also varies with the time of day, with a morning nadir and early evening peak considered normal, and with levels of activity.

Fever is a *normal* physiological process that begins with the synthesis and release of interleukin-1, interleukin-6, tumour necrosis factor, interferon-alpha and other endogenous cytokines by phagocytic cells. These cytokines are then delivered via the bloodstream to the anterior hypothalamus where they stimulate production of prostaglandins, especially prostaglandin E2 (PGE2). PGE2, in turn, raises the set-point of the body's temperature and the body responds to this with a combination of heat preservation (reduced peripheral perfusion) and heat generation measures (shivering).

Fever is not the same as hyperthermia. Hyperthermia is an increase in the body's temperature despite the regulatory thermostat set normally. Thus, individuals with hyperthermia do not exhibit the heat preservation or generation measures associated with fever. This homeostatic failure results in heat production that exceeds the body's own capability of dissipating heat. It carries a significant risk of morbidity and mortality and its characteristics include hot, dry skin, dysfunction of the central nervous system leading to delirium, convulsions and coma.

There appear to be limits on the temperature that the body will attempt to generate in fever that are not seen in hyperthermia. In fever, the body's temperature rises until the new set-point is reached, with the upper limit of temperature as a result of fever being 42°C. Cytokines drive the synthesis of acute phase proteins by the liver, whilst IL-1 is responsible for inducing slow wave sleep, which may explain the sleepiness of febrile children.

Generally speaking, the induction of fever as a result of infection has numerous benefits. It impairs the growth of bacteria and viruses, which may be related to cytokine-mediated reductions in iron and zinc levels. Immunological function is also enhanced at moderately elevated temperatures with increased neutrophil and T-cell lymphocyte production. In spite of this, fever does cause children to be uncomfortable. In addition, it has knock-on physiological effects in terms of increased heart rate, oxygen consumption and carbon dioxide production, which may be deleterious in children whose cardiovascular and respiratory systems are impaired, such as those children with shock.

The value of fever in clinical assessment

Despite its fascination and phobia amongst parents and health professionals, its value as an independent variable in the clinical assessment of a child is

somewhat lacking. There is a weak association between the height of fever and the severity of infection. One study of 683 infants aged between 4 and 8 weeks showed the rate of serious bacterial infection proportionately increased with the height of fever (3.2% in those with fevers 38.1–38.9°C vs 5.2% in those with fevers greater than 39°C vs 26% in those with fever ≥40°C). However, the majority of children with fever will have a presumed non-focal viral infection. Neither is there very strong evidence for the use of fever duration in the prediction of serious bacterial illness.

There has also been some work looking at interpreting response of fever to antipyretic agents and whether this has any value in identifying serious illness. A number of studies have also tested the hypothesis that fever of benign aetiology responds better to antipyretic agents compared with fever due to a serious bacterial illness. Although the evidence is somewhat conflicting, the majority of the published evidence would seem to suggest that we cannot rely on the response to antipyretics to predict serious illness. Thus, the age old adage still stands, there is no single variable which helps in the assessment of the sick child, but the integration of a number of variables, such as temperature, together with the overall clinical picture.

A system-based approach to examination in children

The history may suggest that a particular organ system or area should be examined as a matter of priority. A child referred for a second opinion with a heart murmur clearly will need careful auscultation of the heart and it is often best to undertake this before the child becomes bored and fractious. There are many detailed books that describe how to undertake a professional and polished clinical examination. These can be very helpful when preparing for clinical examinations. It is not our aim to replicate these here; however, some brief details of what should be examined in each system is described to explain some of the science that underpins the physical signs that are not considered elsewhere in this book. Overall examination of any child should include an assessment of their growth and nutrition, and take note of the presence of any dysmorphic features.

Respiratory system

The key elements of examination of the respiratory system are shown in Box 3.1.

Clubbing

This is caused by thickening of tissues at the base of the nail resulting in obliteration of the angle between the

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Box 3.1 The key elements of respiratory examination

1. Hands – look for digital clubbing.
2. Count the respiratory rate, if possible without undressing or disturbing the child.
3. Check the face, mouth and eyes for pallor and central or peripheral (lips) cyanosis.
4. If the child is old enough, ask them to make a big 'cough' and a big 'huff'.
5. Inspection – look at the chest for signs of hyperexpansion (increased anteroposterior diameter), Harrison's sulcus, kyphosis or scoliosis.
6. Palpate – for lymphadenopathy in the neck, the centrality of the trachea, the position of the cardiac apex beat and chest expansion.
7. Percuss – systematically. It often provides helpful clinical information and is a good way of detecting consolidation of the lung and/or the accumulation of pleural fluid.
8. Auscultate in the same regions you percussed, taking note of the breath sounds and any adventitious sounds. In the older child, consider performing vocal fremitus, asking the patient to say '99' in the same regions you have just auscultated.

The order in which this exam is conducted is not vital, but try to keep any painful elements to the end. In a child with pleurisy, coughing and chest expansion may be painful.

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nail base and adjacent skin of the finger. It does not commonly occur until a child is at least 6 months of age and is seen first and is most pronounced in the thumb. Whilst the causes of clubbing are well rehearsed (Table 3.3) by all undergraduate medical students, the underlying cause of clubbing is unknown, although several theories exist. It is clear that clubbing evolves gradually and four distinct stages are recognized. It can (and does) occur acutely in response to severe respiratory infection. Indeed, it was first described by Hippocrates in patients with empyema.

The clinical grading of clubbing is as follows:

- Softening of nail bed
- Obliteration of the angle of the nail bed
- Parrot beak or drumstick appearance
- Hypertrophic pulmonary osteo-arthropathy

Shamroth's sign: Normally a diamond-shaped space is formed when the two thumbs of the child are kept opposed on their dorsal aspect. In clubbing, this shape is obliterated.

Proposed scientific explanations for clubbing

It is possible that there is more than one mechanism by which clubbing occurs and this, in turn, has

Table 3.3 Causes of clubbing

Cardiovascular:	Gastrointestinal:
Congenital cyanotic heart disease	Inflammatory bowel disease
Subacute infective endocarditis	Coeliac disease
	Biliary cirrhosis
Respiratory:	**Miscellaneous:**
Bronchiectasis	Congenital
Lung abscess	Atrial myxoma
Empyema	Thalassaemia
Cystic fibrosis	Hyperthyroidism
Pulmonary fibrosis	
Pulmonary haemosiderosis	

frustrated scientific attempts to provide a neat explanation for the characteristic nail bed changes and the alterations seen in the curvature of the nail.

Many studies have shown that there is an increase of blood flow to the clubbed portion of the finger and most researchers agree that this is the result of distal digital vasodilation. Observation of clubbing in cyanotic congenital heart disease suggests that clubbing is the result of a vasoactive substance that is filtered or removed by the lung. Thus, right to left shunting of blood results in clubbing as this filter is removed. Moreover, children with significant untreated ductus arteriosus and pulmonary hypertension can get isolated clubbing of the toes. Here, blood reaching the hands has passed through the lungs and is oxygenated (and therefore does not result in clubbing), whilst the blood reaching the toes is a combination of blood that has passed through the lung and deoxygenated blood passing from the pulmonary artery through the ductus arteriosus to the descending aorta that has bypassed the lung entirely. This results in differential oxygen saturations and differential clubbing.

Hypoxia itself has been proposed as an alternate explanation for clubbing. Distal tissue hypoxia may result in the production of local vasodilators and this, in turn, might result in clubbing. However, there are many diseases associated with clubbing that do not apparently result in hypoxia or altered pulmonary blood flow, so these explanations are, at best, partial explanations.

Recent research shows that when megakaryocytes (platelet precursors) fail to become fragmented into platelets within the pulmonary circulation, they are easily trapped in the peripheral vasculature of the nail beds, releasing platelet-derived growth factor and vascular endothelial growth factor, promoters of vascularity and, ultimately, clubbing.

Cyanosis

Cyanosis results from an increased concentration of deoxygenated (reduced) haemoglobin. Whilst classical teaching is that central cyanosis is visible only when there is >50 g/L of deoxygenated haemoglobin, more recent evidence suggests that only 20 g/L is required. When haemoglobin levels are within the normal range, this equates to oxygen saturation of approximately 85%. However, in profound anaemia, hypoxaemic children will simply appear pale or grey (see below). Cyanosis associated with desaturation of arterial blood is central cyanosis and cyanosis with normal arterial oxygen saturation is peripheral cyanosis.

In neonates, polycythemia (haematocrit of >65%) results in cyanosis in the presence of normal levels of blood oxygenation. This is particularly evident in the hands and feet and is termed acrocyanosis (also seen in normal infants in the first day of life). This is a form of peripheral cyanosis that reflects sluggish blood flow in the fingers. Circumoral cyanosis is bluish skin around the mouth, which is a form of peripheral cyanosis seen in fair-skinned children due to sluggish capillary blood flow associated with vasoconstriction.

Question 3.4

The relationship between cyanosis and oxygen saturation

A 4-year-old child with iron deficiency anaemia is admitted to the children's ward. You are asked to review her and she appears cyanosed. If her haemoglobin is 80 g/L, what is her likely *maximum* oxygen saturation?

Select ONE correct answer from the list of options:

A. 95%

B. 85%

C. 75%

D. 65%

E. 50%

Answer 3.4

C. 75%.

We know that 20 g/L of deoxygenated blood is required to produce visible cyanosis. If a child is anaemic then cyanosis only becomes apparent at relatively lower oxygen saturation. Therefore to appear cyanosed a child with a haemoglobin of 80 g/L would have 20 g/L of deoxygenated and 60 g/L of oxygenated haemoglobin. The oxygen saturation is likely to be closest to 60/80 × 100 = 75%.

The physiological basis of other respiratory signs including cough, stridor and wheeze are discussed in Chapter 17, Respiratory medicine.

Cardiovascular system (Box 3.2)

Abnormal heart sounds and murmurs

In order to interpret heart sounds, one needs to understand the temporal interrelation of the ECG, ventricular volume changes as well as the venous, atrial, ventricular and arterial pressures during the cardiac cycle.

As sound is a form of energy, generation of the heart sounds or a murmur requires the transformation of kinetic energy, either from blood or cardiac tissues, into sound energy. States which increase the kinetic energy transformed will tend to increase the audibility of the sounds or murmurs. The sounds of the beating heart as heard with a stethoscope are due to reverberations in the blood caused by the closures of the heart valves. There are normally two sounds in rapid succession, followed by a pause, which is twice as long as the time between the two sounds, and then the cycle repeats. The first sound – the louder of the two – is due to closure of the atrioventricular valves (mitral and tricuspid) immediately after the beginning of ventricular systole. The second, shorter sound is due to the closure of the semilunar valves (aortic and pulmonary) as ventricular systole comes to an end. Changes in pulmonary or aortic pressures tend to increase the kinetic energy transformed (think of a door being slammed rather than someone gently closing it) and therefore may augment a particular element of the second heart sound.

Heart murmurs are generated by turbulent blood flow either through diseased valves or extra-valvar connections between the chambers of the heart. Turbulence occurs when there is deviation from laminar flow. This can happen for many reasons. In general terms, it requires the flow of blood across a resistance. As blood will only flow along a pressure gradient, murmurs occur when there is flow of blood from a high to low pressure system across a resistance.

Whilst echocardiography is often necessary to formally reach a diagnosis, pathological murmurs have predictable and relatively consistent findings. The more common patterns seen are summarized in Table 3.4. The murmurs or clicks from the various heart valves are best appreciated when the stethoscope is placed as close as possible to the valve concerned. In children, the distances between these surface markings are small and it is difficult to be certain where a particular click or murmur is loudest; however, understanding the exact position of the heart in the thorax is helpful (Fig. 3.6). In most instances, ejection systolic murmurs are loudest in the upper thorax (above the level of the nipples) and pansystolic murmurs are loudest in the lower thorax (below the level of the nipples). The exception is tetralogy of Fallot, where

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Box 3.2 The key elements of cardiovascular examination

1. Hands – look for digital clubbing and peripheral cyanosis.
2. Pre and post ductal oxygen saturation measurements.
3. Blood pressure – if necessary in four limbs.
4. Check the face, mouth and eyes for pallor, central or peripheral cyanosis, malar flush, dental caries.
5. Palpate peripheral pulses and check for radio-femoral delay.
6. Inspect praecordium for scars, visible pulsations, masses such as those of pacemakers or portacaths.
7. Palpate – for the apex beat, heaves and thrills.
8. Auscultate for the normal heart sounds, added sounds and murmurs, determining the grade, location, radiation.
9. Listen for radiation of the murmur at the back (coarctation) and neck (aortic stenosis).
10. Check the abdomen for hepatomegaly or ascites.

Table 3.4 Pathological murmurs

Murmur	Location	Pathology
Ejection systolic	Upper right sternal edge (carotid thrill)	Aortic stenosis
	Upper left sternal edge (no carotid thrill)	Pulmonary stenosis or ASD
	Mid/lower left sternal edge	Innocent murmur
	Long, harsh, systolic murmur + cyanosis	Tetralogy of Fallot
Pansystolic	Lower left sternal edge (+/− thrill)	VSD
	Apex	Mitral regurgitation
	Lower left sternal edge (+/− cyanosis)	Tricuspid regurgitation
Continuous	Left infraclavicular (+/− collapsing pulse)	PDA
	Infraclavicular (+ cyanosis + lateral thoracotomy)	Blalock–Taussig shunt
	Any site (lungs, shoulder, head)	Arteriovenous fistula
Diastolic murmurs	Left sternal edge (+/− carotid thrill or VSD)	Aortic regurgitation
	Median sternotomy (+/− PS murmur)	Repaired tetralogy of Fallot
	Apical (+/− VSD)	Mitral flow

ASD, atrial septal defect; PDA, patent ductus arteriosus; PS, pulmonary stenosis; VSD, ventricular septal defect.
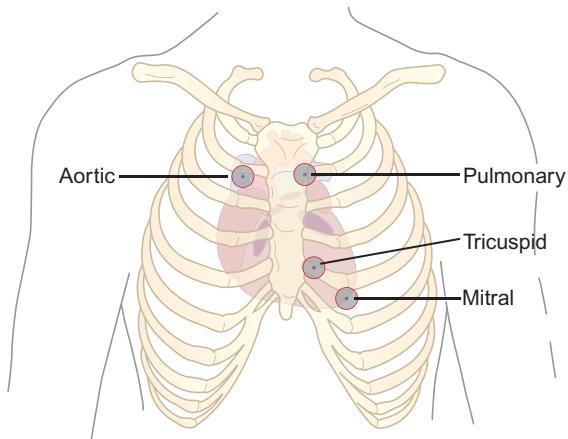
Fig. 3.6 Surface anatomy of auscultation points for the four heart valves. Although the lower left sternal edge is where tricuspid regurgitation is heard maximally, a ventricular septal defect must be considered if a murmur is heard here (see Table 3.4). *(From Levene M. MRCPCH Mastercourse. Elsevier Churchill Livingstone; 2007.)*

the murmur, whilst ejection systolic, is often best appreciated at the level of the nipples. It is lower than expected as the murmur is the result of flow across the subvalvular right ventricular outflow tract.

Innocent heart murmurs

Also called functional murmurs, these arise from cardiovascular structures in the absence of anatomic abnormalities. They can be heard at some point in up to 80% of normal children and are often heard at times of increased cardiac output, such as febrile illnesses or anaemic states.

There are approximately six benign murmurs – five systolic murmurs and one continuous murmur. The five systolic murmurs are:

- *Still's (vibratory) murmur*: the most common innocent murmur in children, unknown cause, but possibly due to turbulent blood flow in the left or right ventricular outflow tract, or vibrations through the pulmonary valve leaflets. Most commonly detected between 3–6 years of age and rarely in infants. Generally low frequency, it has a vibratory quality, mid-systolic grade 2–3/6 heard maximally in mid-left sternal border, and its intensity increases in the supine position and may disappear with Valsalva manoeuvre.
- *Pulmonary flow murmur*: often heard in children between 8 and 14 years of age but is most frequent in adolescents. Represents an exaggeration of normal ejection vibrations within the pulmonary trunk. Grade 2–3/6 harsh, non-vibratory, ejection systolic murmur, heard at the upper left sternal border. Intensity increases when in the supine position.

- *Pulmonary flow murmur of newborns/peripheral pulmonary arterial stenosis murmur*: often present in newborns and disappears by approximately 6 months of age. It represents turbulent flow through a narrowed left or right pulmonary artery. In the fetus, the main pulmonary artery trunk is large but the branches of the pulmonary arteries are relatively hypoplastic because they receive only a small amount of blood flow during fetal life. When the ductus closes after birth, the main pulmonary artery trunk gives off two small branch pulmonary arteries. The flow through these small vessels produces turbulence when there is a faster flow velocity and this is transmitted along the smaller branches of the pulmonary arteries so the murmur can be heard around the chest wall. In general, it is a grade 1–2, low to medium pitched, early to mid-systolic murmur, which can extend past the second heart sound. It is heard best in the back and axilla, and louder in the supine position. It is not, strictly speaking, an innocent murmur – all these children should be followed up with repeat clinical examination. If it persists then echocardiography and cardiology referral may be required.
- *Supraclavicular or carotid bruit*: may present at any age, represents turbulent blood flow through a large diameter aorta into a smaller carotid or brachiocephalic artery. Early systolic murmur, grade 2–3/6, best heard in the supraclavicular fossa or over the carotid arteries.
- *Aortic flow murmur*: secondary to various high output physiological states, such as anaemia, hyperthyroidism, and fever, which cause turbulent flow through the ventricular outflow tract and aorta. A low-grade, non-harsh systolic murmur that is heard best in the aortic auscultation area.

The one continuous murmur is as follows:

- *Venous hum*: commonly audible in children between 3–6 years of age. Originates from turbulent flow through slightly angulated internal jugular veins, or through the superior vena cava at the junction of the internal jugular and subclavian veins. It is a continuous murmur that is more intense in diastole, and is heard best in the supra- and infraclavicular areas. Heard only in the upright position and disappears in the supine position. It may be obliterated by rotating the head or by gently occluding the neck veins.

Features of innocent murmurs can be remembered as five S's: Inno*S*ent murmur = *S*oft, *S*ystolic, a*S*ymptomatic, left *S*ternal edge (summarized in Table 3.5).

Table 3.5 Features of innocent and pathological murmurs

Innocent	Pathological
Asymptomatic patient	Symptomatic
Normal heart sounds	Abnormal heart sounds
No added sounds	Added sounds/clicks
No diastolic component	Diastolic murmur
Localized to left sternal edge with no radiation	Radiates
No heaves/thrills	Heaves or thrills
Intensity Grade 3 or less	Abnormally strong/weak pulses
Musical or vibratory	Cyanosis
Intensity changes with posture	

In the majority of cases, it is evident after clinical examination whether or not the murmur is highly likely to be innocent. In practice, the majority of paediatricians will request an ECG and a CXR in order to be reassured, but normal investigations will not rule out congenital heart disease and the gold standard for assessment is an echocardiogram.

The doctor must communicate effectively with the parents of children who present with innocent murmurs, offering reassurance that it is a normal finding and that no restrictions on the child are warranted.

Many newborn infants with potential shunts will have neither symptoms nor a murmur at birth, due to the pulmonary vascular resistance still being high. Some conditions, e.g. ventricular septal defect (VSD) or patent ductus arteriosus (PDA), may only become apparent at several weeks of age when the pulmonary vascular resistance falls.

Jugular venous pulse

The pressure in the right atrium (the central venous pressure) is normally around 5 mmHg, the equivalent of a column of blood 7 cm high. The internal jugular vein connects to the right atrium without any intervening valves and so acts as a reflection of the right atrial pressures. When sitting at an angle of 45 degrees, the upper end of the distended part of the internal jugular vein should be visible above the clavicle and shows a slight pulsation. Causes of a raised jugular venous pulse (JVP) are fluid overload, heart failure, constrictive pericarditis, cardiac tamponade or superior vena caval obstruction.

Gastrointestinal system

The key elements of gastrointestinal examination are shown in Box 3.3.

Jaundice

Jaundice refers to the yellow appearance of sclera and mucous membranes and the skin when there is an

Box 3.3 The key elements of gastrointestinal examination

1. Hands – look for clubbing, nail changes (leukonychia, koilonychia) and palmar erythema.
2. Face, mouth and eyes – pallor, jaundice, mouth ulcers and oral pigmentation.
3. Inspect carefully for spider naevi – more than three in the area drained by the superior vena cava is abnormal.
4. Inspection – look at the abdomen for scars, distension, masses, striae, prominent abdominal veins and ostia such as gastrostomy, ileostomy and colostomy.
5. Palpate (and percuss) gently and carefully to identify: liver, spleen and either kidney.
6. If the abdomen is distended, percuss for ascites by starting at the umbilicus and percussing away from you. If a change in percussion note is heard, ask the child to roll towards you whilst keeping your fingers at the position dullness was heard. After waiting 30 seconds percuss back towards yourself until dullness to percussion is heard.
7. Auscultate over the abdomen, listen for the presence of bowel sounds and over both kidneys for bruit.
8. Perianal inspection may provide evidence of Crohn's and other diseases; rectal examination is rarely indicated in children.

increase in the concentration of bilirubin within the body (usually only detectable clinically when plasma bilirubin exceeds 50 mmol/L). It is discussed in detail in Chapter 11, Neonatal medicine and in Chapter 21, Hepatology.

Hepatomegaly

Hepatomegaly is a relatively common finding in children with cardiac failure and liver disease, which is described in Chapter 21, Hepatology. When examining for the liver, though, it is helpful to distinguish between times when a liver edge is felt because the liver is enlarged and when the liver edge is felt because the liver has been displaced downwards following overexpansion of the chest.

Splenomegaly

The spleen normally lies in the upper portion of the left abdomen. It is mostly covered (and therefore protected) by the lower portion of the rib cage. Nonetheless, it is common to be able to palpate a portion of the spleen in normal young children. One third of newborns and up to 10% of children will have a spleen palpable. One in 30 healthy young adults will

still have the tip of a spleen palpable on careful examination.

The spleen is the largest lymphoid organ in the body and, along with the lymph nodes, forms the mononuclear phagocytic system (MPS). The spleen consists of white and red pulp lying within a capsule. Blood enters the spleen through the splenic artery and from there passes via arterioles to the white pulp. The white pulp is rich in lymphocytes and macrophages which undertake the important process of antigen processing and presentation enabling an efficient immune response. Blood continues into the red pulp, the sinuses and cords. The red pulp forms most of the spleen. To exit, blood must pass through 1–5 µm fenestrations in the basement membrane of the splenic cords passing into the venous sinusoids. The circulation through the cords is slow, enabling prolonged exposure of blood cells, bacteria and particulate matter to the dense mononuclear phagocytic cells in the red pulp. From the venous sinusoids, blood empties into the splenic vein, which joins the superior mesenteric vein to the hepatic portal vein. There are no valves in the splenic venous system and pressure in the splenic veins is determined by pressure in the hepatic portal vein.

There are many potential causes of splenic enlargement (Table 3.6). It is helpful to think of four major categories:

- The most common mechanism in children is hyperplasia of the MPS, either as a result of infection (stimulation), disordered immune response (autoimmune conditions) or excessive destruction of red blood cells (haemolysis of any cause). Splenomegaly can also be a sign of

malignancy. Half of children with acute lymphoblastic leukaemia will have splenomegaly and it is a frequent finding in all childhood lymphomas and leukaemias.

- The spleen is an important site of haematopoiesis in the first 6 months of life. Therefore, any condition that places an intense demand upon the bone marrow for red cell production (e.g. thalassaemia major, spherocytosis) can also result in splenic enlargement.
- There may be obstructed venous blood flow from liver disease. The lack of valves in the splenic vein means that it is prone to enlargement if there is obstruction at any point in the portal venous system.
- Less commonly, many storage disorders result in splenomegaly, as there is accumulation of abnormal lipids in the splenic macrophages.

Ascites

Ascites is the excessive accumulation of fluid in the abdominal cavity. In adults, 1.5 L needs to accumulate before it can be reliably clinically detected, but in children this volume can be much smaller. A small amount of extraperitoneal fluid is a frequent finding on ultrasound scanning of the acute abdomen. The tendency for fluid to accumulate in the peritoneal space is governed by Starling's law of the capillary. This states that the tendency of fluid to leave the capillaries depends on three factors:

- Hydrostatic pressure: pressure within the vessel
- Oncotic pressure: concentration of large proteins within the plasma
- Vessel permeability, which is dependent on the type of vessel and cytokines, for example, with inflammation

Ascites in liver cirrhosis is multifactorial. There may be renal dysfunction as part of the liver disease causing salt and water retention. There is often portal hypertension which raises the pressure in the arterial side of the capillary bed and makes fluid more likely to leave the plasma. The dilutional effects of salt and water retention on large proteins, especially albumin, reduce the osmolality of the plasma and again this increases fluid losses. If proteins such as albumin are being manufactured in reduced amounts, this again causes a decrease in oncotic pressure, allowing more fluid to leave. Fluid losses overwhelm the ability of the lymphatics to return fluid back to the circulating volume and this builds up in the peritoneal cavity causing ascites.

Other causes of ascites include hepatic vein thrombosis and heart failure. In the latter, the pressures downstream of the thrombus rise and more fluid

Table 3.6 Causes of splenomegaly in children

Infection:
Viral e.g. EBV, CMV
Bacterial
Protozoal
Haematological:
Leukaemia
Lymphoma
Haemolytic anaemia, e.g. sickle cell disease, hereditary spherocytosis
Portal hypertension
Others:
Juvenile idiopathic arthritis
Storage disorders
Sarcoidosis
Amyloidosis

leaves the vessel due to the rising hydrostatic pressure. Secondary liver damage will further exacerbate ascites. Heart failure can cause ascites due to the effect of rising venous pressure and systemic features such as the effects on the renin–angiotensin–aldosterone system coupled with the inability to supply organs such as the liver with their metabolic demands.

Lymph nodes

Question 3.5

Lymph nodes

A 10-year-old girl is referred to your clinic with persistent enlarged cervical lymph nodes.

Regarding the lymph nodes, which of the following statements are true (T) and which are false (F)?

A. Axillary nodes are typically bigger than cervical nodes in children
B. Children of 8–12 years typically have larger cervical lymph nodes than adults
C. Children of 8–12 years typically have larger cervical lymph nodes than infants
D. Palpable supraclavicular lymph nodes of 1 cm are usually benign in children
E. Persistence of cervical lymph nodes of 1 cm diameter in a child of 10 years for more than a month requires further investigation

Answer 3.5

A. False; B. True; C. True; D. False; E. False.

It is common to be referred children with enlarged lymph nodes, particularly enlarged nodes in the cervical region (Fig. 3.7). An awareness of what is common and normal and which patterns of abnormality require further investigation is useful for any paediatrician.

Most children have palpable lymph nodes whose relative size could qualify for lymphadenopathy in an adult. These are most prominent in the anterior cervical, inguinal and axillary regions and continue to increase in size until the age of 8–12, after which atrophy occurs.

- Bilateral anterior cervical lymph nodes of up to 2 cm in diameter are often found in older healthy children or in those experiencing or recently recovering from an upper respiratory tract infection.
- Axillary nodes up to 1 cm and inguinal nodes up to 1.5 cm in diameter are also usually normal. A 1.5-cm inguinal or a 2-cm anterior cervical node, for example, would be considered normal in a child aged 7 years but would warrant further investigation in an infant aged 2 months.
- Supraclavicular nodes of any size at any age warrant further investigation, as they can be associated with malignancy in the chest and abdomen.
- Erythema, warmth, tenderness and fluctuation of a node suggest lymphadenitis of infective origin.
- Nodes that are firm, non-tender and matted together increase the possibility of malignancy.
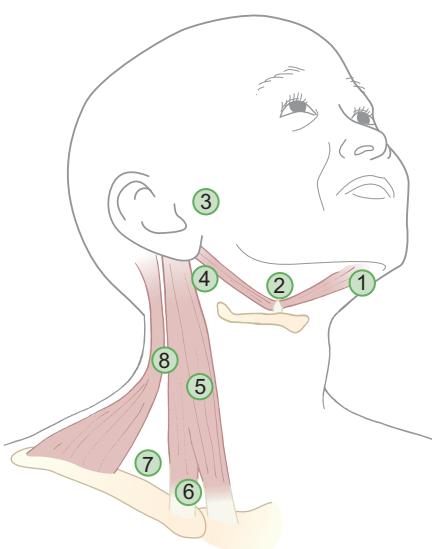
Fig. 3.7 The site of normal cervical lymph nodes. (1) Submental; (2) submandibular; (3) parotid; (4) upper cervical; (5) middle cervical; (6) lower cervical; (7) supraclavicular fossa; (8) posterior triangle (also known as the accessory chain).

Musculoskeletal examination

The paediatric gait, arms, legs, spine (pGALS) assessment is a simple (takes an average of 2 minutes to perform) evidence-based approach to musculoskeletal (MSK) assessment. It is based on the adult GALS (gait, arms, legs, spine) screen and has been shown to have high sensitivity in distinguishing abnormal from normal and detecting significant abnormalities.

pGALS is recommend to be performed in the following scenarios:

- Child with muscle, joint or bone pain
- Unwell child with unexplained pyrexia
- Child with limp
- Child with delay or regression of motor milestones
- The 'clumsy' child in the absence of neurological disease

- Child with chronic disease and known association with musculoskeletal presentations

pGALS will identify and localize joint abnormalities, directing the observer to a more detailed examination of the relevant area(s). The paediatric regional examination of the musculoskeletal system (pREMS) provides a more detailed examination of the relevant areas which is based on the 'look, feel, move, function' principle, similar to that of adult REMS for each joint or anatomical region. It differs by anatomical region, reflecting different pathologies from those observed in adults. pREMS involves active movements performed first and then passively by the examiner and includes the addition of 'measure' for some joints and options depending on the clinical scenario.

pGALS needs to be interpreted in the context of the physical examination elsewhere (e.g. chest, abdomen, neurological examinations); pREMS includes components of a neuromuscular examination depending on the clinical context. For example, the child who is noted to be 'clumsy' with possible delay in milestones warrants a neurodisability assessment (e.g. developmental coordination disorder; cerebral palsy).

Neurological system

A complete neurological examination is a challenge even for experienced paediatricians. It requires patience and skill. It is not performed routinely but is required if there is a neurological problem.

The motor system

Upper motor neuron lesions

Damage to the upper motor neurons gives rise to a characteristic set of clinical features which contrast with those caused by lower motor neuron lesions (Table 3.7).

Injury to the motor cortex or descending motor axons found within the internal capsule leads to contralateral muscle flaccidity that is immediate in onset. This acute phase is more strikingly evident upon examining the upper and lower limbs and results in marked muscle weakness and areflexia, whilst the muscles within the trunk are usually preserved through

Table 3.7 Summary of upper and lower motor neuron lesion findings

Upper motor neuron lesion	Lower motor neuron lesion
Weakness with no muscle atrophy	Weakness with atrophy
Increased tone (spasticity) with sustained clonus	Reduced tone with no clonus
Hyperexcitable stretch reflexes	Reduced or absent reflexes
No muscle fasciculations	Fasciculations

a combination of brainstem pathways that survive or because of bilateral projections of the corticospinal tracts to local circuits which control muscles of the midline. This hypotonic period of upper motor neuron injury is called spinal shock and is a reflection of decreased spinal circuit activity which no longer receives input from the motor cortex and brainstem.

After a variable period of time, there is return of a considerable amount of function, which is not yet clearly understood, and yields the characteristic set of upper motor neuron signs (see Table 3.7). The current understanding of the pathophysiology of spasticity centres around an imbalance between excitatory and inhibitory inputs to the spinal motor neurons such that inhibitory inputs are reduced, meaning excitation is the dominant force. Clonus describes the involuntary rhythmic contractions which occur in response to sudden sustained stretch. Sudden stretch activates muscle spindles, which results in the stretch reflex. The resultant tension activates Golgi tendon organs, causing the activation of an inverse stretch reflex and, in turn, muscle relaxation. If stretch is sustained, the muscle spindles are activated again, leading to a cycle of alternating contraction and relaxation.

Lower motor neuron lesions (see Table 3.7)

The motor unit comprises groups of muscle fibres that are innervated by a single anterior horn cell. Thus, a loss of lower motor neuron function subsequently leads to a loss of muscle fibre contraction and the muscles are weak and flaccid. Over time, muscle fibre groups atrophy with subsequent muscle wasting and fibrillations because of spontaneous depolarization.

Cerebellar lesions

The cerebellum is responsible for coordination and therefore a lesion within one cerebellar hemisphere causes a lack of coordination on the same side of the body. Initially, movement appears normal, but as the target is reached, the accuracy of movement decreases and produces the characteristic 'intention tremor'. In addition, there is a lack of appreciation of distance (dysmetria) that results in past-pointing. Dysdiadochokinesia refers to the impaired ability to produce rapid and accurate alternating movements. If the central vermis of the cerebellum is affected, then the patient has a characteristic ataxic gait.

The cerebellum also has more complex functions which are as yet not well understood. For example, children who have surgery for posterior fossa tumours often develop cerebellar mutism, with the loss of language skills which gradually improve over a few weeks.

For further details of examination of the neurological system, see Chapter 28, Neurology.

Further reading

Arthritis Research UK. <http://www.arthritisresearchuk.org/health-professionals-and-students/video-resources/pgals.aspx>; [accessed 23.07.15]. pGALS demonstration and supportive documents are available as a web-based free resource. pREMS demonstration will also be available.

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Nadya James

Normal child development

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Have an understanding of normal child development
- Understand the scientific basis of normal development
- Be aware of the theory and tools available for assessment
- Understand the concept of 'red flags' and limit ages for developmental milestones
- Understand the importance of repeated developmental assessment over time
- Understand the basis of the Healthy Child Programme

Introduction

One of the greatest joys, and challenges, of paediatrics is that each child is truly different and will follow their own, often unpredictable, developmental path. The result is that there is a wide spectrum of skills that children of similar ages possess, and it is difficult to define what is 'normal'. The concept of defining 'normal' child development arose relatively recently from statistical analysis. One of our roles as paediatricians is to know and understand the process of child development, in order to detect when a child falls outside the limits of what we would expect, and take appropriate action.

Child development encompasses both physical and cognitive change as the child grows. The child moves from a helpless and dependent infant to a mobile and exploratory child, and onwards to an increasingly autonomous adolescent. Skills and knowledge are acquired during the first few years faster than at any other time in the child's life. Developmental surveillance is designed to identify early any signs of developmental problems in order to ensure prompt access to specialist services, early intervention or therapy, and to enable the child to be supported in reaching their full potential. Developmental monitoring is carried out as part of the general Healthy Child Programme

in the UK, but also by medical, educational, and allied professionals whenever contact is made. Parents themselves play a central role, and are equipped with guidance on normal child development through publications (e.g. *Birth to five*) and through advice and contact with professionals such as health visitors.

If concerns are identified or suspected, a more detailed assessment is performed to look at individual areas or overall development. In order to understand the scientific basis of child development, we must first establish a few overriding concepts that explain how things occur, and the order in which they happen.

The key principles are as follows:

- Development commences in the fetus and continues throughout infancy and childhood and into adulthood.
- Development is influenced by both internal (genetic and child-specific) and external (environmental) factors.
- Development is a varied continuum rather than a discreet set of steps or limits.
- Developmental progress builds on what has been achieved before.
- Development is adaptive to the circumstances and situations that the child encounters.

Table 4.1 Primitive reflexes and when they disappear

Reflex	Description	Age by which it should disappear
Sucking and rooting	Coordinated suck and swallow and turning towards the breast. May not develop until 32–36 weeks' gestation	4 months
Grasp	Fist clenches when palm stimulated	5–6 months
Moro	Throws head back, extends then contracts limbs and clenches fists	5–6 months.
Galant	Stroking to the side of the spine causes the body to curve towards the stimulus	4–6 months
Walking	Supporting the infant upright with the soles touching a surface causes each foot in turn to be lifted as if 'walking'	2 months
Asymmetric tonic neck reflex	Extension of ipsilateral arm and contraction of contralateral elbow upon head turning ('fencer's posture')	6–7 months
Babinski	Extension of toes upon stroking lateral border of the foot	2 years

In assessing 'normality' in children, paediatricians need to understand the normal natural history of the changes that occur throughout life (Table 4.1).

Change in neurology with growth

Just as a child's appearance changes from infancy through to puberty and adulthood, so does brain function. We are born with certain things 'hard-wired' into our nervous system that we require for survival. These are discarded when no longer useful, and new abilities take over. An example is primitive reflexes in newborn infants.

Primitive reflexes

One of the first reflexes to develop *in utero* is the sucking (or rooting) reflex, which begins to develop around 32 weeks' gestation. Essential for feeding, premature babies may be born before this reflex is sufficiently developed and require time and practice to attain the skill. Likewise, the rooting reflex, where stimulation of a corner of the mouth/cheek prompts the baby to turn towards the source and open the mouth, makes perfect sense for helping establish breastfeeding. The grasp reflex, with clenching of the fist around whatever touches the palm, can be hypothesized as useful when observing our primate ancestry, carrying infants around clinging to their mother's fur. The Moro reflex prompts the infant to throw the head back, throw their arms and legs out wide, then clench their fists and pull the limbs in again with a cry. One theory is that this evolved as a response to an infant losing its grip on the mother and starting to fall, causing the infant to fling their arms out and grab onto the mother and pull themselves back towards her.

However, these and other neonatal reflexes diminish and disappear at different times over the first year or two. If they fail to do this, it is not only disadvantageous to the infant, but serves as an indicator to the clinician that all is not well. For example, the grasp reflex must be overcome and extinguished if the baby is to be able to voluntarily pick up and release objects and food. Another example is the asymmetric tonic neck reflex (adoption of the 'fencer posture', when the head turns to one side). Initially useful for coordinating gaze and upper limb extension, it becomes counterproductive if every time you turn your head your arm extends outwards on that side. Persistence of the

reflex would hamper ability to bring both hands to the midline or to bring food to the mouth.

The senses

The senses allow us to experience and interpret the physical world. Although we have internal sensors that provide feedback on internal status (for example, baroreceptors and blood pressure), it is the external senses that provide the brain with information that allows us to interact with the world. Sense itself is highly individual, and the interpretation of the same stimulus may differ between individuals, or to the same individual at different times. It is also highly influenced by our emotional state at the time. An example might be the taste of coffee or wine. Both flavours are rarely liked by children, but a taste for them may be acquired as they reach adulthood. A fast-paced piece of music may be enjoyed whilst exercising, but found unpleasant when relaxing at home in the evening. Furthermore, some individuals appear to have enhanced sensitivity to certain stimuli. Children with autism often have increased sensitivity to sound, touch, and taste. This may lead them to actively seek some stimuli, but to find others intolerable. Commonly reported examples include a dislike of loud noise (leading some to require ear-defenders in noisy settings), finding certain tastes and textures of food unpalatable (leading to a restricted diet), and difficulty with things rubbing against the skin (leading to labels being cut out of clothes and items being worn inside-out to prevent the seams touching the skin).

Taste

Taste is governed by the cranial nerves VII and IX, and partly by X. Chemoreceptors in the form of papillae are distributed over the tongue and are able to detect five different tastes. Salt is an important chemical in human physiology, and it is not surprising that it is one of the main flavours we can detect. Similarly, we are designed to recognize and prefer the sweet taste that tells us that a fruit is ripe or that food is a likely source of energy in the form of carbohydrate. Sourness is usually judged as an unpleasant taste in the young child, and signals that a fruit is not ripe and so it may be unwise to eat it. Bitterness also indicates a potentially toxic substance that is best avoided. If you present sour or bitter food to an infant, it will usually be rejected outright. However, an older child is able to overcome this instinct, and actively consume sour sweets and candies.

The final taste is more difficult to define and is described in Japanese as 'umami'. It represents the savoury or 'meaty' taste of foods. The receptors for this taste are activated by the food additive monosodium glutamate (MSG), which is why it is used as a flavour enhancer so widely in many parts of the world. Interestingly, the interpretation of taste seems to be affected by habituation – for example, needing to add more and more sugar or salt to foods over time in order for the full taste to be detected. Disorders causing loss of taste are relatively rare, but may occur if cranial nerve VII or the tongue surface is damaged. Smoking also seems to dull the sense of taste, but this may be more via its effects on the sense of smell.

Question 4.2

Olfaction

Concerning the sense of smell, which of the following conditions is NOT associated with anosmia?

A. Head injury

B. Kallmann syndrome

C. Primary ciliary dyskinesia

D. Rhinoviral infection

E. Temporal lobe epilepsy

Answers 4.2

E. Temporal lobe epilepsy.

Temporal lobe epilepsy is occasionally associated with a sudden appreciation of a smell (which is not truly present). Whilst congenital anosmia is rare (about 1% of total cases of anosmia), diagnosis is frequently delayed as the child will not understand that their sense of smell is diminished. The most common cause of congenital anosmia is Kallmann syndrome. Most cases in childhood are not permanent and relate to blockage of the nasal passages, e.g. commonly rhinoviral infection or more rarely ciliary dyskinesia. Head injury can damage the cribriform plate, severing the olfactory nerves and leading to a permanent loss.

Smell

Often overlooked, smell is one of the most powerful of the senses. It is believed to account for 80–90% of what we interpret as 'taste'. It develops very early, and animals (including humans) rely on the smell of their mother and the mother's milk to identify a parent and to locate the nipple. Governed by cranial nerve I, the axons from thousands of cells expressing the same odour receptor converge in the olfactory bulb. We are able to distinguish the chemical signatures of an

impressive range of substances. However, our sense of smell is weak compared to many other animals.

Smell is a potent emotional and memory trigger, possibly due to the olfactory system's proximity to the limbic system and hippocampus, which are involved in emotion and memory. A smell can rapidly influence our consciousness and behaviour. In animals, chemical messages in the form of pheromones are used to carry signals that are designed to influence the behaviour of other members of the same species; while best known for promoting sexual attraction, they may be competitive (e.g. 'stink fights' in male lemurs) or collaborative (as with ants laying down trails to food). It is unknown if pheromones exist in humans.

Temporary loss of sense of smell is very common, as with the common cold. Permanent loss can occur in head injuries, intracranial tumours, and in the genetic condition Kallmann syndrome (associated with absent or incomplete pubertal development). Some forms of temporal lobe epilepsy also trigger the sense of smell, with an odd smell prior to or during an attack. The olfactory neurons are also remarkable for their capacity to regenerate, which raises the possibility of using them to repair damaged nervous tissue in clinical practice.
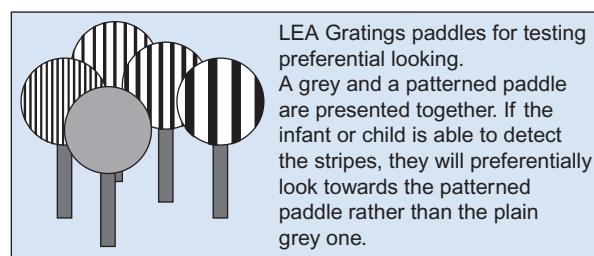
Vision

Good visual function depends on a combination of good visual acuity and sensitivity to targets in the peripheral visual field. Visual acuity is defined as the minimal distance that two targets need to be separated in order to be seen as distinct. An individual with 'perfect' vision can resolve two targets separated by one minute of arc (i.e. one sixtieth of a degree), this is equivalent to 6/6 (or 20/20 US measurement) Snellen vision. The Snellen chart is usually viewed from 6 metres (20 yards) and this gives the numerator; the denominator is the number printed beneath the smallest line the child can read, e.g. a child with 6/36 vision is reading print which an individual with normal vision would see at 36 metres.
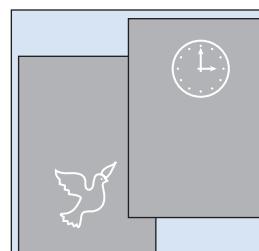
Vision is poor at birth but develops rapidly as the retina and visual pathways mature (Table 4.2). Infant visual acuity is measured by visual behaviour, i.e. the ability to fixate and follow targets or the infant's natural preference to look towards a more interesting stimulus (as tested by preferential looking acuity cards). Toddlers and pre-schoolers can be tested on optotype (letter or picture) charts using matching cards (Fig. 4.1). In eye departments, Snellen charts are being replaced by the more scientific logMAR (logarithmic minimal angle of resolution) charts, which have a uniform five letters per line. A logMAR score of 0.00 is equivalent to 6/6 vision; the higher the logMAR number, the worse the visual acuity. When formal visual acuity testing is not possible, smart phone apps (iSight, iChart2000) can be helpful because they are cheap and portable.
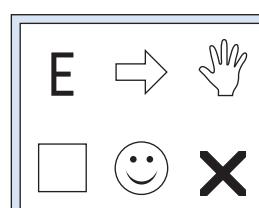
Visual acuity can also be objectively assessed using the visual evoked potential (VEP) pattern reversal test. During this electrophysiological test, skin electrodes

LEA Gratings paddles for testing preferential looking.
A grey and a patterned paddle are presented together. If the infant or child is able to detect the stripes, they will preferentially look towards the patterned paddle rather than the plain grey one.

Cardiff preferential looking cards. The Cardiff Acuity Test is designed for age 1–3 years. Cards are presented at eye level, and the child observed to see if they look up or down towards the picture.

Optotype testing cards. These use symbols or letter matching when the picture is presented at a set distance, and the child verbally identifies it or matches it to symbols on a card.

Fig. 4.1 Types of charts used for testing visual acuity in children.

Table 4.2 Stages of visual development and clinical measurement techniques

Developmental age	Expected mean visual acuity (Snellen)	Visual acuity test	Visual field test
Newborn	<6/60	Fixation to lights	Not possible
0–3 months	6/60–6/38	Fixation to faces/large toys	Visually elicited eye movement
3–24 months	6/38 improving to 6/12	Preferential looking cards (Teller/Cardiff)	Confrontation techniques
2–4 years	6/12–6/9	Picture optotype charts	
5+ years	6/9–6/6	Letter optotype charts	Goldmann perimetry/automated perimetry (Humphrey/Octopus) sometimes possible

are used to measure the cortical activity stimulated from a reversing white/black chequerboard pattern. The visual acuity is quantified by the smallest check size to elicit a cortical reaction and can be particularly useful in non-organic visual loss. Peripheral visual fields are notoriously difficult to test in young children but, by five years, a horizontal field of 150° and vertical field of 130° are expected.

Variable angle squint (ocular misalignment) is common in neonates and reflects the poor visual acuity at that stage of development. By three months, the visual acuity should be sufficient to stimulate ocular alignment. The presence of a squint after three months should alert the clinician that either the vision is poor or the squint is pathological. Ocular and cortical immaturity causes pursuit and saccadic eye movements to be jerky and inaccurate until 3–4 months of age.

Not only does what we see change as we mature, but our interpretation of it also matures. An example of this is arranging two objects on a table in front of a child, so that one partially obscures the other. If asked to draw what they see, a young child will often draw two separate objects side by side or one on top of the other. An older child will be able to marry together what they 'know' (they are two distinct objects) with what they 'see' (one object partially obscuring the other), and draw an accurate picture. Likewise, it is not until mid-to-late childhood that a child will be able to draw a scene as if from a different viewing position.

Beyond 'red reflex' screening of newborns, the next routine visual assessment recommended by the UK National Screening Committee is at age 4–5 years, as an orthoptist-led service. The most common condition to pick up at this age is amblyopia, which is usually treated by patching the 'good' eye to promote visual pathway development in the weaker eye (see Chapter 30, Ophthalmology).

Hearing

The fetus can hear from as early as 19 weeks' gestation. Reaction to low frequency sound develops first, then to higher frequency as the fetus reaches over 30 weeks' gestation. Humans are able to hear sounds between about 20 Hz and 20,000 Hz. We are able not only to distinguish many sounds, but also to determine their location by processing the difference in amplitude and timing of sound received in one ear versus the other.

Around 900 children are born each year in the UK with significant permanent hearing loss, and 1–2 per 1000 have some form of hearing impairment. All children in the UK are offered hearing screening at birth as part of the NHS Newborn Hearing Screening Programme, utilizing otoacoustic emission (OAE). If this suggests hearing loss, a further OAE and, if required, an automated auditory brainstem response (AABR or ABR) is performed (see Box 2.12 and Chapter 31, Hearing and balance). OAE assesses the function of the inner ear, whilst AABR also assesses the auditory nerve pathway.

AABR is offered as routine alongside OAE in infants who are at high risk of hearing impairment, for example those who have been in intensive care or who had high serum levels of ototoxic drugs such as gentamicin. A clear response to testing in an infant does not rule out later hearing loss, and conditions such as chronic otitis media with effusion ('glue ear') are very common causes of later problems. Certain groups of patients are also at high risk and are offered extra screening: those with a family history, children with Down's syndrome, cleft palate, and those with a congenital infection.

The method used to assess hearing in children is determined by their developmental level and ability. Even small infants will usually become still and attend to a gentle rattle or bell near the ear. At around 6–9 months, an infant will actively turn to try and find the source of the sound produced by an examiner, and can be assessed using the distraction test. This test, however, is no longer in routine use.

Visual reinforcement audiometry (VRE) uses the same basic principle, but a speaker replaces the examiner as the source of the sound. Whilst the child is engaged, the speaker emits a tone. If the child stops and looks at the speaker, the examiner provides a visual reinforcement by making a toy placed on the speaker light up. Pure tone sweep testing is still performed at school entry, but may be phased out in future. Older children who can cooperate are able to have formal pure tone audiometry testing.

In addition to formal testing, any parental or school concern about a child's hearing should prompt further evaluation. Clues may be that an infant who was previously babbling has not progressed or has regressed in speech. Speech delay, speech disorders, behavioural difficulties, and social skill concerns at any age may be related to an underlying hearing problem. If a child or infant is identified with significant hearing impairment, early referral to specialist services is essential.

Bone-anchored hearing aids (BAHA) and cochlear implants have revolutionized the management of hearing disorders, and use of non-verbal communication strategies such as sign language and Makaton allow these difficulties to be overcome. The earlier a hearing loss is detected and treated, the better the outcome. Infants with hearing loss who receive sound amplification by 2–3 months (ideally by 6 months at the latest) are more likely to develop and retain the

neural pathways required for later language development. Assessment of hearing and management of hearing impairment are considered in more detail in Chapter 31, Hearing and balance.

Touch

The sense of touch is the first of the senses to develop *in utero*. Primarily a function of the skin, the largest organ in the body, the sense of touch utilizes three different types of receptors: mechanoreceptors (sensitive to pressure and vibration), thermoreceptors (sensitive to temperature), and nociceptors (responsible for pain). Mechanoreceptors include Pacinian corpuscles (the largest, these detect vibration and large pressure change), Meissner's corpuscles (near the surface of the skin, these detect fine touch or vibration), and Merkel's discs (fine discrimination of pressure). These receptors are able to adapt to a sustained stimulus rather than firing repeatedly, hence the fact we do not feel the clothes we are wearing. Ruffini corpuscles detect changes in temperature, and can also detect stretch, as used to sense joint position and proprioception. Nociceptors are free nerve endings that signal adverse stimuli to the brain.

Question 4.3

Accepted cognitive theory

Piaget described four phases in normal cognitive development. The correct order is:

A. Formal operational, concrete operational, preoperational, sensorimotor

B. Preoperational, sensorimotor, concrete operational, formal operational

C. Preoperational, sensorimotor, formal operational, concrete operational

D. Sensorimotor, concrete operational, preoperational, formal operational

E. Sensorimotor, preoperational, concrete operational, formal operational

Answers 4.3

E. Sensorimotor, preoperational, concrete operational, formal operational. See below for discussion.

Cognitive theory

Whilst neurological structure changes with age, there are also rapid cognitive changes. The child's brain is designed to absorb and process new information, even when not being directly taught. Although children attend school and formal education, much of our learning is done beyond the classroom, through play and exploration of cause and effect. We also learn through environmental exposure, so children develop much of their language skills by hearing conversations occurring around them.

Many theories have been put forward about cognitive development. One of the best known was by Jean Piaget (1896–1980). He proposed that cognitive development could be broken down into four stages (Box 4.1). Understanding the stages can help explain how a child interacts and interprets the world around them, and also informs educationalists about how best to engage and support a child with learning. As a child matures they progress through each stage in order, but some may never reach the later stages even as an adult.

Some measures of cognitive ability are included in standard developmental assessments used in routine clinical practice. Examples would include knowing colours, shapes and numbers, problem-solving for

Box 4.1 Piaget theory of development

Sensorimotor (0–2 years): Knowledge is based on experience and the interaction of senses and the environment. There is evolution of the concept of self as distinct from the world, and later to the concept of object permanence (the concept that an object can still exist even when out of sight – e.g. a ball hidden beneath a blanket). Use of language and symbolism appears.

Preoperational (2–7 years): The child is egocentric with difficulty seeing things from another's point of view. There is belief that all events are related to the self, animism (objects are like people, e.g. the table bumped my leg because it is mean), precausal thinking (e.g. rainbows are there because someone paints them in the sky), and magical thinking (e.g. if I say something is true, it becomes true). Symbolism and symbolic play appear, there is use of imagination, and the child has a keen interest in asking questions and gaining knowledge about how and later why things are.

Concrete operational (7–11 years): There is awareness of their own versus others' thoughts and feelings. Skills develop in the field of logic and problem-solving. There is interest in categorization, classification and lists (e.g. types of animals, football score tables, collecting things), and ability to generalize information from specific observations.

Formal operational (11+ years): This encompasses the ability to handle abstract concepts and to use deductive reasoning in problem-solving. Not all adults reach this stage.

puzzle boards, being able to select which of two objects is bigger or smaller, or understanding concepts such as that a bird flies or that a horse runs fast. Other aspects of thinking require more specialized assessment, such as the higher cognitive functions of executive planning or understanding and using the complex social rules that govern teenage peer–peer interaction.

High quality pre-school education is associated with improved cognitive and social development. Sure Start Local Programmes, and their successors the Sure Start Children's Centres, were aimed at supporting young children and their families by integrating early education, childcare, healthcare and family support services in disadvantaged areas. The children in areas where these schemes were set up were found to have low cognitive and language development at three years of age, being on average roughly one standard deviation below the population mean. The children in these areas were followed up at 9 months, 3 years and 5 years, with a subset reassessed at 7 years. At five years, children were less likely to be overweight and had better physical health in Sure Start locations. Results at age 7 years suggested a reduction in use of harsh discipline and a more stimulating home environment as a result of the scheme. There was also an association with increased life satisfaction and other markers of function such as a less chaotic home environment.

Studying normal development

Although we are not yet at the stage where we can directly 'see' a thought, we are able to get a glimpse into brain function during tasks, sensory stimulation, and even thinking about specific things. This can be by measuring electrical activity (electroencephalogram (EEG) and brainstem-evoked responses), metabolic activity of areas of brain cells using radiolabelled molecules such as glucose (positron emission tomography (PET)), and changes in blood oxygenation and flow to different parts of the brain (functional MRI). Some of these techniques are already well established in paediatric practice, for example the EEG when looking for abnormal discharges suggesting epileptic activity, and in the use of brainstem evoked potentials in response to auditory clicks as part of the newborn hearing screen using automated auditory brainstem response (AABR).

In the absence of being able to directly 'test' the brain and its development *in vitro*, we must study the observable brain output *in vivo*, i.e. the functioning child in the real world. This is challenging, as in order to detect the abnormal, we must first define what is normal. A recent systematic review suggested that paediatricians are better at identifying children who clearly do not have a developmental or behavioural concern than detecting those with a genuine developmental problem.

The difficulties in accurate developmental assessment include:

- Development is a continuum, not a strict set of 'pass–fail' cut-offs
- Children vary widely, creating a large spectrum of normal
- A child's performance at a task may be more related to what mood they are in than their actual level of skill
- Delay in one domain of development (e.g. language) can impact on another (e.g. social skills)
- Many assessment tools are geared towards specific populations and assume a shared first language between assessor and child
- Development is influenced by many variables, including prenatal, perinatal, and postnatal factors
- The utility of any assessment tool is closely linked to the appropriate tool being selected, and the familiarity of the assessor with using the tool correctly.

As development encompasses so many elements, developmental skills and milestones tend to be split into 'domains'. The number of domains used and their names differ from assessment to assessment, but usually are a variation of the domains listed in Box 4.2.

There are useful tools which can be used to assist developmental assessment. They are based on observations of large numbers of children using standardized assessment methods. Some are based on direct observation of a child, some on parental report, and some by completion of set tasks by the child. In the UK, the most widely used assessment methods are the Denver II©, Griffiths, and Ages & Stages Questionnaire™.

Because children vary in age when they acquire skills, milestones are often quoted as a range of ages at which skills are achieved rather than a set time point. For example, Denver II© utilizes shaded boxes to denote the age at which a milestone was achieved by 25%, 50%, 75% and 90% of children in the reference population (a normative sample of English-speaking children from Colorado, USA). 'Limit ages' are also set, denoting the age at which we would have expected a child to achieve a milestone, and these are usually two standard deviations from the mean. For example, Denver II© illustrates that 25% of children walk at 11 months, 50% at just over 12 months, 75%

Box 4.2 Commonly used developmental domains

Gross motor/locomotive: Large motor function and movement. This can involve quite specific neuromuscular assessments of tone and power, ability to perform tasks, or measures of coordination and function.

Fine motor/hand–eye coordination: Skills involving the small muscles of the hands and manipulation of objects, and the integration of visual input and motor function. Is reliant on both visual function and neuromuscular function.

Language/speech and hearing: This can refer to assessment of produced speech (both quality and higher content), ability to understand and comprehend and produce verbal or non-verbal communication, use of symbols, or understanding of pragmatic (social) language.

Social/personal: Interaction with the environment and other people, understanding of self versus non-self, awareness of social rules and conventions, ability to self-care and be independent.

Cognition/reasoning: Higher cognitive functions and ability to problem-solve.

at just over 13 months, and 90% at 15 months. We would expect 97.5% of children to be walking at 18 months, and this is traditionally the 'limit age' set for independent walking.

Question 4.4

Normal speech development

Ethan is two years old and has around six words that he uses appropriately. He can follow a one-stage command, and will point to named pictures of animals in a book but cannot name them. He is able to fetch familiar toys on request, and enjoys joining in nursery rhyme songs. He cannot identify colours, and does not understand prepositions such as 'under' or 'in'. He is unable to point to named parts of the body.

On his developmental assessment, select the ONE statement that is of most concern:

A. By this age, we would expect Ethan to know some colours

B. By this age, we would expect Ethan to be able to name some animals

C. By this age, we would expect Ethan to no longer use jargon

D. By this age, we would expect Ethan to point to major body parts when asked

E. By this age, we would expect Ethan to understand prepositions

Answers 4.4

D. By this age, we would expect Ethan to point to major body parts when asked.

Speech and language development

Speech and language development requires special mention, as the spectrum of 'normal' is especially wide in this domain. Speech requires the combination of physical skills, cognitive skills, intact hearing, and the desire to communicate. Problems in any one of these areas can impair acquisition of meaningful language. On a physical level, intact neuromuscular control of the vocal apparatus permits a newborn baby to utter their first sounds – usually a lusty cry. Soon, however, the infant will learn that crying can be used to communicate, and uses it to signal hunger, distress or fatigue. Through experimenting, sounds become tuneful babble followed by polysyllable sounds. Subsequent speech development diverges widely between different children. This can be influenced by their temperament, presence or absence of siblings, a bilingual home situation, and use of other methods of communication (for example, good non-verbal skills).

Assessment of speech and language, therefore, is influenced by the child's circumstances and the rest of their development. A child who has only two words at eighteen months, but who is sociable and interacts well and has no difficulty in any other domain, is very likely to be chatting away freely within a few months regardless of any intervention. Conversely, the 18-month-old child who has only two words but also has no eye contact and no social responsiveness, would suggest that further assessment should be performed.

Speech and language development causes concern to many parents. It is more than acquisition of words, and involves both receptive and expressive functions. Humans have a universal habit of speaking to young children and babies in a special way – usually with higher-pitched intonation, simplified vocabulary, short sentences and with exaggerated vocalizations or expressions. This is called infant-directed speech or 'motherese' and it seems important for helping a baby to acquire language.

The spoken language consists of four main elements:

- *Phonology* – the structure and form of speech sounds
- *Semantics* – the vocabulary and use of words to convey meaning
- *Grammar* – the syntax (sentence structure) and morphology (use of tense, etc.)

- *Pragmatics* – the social and situational use of language

Children with hearing impairment or oromotor dysfunction may have particular errors in phonology, and those with autism spectrum disorders classically have semantic and pragmatic language difficulties. Young children will often make grammatical errors that improve with time.

The order in which children learn language tends to follow a pattern. In the infant, this is through vocalizations which become tuneful babble. Although 'mama' or 'dada' are favoured first words, they are not said with true meaning for some time after they are first uttered. A ball-park age for true spoken words is around 12 months old, and is often simple nouns (such as a name or object) or a social term (such as 'hiya').

A child's vocabulary expands rapidly during the second year of life, and a child may have between 100 and 500 words by their second birthday. They understand far more, and can follow single-stage commands. They may start to produce two-word sentences. At this age, it is normal to still have a lot of 'jargon', which is meaningless sounds used in place of true words, but still having pace and intonation as if having meaning. Likewise, many words will still be unclear or with speech sounds missing or substituted, and the pace (and volume!) of speech may not be correct. The use of pronouns (I, we, you) starts to appear but may be confused. We would expect a two-year-old like Ethan to be able to point to major body parts when asked, but not yet to be able to name them. Similarly, he may be able to point to the correct picture of a familiar animal, but not yet know the name. Colours and concepts such as 'in' or 'under' do not appear until later (see Fig. 4.2).

An undiagnosed hearing impairment is at the forefront of considerations when assessing a child with speech delay, but many children appear to 'catch up' with their language skills without any intervention. Difficulty communicating is frustrating for both the child and the parent, and referral to speech and language therapists (SLT) may be appropriate. SLTs can give guidance to parents on how to promote language acquisition, and children with difficulties may be taught to use signs in order to supplement their language skills.

Commonly used developmental screening tools

Denver II©

The Denver Developmental Screening Test©/DENVER II© is a widely used assessment from birth to 6 years. It is relatively quick to administer and does not require much equipment. Some items may rely on information from the parent or carer, e.g. if the child can brush their teeth.

The assessment allows comparison with the reference population. The more tasks that 90% of the reference population (but not the individual child) achieved, the more likely the child has a developmental problem requiring further assessment.

Much of the equipment needed can be found in a standard paediatric clinic. It includes a ball to throw or kick, some one-inch cubes, a cup, crayons, a bell or rattle, and some simple toys.

Advantages

- Minimal equipment required
- Entire assessment can be completed in around 20 minutes
- Quick and easy to learn
- Allows for parental report of items not observed in clinic
- Gives estimated age at which 25%, 50%, 75% or 90% of children achieve a skill, which is a useful rough gauge of how a child's result compares to the population
- Can be used to monitor progress over time
- Parents may find the pictorial representation of progress helpful
- Screening can highlight children requiring further evaluation

Limitations

- Does not detect subtle difficulties
- Single observation/assessment may miss problems
- Only covers up to 6 years of age
- Only detects around 50% of children with a developmental need
- Has fallen out of use in many organizations
- At present, the Denver II©, like many other developmental assessment tools, is not employed for universal screening of well children. It can still, however, be a useful tool in clinical practice.

Case history

Nara – use of Denver II© chart to follow development of preterm infant

Nara is brought to see the paediatrician at the age of $2\frac{1}{2}$ years. She was originally seen at 18 months of age due to developmental concerns, but then her family moved abroad and she was lost to follow-up. She is the only child of healthy parents.

She sat unaided at 6 months (50% of infants accomplish by this age) and walking was delayed

at 22 months (90% of children are walking by 15 months). At 30 months, she can run but not manage steps (90% can achieve by 22 months) or kick a ball (90% can achieve by 24 months). She 'jabbers' happily in clinic. Her parents report that she will say 'Mama' and 'Dada', and has three recognizable words (90% of children achieve six words by 22 months). She can point to two named pictures (90% can achieve by 24 months) but not name any herself.

Nara enjoys the blocks, and builds a tower of eight cubes easily (only 50% can do this at 30 months). She also helps with dressing and demonstrates that she can put on her T-shirt herself (25–50% can achieve at 30 months), and her parents report she routinely brushes her own teeth alone (less than 25% can achieve at 30 months) and washes her own hands (75–90% can do).

A copy of her Denver II© chart from when she was seen aged 18 months (Fig. 4.2) is still available in her file, and the new findings are plotted alongside previous results. The chart facilitates recognition of areas requiring further evaluation.

Griffiths MDS

Griffiths Mental Development Scales (revised) assess multiple developmental domains. These scores can be combined to provide a general developmental quotient (GDQ) and separate subquotients (DQs) for each area of development. Two scales exist: 0–2 years and 2–8 years. In the 0–2 year scale, five subscales are covered, namely Locomotor, Personal–Social, Language, Eye-and-Hand Coordination, and Performance. At 2–8 years, there is an additional Practical Reasoning subscale.

As well as a detailed overview of development at the time, it can also be used to monitor progress and response to interventions. It is a test that requires specific training and experience to use, as well as different sets of test items for each scale. It takes around an hour to administer, and often longer to score and write the report. Its use tends to be restricted to paediatricians and psychologists who specialize in developmental concerns.

Bayley-III Screening Test

The Bayley-III Screening Test is used for children aged 1–42 months who require more detailed evaluation. It takes 15–30 minutes. The full Bayley-III takes up to 90 minutes to perform. Social–emotional and adaptive behaviour are also assessed by parental questioning. Performance is compared to others of the same age.

Like the Griffiths MDS above, the full Bayley-III is used mainly by specialist paediatricians and researchers and requires extensive training to be able to perform it correctly. The Bayley-III has been used extensively in research projects, including landmark studies such as the EPICure series which examine the long-term outcome for infants born at 22 to 26 weeks' gestation, and form the basis of much of what we currently know about this topic.

PEDS

The Parents' Evaluation of Developmental Status (PEDS) is a screening tool for ages 0–8 years based on reported abilities. It is very quick to administer, having only ten questions, and aims to cover areas of concern about development, behaviour, and emotional/mental health. It can be performed as a clinician-led interview or as a self-report questionnaire by a parent. It is used to highlight areas of concern that require further exploration. Some clinicians give it to parents in the clinic waiting room, and then review it with the family during the consultation. Although useful as a stimulus to discussion, it cannot replace a clinical examination and observation for evaluating development.

PDQ II

The Pre-screening Developmental Questionnaire (PDQ II) is designed for children aged from birth to six years. It is completed by parents or carers, but requires a brief initial explanation by the clinician. It takes most parents around ten minutes to complete. It is designed to highlight areas for the clinician to explore in more detail.

ASQ

The Ages & Stages Questionnaire™ (ASQ) is used between 4 months and 5 years of age. A questionnaire-based screening tool, it is administered using a different proforma for different ages. It covers gross motor, fine motor, problem-solving, communication and social aspects of development. Each aspect has six questions, giving 30 questions overall. The questionnaire is designed to be completed with parents or carers along with the clinician. It takes around 15 minutes to complete and creates a score for each area. There are cut-offs for 'normal' that can prompt further discussion or referral.

M-CHAT™

The Modified Checklist for Autism in Toddlers (M-CHAT™) is available for clinical, research, and educational purposes. It is specific for screening toddlers between 16 and 30 months of age to assess autism spectrum disorders (ASD). It is not diagnostic, but identifies children who require further evaluation.
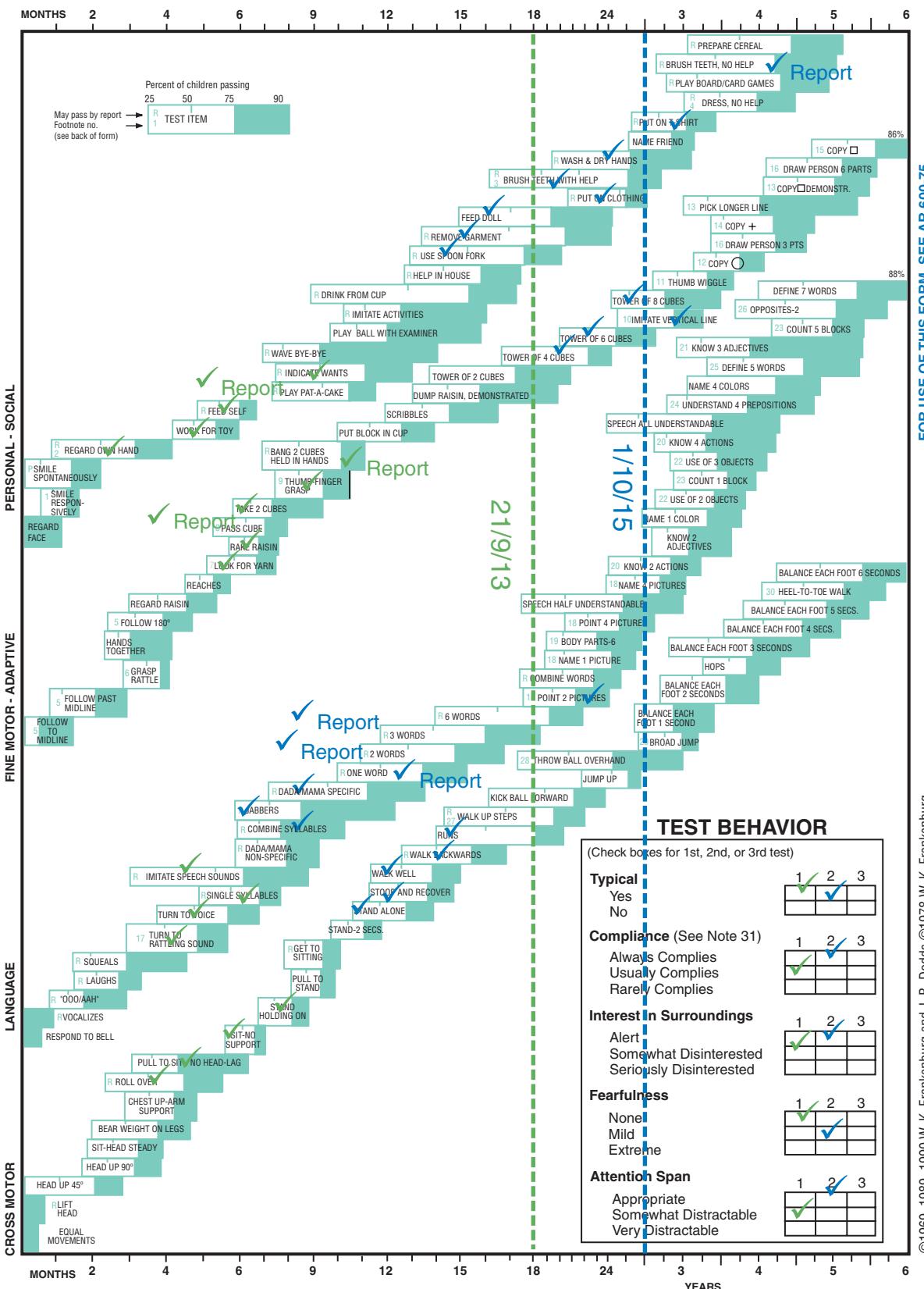
Fig. 4.2 **Completed Denver II© profile for Nara.** *(Chart © Denver Developmental Materials Inc.)*

Other assessment tools

Other useful assessment tools are listed in Table 4.3.

Developmental concerns

Developmental scales and detailed structured assessments are useful for research. The busy clinician wants to know if the child we are seeing is developing normally (reassure), potentially abnormally (further assessment/investigation), or definitely abnormally (urgent assessment/investigation). In order to help in making this decision, there are a number of warning signs or 'red flags' that highlight children who need a more thorough evaluation (Table 4.4). These include the 'limit ages' as mentioned above.

However, there are caveats to the use of red flags and limit ages: each child varies greatly in what rate of development is 'normal' for them. If every child who fell foul of a red flag was referred to a paediatrician, the service would rapidly be overwhelmed. Therefore, judgement and discretion must be used.

Interaction of domains

Although we tend to separate development into discrete domains for the purpose of assessment, the domains are inextricably interlinked and impact upon each other. Speech and language delay frequently coincides with social skills delay. This is because the skill to communicate is so important in socializing. A child who cannot make themselves understood or cannot comprehend the communication of others is going to find it harder to integrate effectively at nursery. Likewise, a child with poor vision will have impaired fine motor skills, but also lacks the drive of seeing an interesting object on the other side of the room to encourage them to get up and walk.

Table 4.3 Some other useful assessment tools

Neonatal and infant	The Neonatal Behavioral Assessment Scale (NBAS), also called 'the Brazelton' after its originator Bayley Infant Neurodevelopmental Screener (BINS)
Pre-school child	Child Development Inventories (CDI) Pediatric Symptom Checklist Battelle Developmental Inventory Screening Test (BDIST)
Older child	Strengths and Difficulties Questionnaire (SDQ) Behavior Assessment System for Children, 2nd Edition (BASC-II) Note: It may be appropriate to use a developmental assessment tool designed for a younger child in cases of significant developmental delay.

Question 4.5

A child who is not walking at 18 months

Jonah is referred to the local paediatrician because he is not yet walking at 18 months of age, but shuffles along the floor on his bottom. He is not saying any words but responds to his name. On examination, the power and tone in his legs is reduced.

Which of the following statements about his development is correct? Select ONE correct answer.

A. His mother can be reassured that his development is normal as he bottom shuffles.

B. Grabbing objects more proficiently with his right hand is normal for his age.

C. His speech is within normal limits for his age.

D. The findings suggest developmental delay.

E. This represents deviated but normal development

Answers 4.5

D. The findings suggest developmental delay.
He has delayed walking and reduced power and tone in his legs and his speech is delayed.

Table 4.4 Red flags of development: conventional 'limit' ages by which a milestone should be achieved

Gross motor	Fine motor	Speech and language	Social and cognitive
Sit unsupported: 9 m	Clear hand preference: <1 y	Babble: 7 m	Smile: 8–10 w
Stand alone: 12 m	Pincer grip: 12 m	Respond to name: 12 m	Look for dropped object: 12 m
Walk alone: 18 m	Scribble: 2 y	Six words: 18 m	Spoon-feed self: 18 m
Run: 2 y	Copy a line: 3 y	Two-word sentences: 2 y	Symbolic play: 2.5 y
Jump (two feet): 3 y	Draw person with six parts: 5 y	Name four colours: 4 y	Dress alone: 4 y
Unilateral weakness at any age	Parental concern about eyesight at any age	Parental concern about hearing at any age	Lack of emotional warmth or eye contact at any age

Patterns of development

There are several patterns of development: normal development, developmental delay, plateau, reaction to acute severe brain injury, deviated but normal, leapfrog and regression (Fig. 4.3).

Normal development

This is the pattern of development of 90% of children at a specific age.

Delayed development

The delay may affect only gross motor function, for example a child with spina bifida and lower limb weakness. The delay may be across more than one domain, for example a child with hypotonicity and speech and language delay due to Down's syndrome. Thinking beyond muscle mechanics as a potential cause, is the child given the opportunity to learn to walk, or kept strapped into their buggy for most of the time?

Plateau or static development

This is where a previously developing child does not progress any further (e.g. after a brain injury), or where there are physical barriers to further progress (e.g. a child with quadriplegic cerebral palsy, who is able to independently manoeuvre themselves across the floor, but is unable to walk without assistance).

Deviated but normal development

The archetypal example of this is the bottom shuffler. This often runs in families, and a proficient bottom shuffler is remarkably agile and speedy at getting from place to place. The bottom shuffle phase often replaces the crawling stage, and 97.5% of bottom shufflers will be walking independently by 27 months of age. A caveat is that some children, like Jonah in the case

above, may bottom shuffle due to an underlying problem such as hypotonicity, muscle weakness, or structural malformation.

Leapfrog development

In this pattern, entire stages of development are missed out completely. An example is where a child goes straight from sitting to walking, with no crawling or other stages in-between.

Regression

A child who was previously achieving a skill (e.g. walking or talking) loses the ability. This is a serious indicator of pathology and is a 'red flag' at any age.

Delay in multiple domains

Delay that is found in two or more domains is sometimes (rather imprecisely) called 'global developmental delay'. However, this is a crude term, as many children with multi-domain delays are affected to different degrees in different areas. For example, a child with mild motor and language delay may have excellent social skills but markedly reduced cognitive skills. It is therefore more informative to qualify any description of a child with developmental concerns with the areas affected rather than use the blanket term 'global developmental delay'.

Special cases – the preterm infant

With the advances in maternal and neonatal medicine, there is an increasing population of children who were born extremely preterm. This raises a dilemma for the clinician wanting to assess their development, as their chronological age and their post-conceptual age may be over four months apart. This makes defining what constitutes normal development problematic. Should we be concerned that an infant is not yet sitting alone at 9 months if they were born at 24 weeks' gestation? Should we assess them taking into account 16 weeks of prematurity, which makes them only 5 months post their due date? Do ex-preterm children 'catch up' with their full term peers, and if so when? What is the likelihood of an ex-preterm infant having long-term developmental impairment? These are all important questions for the paediatrician to consider.

Several studies have tried to look at the development of ex-preterms in more detail in order to help answer some of these questions. The EPICure study has been following up two cohorts of children born very preterm in the UK at <26 weeks' gestation (born in 1995 and 2006). The original study found that at 30 months of age, nearly a quarter were classed as


PATTERNS OF DEVELOPMENT
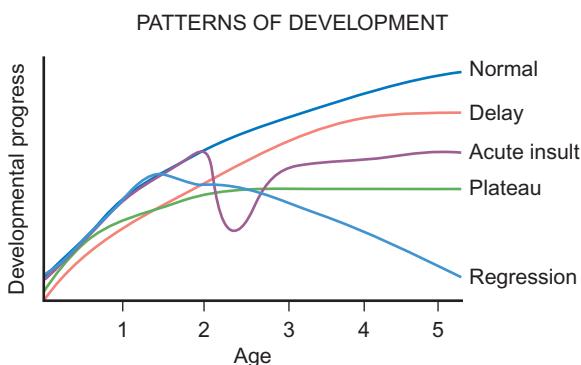
Fig. 4.3 Some patterns of development.

severely disabled. By 6 years of age, 85% of those who had been classed as severely disabled at 30 months still had moderate-to-severe cognitive disability. In contrast, the lesser degrees of disability diagnosed at 30 months had little correlation with disability at 6 years, and many who were thought to have no impairment at 30 months subsequently developed mild disability or impairment, showing the difficulty in predicting future performance and the importance of long-term follow up.

Since the original EPICure study, the number of infants born extremely preterm who survive has increased even further. However, the pattern of major neonatal morbidity (such as major abnormality on cranial ultrasound and retinopathy of prematurity) and the proportion of survivors affected has remained relatively unchanged, suggesting that there will be increasing numbers of children who were born preterm and go on to have developmental difficulties.

How should we assess the progress of extremely preterm infants compared to normalized data that has been based on a healthy population? There is no universally accepted policy, and their development is often measured in terms of progress made as opposed to pass/fail in age-determined skills. In some ways it can be likened to correcting for gestational age on growth charts, with both the post-conceptual and chronological age used as reference points. In practice, most clinicians correct for prematurity in developmental assessment up to the age of two years.

The child development team and the Healthy Child Programme

Systematic reviews have demonstrated that outcomes for children are substantially better if developmental problems are detected early and services are provided. Furthermore, intervention is associated with improved health outcomes for children, improved school performance, and decreased need for special education services.

The UK 'Healthy Child Programme: Pregnancy and the first five years' was published in 2009, and set out standards for an early intervention and prevention public health programme designed to give 'every family a programme of screening tests, immunizations, developmental reviews, and information and guidance to support parenting and healthy choices – all services that children and families need to receive if they are to achieve their optimum health and wellbeing'. This combined aspects of screening, developmental reviews, immunizations, health promotion, and signposting to information and services

for all children and their families. Furthermore, it sets out guidance for promoting child development, including language, support and monitoring for those identified as having developmental needs, and targeted services for those with significant needs or concerns (see Box 2.9 and Chapter 2, Epidemiology and public health).

The Healthy Child Programme is the first time that so many aspects of child health have been combined in a national initiative. A particular difference in this model, as opposed to previous schemes, is the emphasis on health promotion and providing holistic support for families.

Although designed to link through all ages, from pre-birth to adulthood, the Healthy Child Programme places particular emphasis on service contact and health and developmental assessment at the following points, with health promotion at each contact. For some time points, the contact will be face-to-face or at a clinic, others are by questionnaire.

The Healthy Child Programme includes:

- By the 12th week of pregnancy – antenatal screening and maternal health
- At the neonatal examination – hearing, testes, hips, red reflex, general exam
- At 5–8 days – newborn biochemical screening
- At the new baby review (around 14 days old) – support and health promotion
- At the baby's 6–8-week examination – hips, testes, red reflex, heart, growth, general exam
- By the time the child is 12–13 months old – up to date with immunizations, developmental review
- Between 2 and 2½ years old – development and health review
- Pre-school – immunization and general review
- School entry – vision, hearing and growth
- Primary school (5–11 years) – general review
- Transition (11 years) – physical and psychological health review
- At 13–16 years – immunization, HPV vaccination in girls
- Transition (16 years) – physical and psychological health review.

Members of the team providing universal services for all children include the midwifery service, health visitors, community nursery nurses, school nurses, practice nurses and general practitioners. Although not regarded as health practitioners, teachers have a critical role alongside their medical colleagues. Other practitioners who may be involved throughout a child's life include nursery staff, early years intervention teams, specialist teachers for those with disabilities, and family support workers. For children suspected

or found to have developmental concerns, the physio-therapy, occupational therapy, speech and language therapy, orthotist (prevents or corrects deformities with orthoses), and play therapists will work with the child and their family. Another central role is that of the paediatrician, in particular the community paediatrician with their specialist skills in child development and neurodisability. Finally, social workers, voluntary and charity organizations, and youth leaders are all part of the jigsaw that forms the three sides of the Common Assessment Framework (CAF) triangle (see Chapter 8, Child protection). This format is used when drawing up documents to analyse the requirements of a child with extra needs, drawing on the three areas of 'parenting capacity', 'child's developmental needs' and 'family and environment'. This strategy

therefore includes non-medical factors, and this is important as psychosocial risk factors often are better predictors of developmental delays and problems than are medical issues.

Further reading

Department of Health. Birth to five. Crown copyright 2014.
e-LfH. The healthy child programme. <http://www.e-lfh.org.uk/programmes/healthy-child-programme>; [accessed 30.07.15]. Includes an extensive training package covering all aspects of child development, screening, immunization, safeguarding, family health and parenting.
Marlow N, Wolke D, Bracewell MA, Samara M; EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2005;352:9–19.

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Hayley Griffin, Katherine Martin, Nadya James

Developmental problems and the child with special needs

Question 5.1

The epidemiology of disability

Which of the following statements BEST describes the epidemiology of disability in the UK? Select ONE answer only.

A. All children with a disability should be seen at a pupil referral unit

B. Around half of children with a disability have a Statement of Special Educational Needs, and around half of these attend a mainstream school

C. Disability typically affects 1–2% of the childhood population and most children in the UK with a disability attend a state-funded special school

D. Most children with a Statement of Special Educational Needs have either a physical disability or a sensory impairment

E. Nearly all children with a disability have a Statement of Special Educational Needs and attend a mainstream school

Answer 5.1

B. Around half of children with a disability have a Statement of Special Educational Needs, and around half of these children attend a mainstream school. See below for discussion.

Definition and numbers

In the UK, there are 770,000 children under the age of 16 years with a disability. This is about 1 child in 20. In January 2013, 229,390 children in England (2.8% of school-aged children) had a Statement of Special Educational Needs (SSEN), which is a legal document that sets out the special educational help which a child must receive by law. The document is issued by the local education authority (LEA) and is based on the needs, following assessment, of the individual child, drawn up from reports from health services (if applicable) and education. The percentage of children in receipt of an SSEN has remained unchanged for the past five years. Most children (53%) with an SSEN attend a mainstream education setting. Other settings include state-funded special schools (39.6%), independent schools (4.9%), non-maintained special schools (1.8%) and pupil referral units (0.7%).

The most common types of need for which children receive an SSEN are moderate or severe learning disability, speech, language and communication needs, behaviour, emotional and social difficulties, and autism spectrum disorders (ASD). The percentage of SSENs issued to children with a physical disability is around 6%, with children with sensory impairments making up another 5%.

At the end of 2014, a new system was launched in England for the assessment of a child's needs. This replaced the SSEN and is called the Education, Health and Care Plan (EHCP). The purpose of this multi-disciplinary assessment is to provide a more holistic view of a child's needs and includes assessments from health services, education and social care, as well as input from the family and child or young person themselves, before a document detailing a child's needs in each of these areas is drawn up. The new process is designed to be more rapid, with a target of completion in six months and to have more involvement of the family.

Causes of developmental problems

Early identification of children with severe or complex needs is required to ensure that early intervention programmes are initiated to offer support to parents and to ensure that a child's developmental potential is reached. A child with disordered development must be investigated rationally in line with a good clinical history and full physical examination, ensuring that a thorough assessment of the child's development in all areas is made. There are many potential causes of developmental problems in children, and these may be broadly classified as prenatal, perinatal, and postnatal (Table 5.1).

A great deal of information can be gained from observing the child playing in the clinic room, and it is sometimes of value to observe the child in other settings, such as nursery, school or in the child's home. Investigation to look for an underlying aetiology informs discussion with parents, identifies treatment opportunities, guides management, and can be helpful for future pregnancies.

The clinical manifestations of disordered development

This section will deal with different presentations of disordered development, subdivided into the broad developmental categories. In reality, however, impairment in one area of development often co-exists with developmental impairment in another area.

Gross motor development

Children who present predominantly with motor difficulties, and who have an underlying pathology, are usually hypotonic, hypertonic, or have a global learning disability which impairs their intellectual ability to acquire motor skills.

Table 5.1 Potential causes of developmental impairment

Prenatal	Perinatal	Postnatal
Genetic Single gene disorders (inherited or new mutation) Chromosomal microduplications or deletions Aneuploidy or tetraploidy	**Preterm birth** 55–60% of children born at 24–25 weeks' gestation have some degree of impairment, with around 15% having severe impairment (EPICure 2)	**Infection** Meningoencephalitis (viral or bacterial)
Toxins Alcohol (fetal alcohol spectrum disorder) Smoking (intrauterine growth restriction) Medication (e.g. valproate and spina bifida) Recreational drugs (e.g. stimulants)	**Infections** Bacterial (e.g. Group B streptococcal or other bacteria) or viral	**Traumatic brain injury** Accidental or non-accidental Drowning Hanging/strangulation Road traffic accidents Conflict related (e.g. war-affected areas)
Infections Congenital infection (e.g. toxoplasma, rubella, CMV, etc.)	**Hypoxic-ischaemic encephalopathy**	**Brain tumour** Direct effect or treatment
Other Placental insufficiency and growth restriction Intrauterine cerebral arterial or venous infarction Congenital brain malformation (e.g. lissencephaly)	**Physical** Traumatic brain injury	**Inborn errors of metabolism** Impact on development often only after independent of placental support
Note: 75–80% of cases of cerebral palsy are due to antenatal events rather than injury occurring around the time of birth		**Environmental** Inadequate nutrition Psychosocial adversity

Upper motor neuron lesions

Question 5.2

Cerebral palsy

An 18-month-old child attends the child development centre for a thorough assessment with a suspected diagnosis of cerebral palsy. Which of the following clinical features would be most likely to suggest an alternative diagnosis? Select ONE answer only.

A. Dystonia

B. Family history of cerebral palsy

C. Hyperkinesia

D. Prematurity

E. Spasticity

Answer 5.2

B. Family history of cerebral palsy. The explanation is considered below.

Upper motor neuron lesions usually present with hypertonia. The most common disabling condition in children with hypertonia is cerebral palsy, particularly of the spastic and dystonic type, where there is loss of the usual balance of excitatory and inhibitory muscle control.

Cerebral palsy

Cerebral palsy is a descriptive term which has been defined as 'a group of permanent disorders of movement and posture causing activity limitation that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour, by epilepsy, and by secondary musculoskeletal disorders'.

Children with cerebral palsy are not always hypertonic, but there are four main clinical types, some of which have well-described associations with underlying pathologies (Table 5.2).

1. *Spasticity*: This is a velocity-dependent increase in tonic stretch receptors. Assessment of spasticity must be dynamic and is often described as feeling like a 'clasp knife'.
2. *Dystonia*: This is spasm and sustained contraction of a muscle, leading to abnormal posturing. In time, it can lead to contractures. It is often described as feeling like 'lead-pipe rigidity'.
3. *Ataxia*: Uncoordinated movements linked to a disturbed sense of balance and depth perception.
4. *Choreo-athetoid*: Hyperkinesia (excess of involuntary movements). These are often writhing in nature.

Children with cerebral palsy often have a mixed picture of movements, and this classification does not accurately describe how severely disabled the child is by their movement disorder. The Gross Motor Function Classification System (GMFCS) scale is useful as it describes the functional ability of a child's gross motor skills rather than focusing on the individual type of cerebral palsy.

Cerebral palsy can be mimicked by several other conditions and before making a firm diagnosis

Table 5.2 Common patterns of cerebral palsy*

Pattern of cerebral palsy	Area of brain commonly affected	Potential causes
Unilateral spastic (~25%)	Infarction within distribution of middle cerebral artery (Left middle cerebral artery distribution more commonly affected than right)	• Intrapartum asphyxia • Ischaemia (stroke) in late third trimester • Intraventricular haemorrhages (IVH) related to preterm birth
Bilateral spastic (~55%, roughly equal proportions diplegia to quadriplegia)	Bilateral cerebral hemisphere infarction Cerebral dysgenesis	• Genetic • Infections in early pregnancy (CMV, toxoplasmosis) • Vascular accidents/malformations Less commonly: • Neonatal meningitis or metabolic insult • Postnatal causes
Dyskinetic (~15%)	Discrete gliotic lesions in the putamina and thalami	• Acute profound asphyxia in late third trimester or intrapartum (e.g. cord prolapse, antepartum haemorrhage, uterine rupture) • Bilirubin encephalopathy (kernicterus)
Ataxic (~5%)		• Abnormal development of cerebellum • Dysmorphic syndromes Less commonly: • Postnatal infection or trauma

*Many patients have a mixed clinical picture, and hypotonic cerebral palsy is also recognized.

Table 5.3 Conditions that can mimic cerebral palsy

- Spinal cord tumours
- Channelopathies
- Sandifer syndrome
- MECP2 duplication
- Congenital dopa-responsive disorders
- Genetic spastic paraplegia
- Some metabolic conditions (GLUT1 deficiency, glutaric aciduria type 1)
- Ataxia telangiectasia

the differential diagnosis needs to be considered (Table 5.3).

Particular care should be taken when there is a 'family history' of cerebral palsy to check that there is not an underlying inheritable cause. One must also ensure that a child who presents with 'ataxic cerebral palsy' does not have a treatable or definable underlying cause.

Question 5.3

Management of cerebral palsy

Regarding the management of cerebral palsy, which of the following statements are true (T) and which are false (F)?

A. Baclofen passes freely across the blood–brain barrier
B. Botulinum toxin has permanent effects
C. Dantrolene commonly causes sedation
D. Diazepam mainly acts upon GABA receptors within the muscle
E. Tizanidine acts centrally, mainly within the motor cortex, on alpha-2 receptors

Answer 5.3

All false (see below).

Management of cerebral palsy

Meeting the child and family's complex needs requires a multi-disciplinary team (see below). Here, we will describe some of the drugs and procedures which may be helpful.

Specific drug management of spasticity

Drugs used in the management of spasticity and their sites of action are shown in Figure 5.1.

Diazepam: Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter regulating neuronal excitability in the nervous system. It has a direct effect on muscle tone. Diazepam is a GABA agonist. Due to its central location of action, it relieves spasticity and muscle spasms, but it has additional effects of
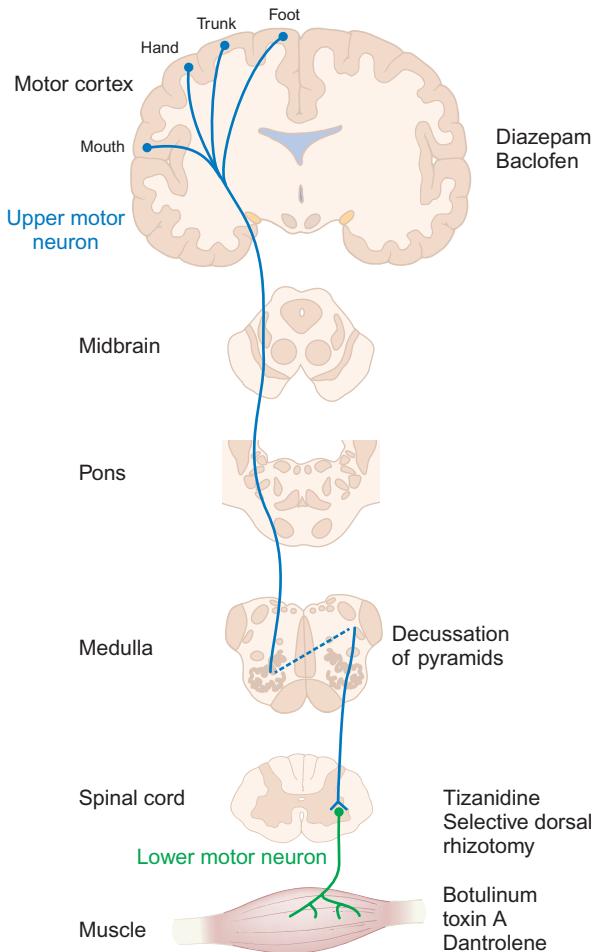
Fig. 5.1 Drugs and their sites of action in the management of spasticity.

sedation and acts as an anxiolytic. Long-term use can create dependency, but short-term use can be helpful for painful spasms (for example, after surgery), or to break cycles of distress and increasing spasticity.

Baclofen: Baclofen is also a GABA agonist and inhibits neuronal transmission at a spinal level. Its main adverse effect is sedation, which often limits its use. Its passage into the CSF when given orally is poor and high doses are often needed. When used intrathecally, via a surgically implanted continuous-delivery pump, only a tiny fraction of the equivalent oral dose needs to be given. This allows greater efficacy with fewer adverse effects.

Tizanidine: Tizanidine is an alpha-2 adrenergic receptor agonist and acts at the spinal level to help relieve spasms. It is particularly useful in children who are severely disabled by cerebral palsy and in those with night-time spasms, as it commonly has a sedative effect.

Botulinum toxin A: Botulinum toxin A works by chemically denervating the muscle, allowing the

muscle to relax and thus improving function and cosmesis in some cases. It works by cleaving synaptosomal-associated protein (SNAP-25), which is a cytoplasmic protein which aids in the process of attaching the synaptic vesicle to the pre-synaptic membrane. This then stops the release of acetylcholine at the synapse and blocks neurotransmission. The effects gradually wear off (over about 3–6 months) as the myelin sheath retracts and new terminals are made, which form contacts with the myocyte to resume neurotransmission.

Dantrolene: Dantrolene works on spasticity and spasms by affecting the calcium uptake into skeletal muscles and decreasing the free intracellular calcium concentration. Sedation is less of a problem with dantrolene than with the other drugs mentioned, but it should be used cautiously as it can cause hepatic dysfunction and blood dyscrasias.

Other treatment for spasticity

Selective dorsal rhizotomy (SDR): There has been renewed interest in the use of selective dorsal rhizotomy to treat spasticity, particularly in the more mobile groups of children with cerebral palsy (GMFCS levels 2 to 3). This surgical procedure divides some of the lumbar sensory nerve roots, thus interrupting the

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Question 5.4

The hypotonic (floppy) infant

A male infant is born at term but develops unexpected respiratory distress in the first few hours of life. He is admitted to the neonatal intensive care unit and started on antibiotics. Upon examination, he is noted to be hypotonic.

From the following list of possible anatomical locations (A–I), pick the area predominantly affected by pathology in each of the conditions (1–4) listed below:

A. Anterior horn cell

B. Cortex

C. Cerebellum

D. Muscle

E. Neuromuscular junction

F. Peripheral nerves

G. Spinal cord

H. Spinothalamic tract

I. Unknown

1. Spinal muscular atrophy
2. Congenital myasthenia gravis
3. Down's syndrome
4. Congenital myotonic dystrophy

Answer 5.4

1. A. Anterior horn cell
2. E. Neuromuscular junction
3. I. Unknown
4. D. Muscle

See below for discussion.

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sensory–motor reflex arc responsible for increased muscle tone. Pre-operative assessment must include bladder assessment due to the risk of affecting continence, and children and families must be counselled about the risks. The child's general level of gross motor function is unlikely to change significantly, but there may be improvements in quality of gait together with improved comfort and ability to tolerate splints and postural management programme.

Central hypotonia

It is helpful to make a clinical distinction between central hypotonia (affecting predominantly the head and trunk), generalized hypotonia and weakness (affecting all aspects), and peripheral hypotonia (affecting predominantly the limbs). Moderate to severe central hypotonia (other than in a few specific cases) tends to be identified in the neonatal period, where these babies may present with respiratory difficulties, feeding difficulties or as a 'floppy baby'.

Investigations may include:

- Microbiological tests (if presenting in neonatal period, to rule out sepsis)
- Neuroimaging
- Blood ammonia and lactate levels (inborn errors of metabolism)
- Plasma and urine amino acids and urine organic acids (organic acidaemias)
- Very long chain fatty acids (peroxisomal disorders)
- Microarray-based comparative genomic hybridization (microarray-CGH)

Specific disorders to be considered include: aneuploidy (e.g. Down's syndrome), single gene disorders (e.g. Prader–Willi syndrome), metabolic disorders (e.g. peroxisomal disorders) and structural (e.g. structural brain malformations). We present these below as examples of how these different disorders may present.

Down's syndrome

Down's syndrome is caused by an additional copy of chromosome 21, either due to non-disjunction (most commonly), by a rearrangement of genetic material, called an unbalanced translocation, where extra genetic

material associated with chromosome 21 is inherited, or by mosaicism (see Chapter 9, Genetics).

Babies with Down's syndrome have typical dysmorphic features and are centrally hypotonic. They show delay in all of their developmental milestones and may have initial feeding difficulties. They may have associated congenital anomalies, including heart defects (present in up to 50% of infants). Children with Down's syndrome will have ongoing additional physical and learning needs throughout childhood and into adulthood.

Many newborn children with Down's syndrome have flaccid muscles and are described as 'floppy'. In some children, this disappears as the child develops, but many remain in this 'floppy' state. There are a few follow-up studies of infants with Down's syndrome and it seems that this infantile floppiness does improve over time. There is a fairly widespread belief that the children remain with a degree of hypotonia and this state is often invoked as being responsible for much of their delay in motor milestones and impaired motor function.

However, this is controversial since there is no proper agreement as to either the exact cause or the definition of hypotonia and there is no consensus as to how to measure it. Some recent studies have shown that the hypotonia seen when children and adults with Down's syndrome are not moving (i.e. their tendency to have more 'floppy' muscles at rest) does not actually impair coordinated movement. The fact that the muscles are floppy at rest suggests there may be some peripheral component to the observed hypotonia.

Prader–Willi syndrome

Prader–Willi syndrome is caused by a deletion on the long arm of the paternally inherited chromosome (15q13) in 70% of cases, or due to maternal uniparental disomy (25%). The remaining 5% are due to an imprinting defect, and only this form carries an increased risk for future pregnancy.

Prader–Willi syndrome should be considered in babies with feeding difficulties, those requiring nasogastric tube feeding, sticky saliva, extreme hypokinesia and a combination of central hypotonia and limb dystonia. Children with Prader–Willi syndrome also have distinctive facial characteristics and other dysmorphic features. Despite initial poor feeding, children with Prader–Willi syndrome begin to show increased appetite as they grow. This can lead to excessive eating (hyperphagia) and life-threatening obesity. They also have hypogonadism, causing immature development of sexual organs and delay in puberty. Learning disabilities can be severe. They tend to be particularly impaired in their emotional and social development.

Peroxisomal disorders

Peroxisomes are spherical organelles within cells containing important oxidative and other enzymes. Babies with peroxisomal disorders tend to present with extreme hypotonia of the neck in the context of general neonatal hypotonia.

Peroxisomal disorders can be divided into two categories:
- 'Global' peroxisomal disorders, where few or no peroxisomes are generated or where there are single peroxisomal enzyme defects that induce a similar phenotype.
- Adrenoleukodystrophy, which is an X-linked inherited condition, caused by a defect in the gene that codes for one of the ATP-binding transporters within the cell.

Measurement of very long chain fatty acids may detect some peroxisomal disorders, but there is no 'metabolic screen' which will detect all of them. Results must be correlated with clinical findings.

Particular clinical features which should be sought where a peroxisomal disorder is suspected in a hypotonic child include:
- Neonatal seizures
- Retinal blindness (Leber amaurosis)
- Sensorineural deafness
- Dysmorphic features of specific syndromes (e.g. Zellweger)
- Hepatomegaly
- Leukodystrophy
- Neuronal migration defects

Suspicion of a peroxisomal disorder should be present where a school-age boy shows developmental regression in the context of previously normal development (although there may be a number of other causes for this) and in older girls with spastic paraplegia.

Brain malformations

This category is very broad. There are many structural malformations within the brain which can lead to abnormal tone. One needs to ensure that the malformation is not caused by a metabolic disorder, which may require specific management.

Neuromuscular disorders

Neuromuscular disorders are conditions that lead to the impairment of muscle function, either directly or indirectly. In terms of pathophysiology, there are four major sites of pathology to consider: anterior horn cells, peripheral nerves, neuromuscular junction and muscle.

Anterior horn cells

Nerve impulses generated in the anterior horn cells lead to activation of muscle fibres. Anterior horn cell disease usually leads to a specific pattern of weakness depending on the affected part. This is because medial cells innervate proximal muscles, whilst lateral cells innervate more distal muscle groups.

Disruption of anterior horn cells can lead to denervation, and the damaged alpha motor neurons produce spontaneous action potentials. These spikes cause the muscle fibres that are part of that neuron's motor unit to fire. This causes muscle twitches. We observe them as fasciculations. Reflexes are also lost.

As further degeneration occurs, only the remnants of the axon close to the muscle fibres remain. These individual axon fibres can also generate spontaneous action potentials; however, these will only cause individual muscle fibres to contract, resulting in fibrillation on electrophysiological testing (rarely performed nowadays).

Spinal muscular atrophy

This is an autosomal recessive genetic condition caused by a defect in the *SMN1* gene on chromosome 5, which encodes the SMN protein. SMN is necessary for the survival of motor neurons and where there is a deficit of this protein, death of neuronal cells in the anterior horn of the spinal cord occurs. The muscles with the largest number of motor neurons, i.e. those with the biggest mass, are the most severely affected; namely, the proximal muscle groups (e.g. trunk, neck, and hip muscles).

There is a spectrum of clinical severity in this disorder, but all types can be confirmed by testing for *SMN1* gene deletion. In type 1 (Werdnig–Hoffmann disease), the most severe form of the disease which presents in infancy, there are the characteristic features of anterior horn cell disease, including tongue fasciculations, which are almost pathognomic. Children are hypotonic and areflexic and develop early respiratory symptoms. Death is usually within a matter of weeks or months.

At the same location as *SMN1* is a centromeric gene, *SMN2*, which also codes for SMN protein. Most people have two copies of *SMN2*. In a child with SMA, the presence of normal copies of *SMN2* can partially compensate for the absence of normal *SMN1* function. If a child with SMA has only one or no copies of *SMN2*, their clinical course will be more severe.

Electromyography (EMG) and muscle biopsy findings are non-specific and, if there is clinical suspicion of spinal muscular atrophy, molecular genetic studies should be requested.

Spinal muscular atrophy with respiratory distress

Spinal muscular atrophy with respiratory distress (SMARD) may present between 6 weeks and 6 months of life, with respiratory failure secondary to diaphragm weakness. The diagnostic test for this disorder is to look for mutations in the *IGHMBP2* gene. The condition follows an autosomal recessive inheritance. Diaphragm eventration tends to be associated with this disorder.

Cervical cord damage

Congenital malformation of the cervical cord or injury during the intrapartum period can cause long-term disability. It may be difficult to differentiate between signs and symptoms related to a neonatal encephalopathy and those related to cord abnormalities, and MRI of the cervical cord and nerve routes is diagnostically useful.

Peripheral nerve problems

In disorders of the peripheral nerve, distal involvement is a key feature, especially at the onset. There may be both motor and sensory features. A good example of this is hereditary motor and sensory neuropathy (HMSN) type 1a (Charcot–Marie–Tooth syndrome), which is caused by gene mutations that cause defects in neuronal proteins, and in most types this affects the myelination of the peripheral nerves. Nerve conduction studies show reduced nerve conduction velocity.

Purely demyelinating disorders include Guillain–Barré syndrome. In this acute disorder, the motor fibres are affected most severely, with little or no loss of pain and temperature sensation. The explanation for this is that type I and II nerve fibres are myelinated, and have reasonably fast conduction velocities, whilst type III and IV fibres, which are responsible for pain and temperature control, are lightly myelinated and unmyelinated, respectively.

Neuromuscular junction problems

A nerve impulse which reaches the neuromuscular junction activates calcium channels, which in turn leads to regulation of acetylcholine. Acetylcholine leads to muscle contraction via further post-synaptic action.

When acetylcholine is depleted or its regulation is affected, features such as fatigability and diurnal variation become salient in the history of the presenting complaint. This is reflected in clinical conditions affecting the neuromuscular junction, such as congenital myasthenic syndromes and myasthenia gravis.

Myasthenia

Congenital myasthenic syndrome can be divided into three types, depending upon where the defect is: pre-synaptic, synaptic or postsynaptic.

Most children with congenital myasthenic syndrome have a gene mutation in one of several genes encoding the acetylcholine receptor, leading to a deficiency at the endplate. Most of these gene mutations are autosomal recessive in their inheritance and lead to loss of function of the protein which they encode.

Congenital myasthenic syndromes should be considered in any infant presenting with stridor, respiratory difficulties (including apnoeas) and feeding difficulties, in the context of general hypotonia.

Intravenous edrophonium (Tensilon) testing may be difficult to interpret and a trial of pyridostigmine or neostigmine prior to a feed may be easier for assessing response and, therefore, making a clinical diagnosis.

A thorough clinical history needs to be taken and the child's mother assessed for evidence of maternal myasthenia. There are a number of genes which have been identified as being associated with this disorder, and genetic testing needs to be carried out at a national myasthenia reference laboratory.

Alternatively, stimulation single-fibre electromyography (StimSFEMG) may be helpful to detect a decremental response following repetitive nerve stimulation.

Question 5.5

Duchenne muscular dystrophy

A four-year-old boy is noted by teachers to be unable to keep up with his classmates in physical exercise. He tires easily and has difficulty climbing stairs. There are concerns about his reading and writing. His creatine kinase test is grossly elevated at 18,000 IU/L. He is suspected to have Duchenne muscular dystrophy (DMD).

Concerning DMD, which of the following statements are true (T) and which are false (F)?

A. Dystrophin protein is mainly found in skeletal and cardiac muscle.
B. Calf pseudo-hypertrophy occurs because damaged muscle fibres are replaced by adipose and connective tissue.
C. The characteristic early feature of Gower's sign is use of the hands climbing up the legs in order to stand.
D. Corticosteroid therapy is used to preserve mobility and prevent scoliosis.
E. The creatine kinase is raised because of muscle necrosis.

Answer 5.5

A. True. This is why absence or depletion of dystrophin protein results in muscle weakness and cardiomyopathy.
B. True.
C. False. The key early feature is needing to turn prone in order to stand; climbing up the legs is a late feature.
D True.
E. True. Creatine kinase is an enzyme which is abundant in skeletal muscle and has a role in producing ATP from creatine (as an alternative to the Krebs pathway). It leaks into the blood in significant quantities in conditions that lead to muscle necrosis.

Muscle problems

Congenital myotonic dystrophy

Two types of myotonic dystrophy exist. Type 1 (Steinert disease) tends to present earlier and affected children can show signs from birth. Type 2 tends to be detected later and is a less severe form of the condition.

Myotonic dystrophy is inherited in an autosomal dominant pattern and is one of several known trinucleotide repeat disorders. The gene for myotonic dystrophy type 1 is located on the long arm of chromosome 19. Mutations in this gene lead to expansion of the cytosine–thymine–guanine (CTG) triplet repeat in the *DMPK* gene, which codes for myotonic dystrophy protein kinase. The greater the number of trinucleotide repeats, the more severely affected the child will be.

Where congenital myotonic dystrophy is suspected, maternal examination, electromyogram and molecular genetic analysis for trinucleotide repeats will confirm the diagnosis.

Duchenne muscular dystrophy (DMD)

This is the most common muscular dystrophy. It should be suspected in any boy with delayed motor milestones and can be associated with learning difficulties, disordered speech and features of an autistic spectrum disorder, just to name a few of the important co-morbidities. Boys often have pseudohypertrophy of their calves.

It is caused by a mutation of the dystrophin gene, which codes for dystrophin, a protein usually found in muscles. This gene can be found at locus Xp21 and is inherited in a recessive X-linked pattern, but it can rarely affect girls. Dystrophin is an important structural component within skeletal and cardiac muscle.

It is a rod-shaped protein bound at one end to the sarcolemma and to the outermost actin filaments of the myofibril at the other end. It therefore provides a cytoskeleton for the muscle fibre. Absence of dystrophin allows excess calcium to penetrate the muscle cell membrane, causing alteration of signalling and leading to muscle degeneration and death.

Where DMD is suspected, blood creatine kinase level should be measured, and genetic testing undertaken to identify the specific exon mutation if it is elevated. The muscle-specific form of the dystrophin gene is formed of 79 exons and analysis can usually identify the specific type of mutation. If genetic testing fails to find a mutation, muscle biopsy is useful to demonstrate the absence of dystrophin on staining and this is confirmatory of a diagnosis of DMD.

Becker muscular dystrophy is the milder phenotype, also caused by dystrophin gene mutations.

Medical issues common to children with neurodisability

There are a number of medical problems which are more common in children with disability. These include:

Gastro-oesophageal reflux disease (GORD)

Gastro-oesophageal reflux (the non-forceful regurgitation of gastric contents into the oesophagus) is more common in children with neurodevelopmental problems for a number of reasons. Intra-abdominal pressure may be increased for structural reasons such as scoliosis, the lower oesophageal sphincter may be functionally immature as a reflection of abnormal muscle tone elsewhere in the body, and difficulties in upright positioning may also exacerbate gastro-oesophageal reflux.

First line management is postural, with supportive upright seating and sleeping positioners, along with adjustment of feed consistency if required. In addition, pharmacological agents to alter acid production or gastric motility are used:

- *Proton-pump inhibitors* (e.g. omeprazole, lansoprazole, esomeprazole): These medications block the hydrogen–potassium adenosine triphosphatase enzyme system of the gastric parietal cell, the 'proton pump', inhibiting acid production.
- *H_2-receptor antagonists* (e.g. ranitidine): Histamine H_2-receptor antagonists reduce gastric acid output by the antagonism of histamine H_2-receptors.

- *Dopamine receptor antagonists* (e.g. domperidone): Dopamine receptor antagonists stimulate gastric emptying and small intestinal transit. They also help with GORD by enhancing the tone of the oesophageal sphincter.
- *Compound alginate preparations* (e.g. Gaviscon, Gaviscon Infant, Peptac): These medications increase the viscosity of stomach contents and can protect the oesophageal mucosa from acid reflux. Some preparations form a viscous substance which floats on the surface of stomach contents, thus reducing episodes of reflux.

In children with severe symptoms of GORD, surgical intervention such as a Nissen's fundoplication may be considered. Here, the gastric fundus is plicated around the lower end of the oesophagus and sutured into place, reinforcing the lower oesophageal sphincter.

Respiratory complications

Neurological disturbance in children with neurodisability impairs the ability of the child to protect their airway, leading to acute or chronic ('silent') aspiration and liability to chemical pneumonitis or secondary infection with anaerobic organisms. The neural control centres responsible for coordination of breathing and swallowing are contained in the dorsomedial and ventrolateral medullary regions of the brainstem. The areas involved in the swallow-related motor output to the muscles of the mouth, pharynx and larynx include:

- The trigeminal motor nucleus located near the level of the mid pons
- The facial motor nucleus located at the level of the caudal pons
- The nucleus ambiguus, running rostrocaudally in the medulla
- Hypoglossal motor nucleus.

There is also an element of cortical control in the coordination of respiration and swallowing.

The underlying mechanism leading to aspiration may be abnormal tone of the facial and swallowing muscles or may be part of a condition causing abnormal tone throughout the body (e.g. cerebral palsy or spinal muscular atrophy). Direct damage to the swallow and respiration control centres may occur for a number of reasons, including traumatic brain injury, stroke or brain tumour.

Children with disability may also have structural impairment to chest movement and lung capacity (for example, scoliosis), and difficulty clearing respiratory secretions. This can be due to direct weakness (e.g. spinal muscular atrophy) or due to reduced cough reflex (e.g. brain injury).

In addition to the above factors increasing risk of aspiration and thus lung infection, abnormal immune function may be a part of the underlying disorder. An example is Down's Syndrome, where low tone combines with structural differences and impaired immunity, including low levels of blood immunoglobulins and impaired vaccine responses as well as abnormal lymphocyte subsets.

Drooling

Children with neurodevelopmental conditions may continue to drool beyond the age of 4 years (which is the age up to which drooling may be considered normal). This may be due to a number of reasons, including:

- Abnormalities in swallowing (as discussed above)
- Difficulties moving saliva to the back of the throat
- Poor mouth closure
- Tongue thrusting.

Intervention may be conservative, including rewarding and behavioural methods, pharmacological or surgical.

Pharmacological interventions may include:

- *Anti-muscarinic drugs* (e.g. hyoscine hydrobromide, glycopyrronium bromide): These agents reduce drooling by acting as a competitive antagonist at muscarinic acetylcholine receptors, specifically M_1 receptors. This causes blockade of the parasympathetic innervation to the salivary glands, causing reduction in saliva production.
- *Botulinum toxin*: Botulinum toxin inhibits acetylcholine release in nerve terminals, mainly at the neuromuscular junction, but also in sympathetic and parasympathetic ganglion cells and in postganglionic parasympathetic nerves. It may be injected directly into the parotid gland to inhibit parasympathetic innervation and reduce saliva production.

Surgical interventions may include:

- Diversion of parotid ducts into the tonsillar fossae region, so that saliva is directed into the pharynx rather than the front of the mouth.
- Salivary gland resection.

Constipation

Although constipation is common in the paediatric population as a whole, its prevalence is much greater amongst children with neurodisability. This may be due to a number of factors, including abnormalities of muscle tone, which includes the muscle of the bowel wall, restricted diet low in fibre due to difficulties in chewing and swallowing, and mobility difficulties (normal upright mobility will aid transit of waste through the bowel). Treatment is via diet and lifestyle modification in combination with one or more laxatives.

- *Stimulant laxatives* (e.g. bisacodyl, docusate sodium, glycerol suppositories, senna, sodium picosulphate): These drugs increase intestinal motility. Care should be taken to use in conjunction with faecal softeners where necessary to lessen the possibility of abdominal cramps.
- *Osmotic laxatives* (e.g. lactulose, macrogol 'Movicol', phosphate enema 'Fleet enema', sodium citrate enema 'Microlax enema'): Osmotic laxatives either draw fluid from the body into the bowel (lactulose), or are taken with fluid which is then retained within the bowel lumen (Movicol).

Temperature regulation

Children with complex neurodisability can present with hypothalamic dysfunction and temperature dysregulation. The body's thermoregulation centres are in the anterior hypothalamus (preoptic area) and receive input from peripheral thermoreceptors in the skin and mucous membranes and from central thermoreceptors, including the hypothalamus itself. The sensory signals from the preoptic area and those from the peripheral thermoreceptors are combined in the posterior hypothalamus to control the heat producing and conserving actions of the body via the autonomic sympathetic nervous system and neuroendocrine system (e.g. shivering, piloerection, skin vasoconstriction). In addition, a child with neurodisability may be unable to voluntarily respond to temperature change, for example by seeking warmth.

Sleep difficulties

Many disabled children have difficulties with sleep initiation or maintenance. A good sleep consultation should consider if sleep is disturbed by pain (e.g. from constipation, GORD or orthopaedic pain), by epileptic seizures, or by sleep disorders such as sleep-disordered breathing.

Often children with neurodevelopmental disorders have circadian rhythm abnormalities. This is particularly common in children with ADHD, which has been shown to be genetically linked with polymorphisms in genes common to ADHD and circadian rhythm. The other group of children in which circadian rhythm disturbances are more common is those with visual impairment, where environmental clues about sleep can be missed.

Sleep should be managed initially with advice about good sleep hygiene and explanation of the

sleep–wake cycle, including normality of short periods of wakening during the night. Children should learn how to self-soothe back to sleep during these periods of awakening from less than a year of age. This ability may be impaired or delayed in children with neuro-developmental disorders.

In children where sleep initiation is an ongoing difficulty, despite a well-established and healthy bedtime routine, melatonin may be used to promote sleep. Melatonin is a hormone that is naturally produced by the pineal gland in response to stimulation of the suprachiasmatic nucleus at the onset of darkness. Circadian clock mechanisms involve periodic gene expression, which are synchronized by the hypothalamic suprachiasmatic nuclei. The products of these clock genes (*per*, *frq*, *clock*, *tau*) and their biochemical roles are not known. Supplemental melatonin can help by promoting sleep initiation. Short-term use of sedating antihistamines, such as alimemazine, or hypnotics, such as chloral hydrate, may be considered in selected cases, but as a last resort where sleep difficulties are severe or disabling in themselves.

Orthopaedic complications

Hip subluxation and dislocation

Hip subluxation or dislocation occurs in 60% of children with cerebral palsy who are not walking at the age of five years. It can result in pain, increasing deformity, inability to sit, functional restrictions and may lead to spinal deformity. All children with conditions causing disorders of muscle tone are at risk of hip dislocation, those with hypertonia are at a greater risk than those with hypotonia. The mechanism by which hip dislocation/subluxation arises is not known. It is thought that a hip joint which is normal at birth may develop change in proximal femoral anatomy, due to the effects of delayed motor development and tonal asymmetry. Spasticity and shortening of muscles around the hip joint and lack of ambulation will also impact on bony development and joint position.

There are two elements of hip subluxation/dislocation: acetabular dysplasia and femoral head displacement. Current guidance is that children with bilateral cerebral palsy should have routine surveillance of the migration indices of their hips by measurement of the migration percentage on an anteroposterior pelvic X-ray. A hip migration percentage of 33% or more is suggestive of hip subluxation or dysplasia, but the exact figure at which dislocation is said to have occurred is not universally agreed.

Spinal deformity

Scoliosis is a lateral curvature of the spine, although in reality it is a complex three-dimensional deformity. Children with abnormal tone are at increased risk of spinal deformities due to motor impairment due to absence of normal weight bearing and movement. Spasticity or low tone can lead to abnormal forces on the spine leading to curvature. Children with neuro-disability should be assessed regularly for clinical evidence of spinal deformity and referred promptly for prompt assessment by a specialist spinal team where spinal deformity is detected.

Sensory development

Vision

Fine motor and vision are often considered alongside one another as visual impairment is invariably linked to other developmental domains. As well as the obvious link to fine motor skills, visual dysfunction also impacts on social development, and autism spectrum disorders are more common in this group. Visual problems are considered in more detail in Chapter 30, Ophthalmology.

Hearing and speech

Hearing impairment and the disordered development of speech are also inextricably linked and diagnosis of one should prompt assessment of the other. Where a child presents with disordered speech development, it is useful to ascertain where the difficulty in communication lies:

- Is there a problem with finding words (expressive dysphasia)?
- Is there a problem producing the sounds, which makes speech unclear (dysarthria)?
- Does the problem lie in the unusual use of speech patterns or unusual use of learned patterns of speech or phrases (semantic or pragmatic disorder)?
- Is there a problem in understanding others' communication or instructions (receptive dysphasia)?

Differentiating between these different forms of communication difficulties helps to delineate what the likely underlying problem is. To think of this simplistically:

- Difficulties in producing speech sounds or expressive speech disorders may co-exist with coordination disorders. Where a child has difficulty in the coordination of their limbs or other body parts, for a variety of reasons, as discussed earlier, they may also have difficulties in coordinating their orofacial muscles leading to unclear or poorly cohesive speech.
- In a child who has an unusual use of speech, even though their speech may appear well developed for age, a diagnosis of autistic spectrum

disorder must be considered. Children with autistic spectrum disorder may use phrases inappropriately that they have memorized or that are out of context.

- The level of a child's understanding should be assessed as part of the developmental assessment and as a part of the assessment of their utilizable communication skills. Impairment in learning skills or understanding may indicate a learning disability. Learning disability as a continuum of global developmental impairment will be dealt with later on in this chapter.

There are also specific syndromes which lead to disproportionately disordered speech development relative to the rest of a child's developmental profile. Conditions such as DiGeorge syndrome (22q11.2 deletion syndrome) can lead to this type of patchy developmental profile.

When assessing a child's speech development, it is extremely important to enquire as to whether there are any associated feeding difficulties. Again, children who have poorly coordinated orofacial muscle control are more likely to have feeding difficulties, including choking and difficulty in swallowing some textures of food.

A specific subgroup of children with impaired speech acquisition have a condition known as Worster-Drought syndrome, which is a congenital suprabulbar paresis. It is a form of cerebral palsy which specifically affects the bulbar muscles and causes feeding difficulties and disordered speech development and, in some cases, is thought to be genetic in origin.

Social development

There are a number of developmental disorders which can present with impaired social and emotional development. The most classic of these is autistic spectrum disorder, which will be discussed later in the chapter. However, social delay may be a reflection of another disability and thus improve when the underlying disorder is treated. For example, facilitating communication by use of a cochlear implant in sensorineural deafness, or providing vision aids for a child with visual impairment.

Global developmental impairment and learning disability

Children who show disordered development in two or more areas of gross motor, fine motor/vision, hearing/speech or social development are often described as having 'global' developmental impairment. This can be

an unhelpful term, and it is good practice to describe the affected domains directly. The term developmental delay has the disadvantage that it may suggest that development will catch up, which is often not the case.

Developmental impairment can be described using a developmental quotient (developmental age as a percentage of chronological age). It is broadly predictive of the degree of learning disability, the term more commonly used once a child reaches school age.

Learning disability, as defined by the World Health Organization, is '…a state of arrested or incomplete development of mind'. A person with a general learning disability is said to have a significant impairment of intellectual, adaptive and social functioning, and that this was evident from childhood. Intelligence quotient (IQ) has been used to define the severity of learning disability, with the conventional classification of an IQ of 50–70 being mild, 35–49 moderate, 20–34 severe, and <20 a profound learning disability.

Investigations into the underlying cause of a global developmental impairment may provide information to allow genetic counselling for future pregnancies, exclude treatable disorders and highlight need for other health screening, e.g. for cardiac abnormalities in certain chromosomal disorders.

Appropriate investigations will depend on individual history and examination but may include:

- MRI scan of the brain (hypomyelination, structural anomalies)
- Electroencephalogram (EEG) – unlikely to be diagnostic in itself but can be useful in some circumstances as supportive evidence for a suspected diagnosis where confirmatory testing so far has been negative or is not available – (epileptic encephalopathies (although this is usually suspected on history), Angelman syndrome (posterior high voltage 3–4 second sharps with smaller spikes on eye closure), MECP2 duplication in boys (slow background), cortical dysplasia (excess fast activity), Landau–Kleffner syndrome (temporal spikes and bilateral slow-wave discharges)).
- Microarray-CGH genetic testing (Box 5.1)
- Urine biochemistry (inborn errors of metabolism, mucopolysaccharidoses)
- Thyroid function tests
- Urea (urea cycle defects)
- Creatine kinase (muscle disorders)
- Ammonia (increased in urea cycle defects)
- Lactate (raised in some mitochondrial disorders)
- Plasma amino acids
- Transferrin isoenzymes (glycosylation disorders)
- In some cases, measuring neurotransmitters in CSF may be useful.

Developmental regression

A history of developmental regression should prompt immediate referral for investigation into underlying aetiology and ensure that there is no treatable cause.

Listed below are the more common causes of developmental regression, although developmental regression itself is rare.

Landau–Kleffner syndrome

Landau–Kleffner syndrome is a rare epileptiform disorder, characterized by the emergence of developmental issues and marked regression of language skills, together with an abnormal EEG. It usually begins between 5 and 7 years and affects twice as many boys as girls. Some 70% have epileptic seizures and in 85% the EEG pattern develops into electrographic status epilepticus of slow-wave sleep.

The cause is unknown, although many theories have been postulated, including genetic, infective and inflammatory causes. Oral steroids are often helpful. The prognosis depends upon a number of variables and encompasses a spectrum of outcomes, although most children have ongoing moderate language deficits.

Leukodystrophy

Leukodystrophy describes a group of conditions characterized by progressive degeneration of the white matter of the brain. They are caused by abnormal growth or development of the myelin sheath and are genetic in origin.

Myelin is made up of at least ten different substances and leukodystrophy occurs when a genetic defect alters the way these substances are metabolized (enzyme action) or produced.

Initially, developmental milestones are attained as expected, but then children show progressive regression in their gross motor skills, speech, ability to eat, vision, hearing or behaviour.

Examples of leukodystrophies include:

- Metachromatic leukodystrophy (deficiency of arylsulphatase enzyme)
- Adrenoleukodystrophy (disorder of peroxisomal fatty acid beta oxidation and accumulation of very long chain fatty acids)
- Krabbe disease (deficiency of galactocerebrosidase enzyme)
- Pelizaeus–Merzbacher disease (defect in gene coding for myelin proteolipid protein 1)
- Canavan disease (deficiency of aspartoacylase enzyme)
- Alexander disease (defect in gene coding for glial fibrillary acidic protein).

In general, the prognosis for children with leukodystrophy is poor, although this varies between the different types. Management should be directed towards symptomatic and supportive care. Clinical trials looking at gene replacement, bone marrow transplantation and enzyme replacement have been undertaken.

MECP2 duplication syndrome

This condition occurs almost exclusively in males and, although many children show disordered or impaired development from infancy, some affected boys show developmental regression and seizures.

MECP2 duplication syndrome is caused by duplication of genetic material on the long arm of the X chromosome. Genes other than the *MECP2* gene may also be involved.

Management is symptomatic, based on the clinical manifestations of the syndrome.

Rett syndrome

Rett syndrome is a disorder of the grey matter of the brain, mostly affecting girls, but it has also been seen in a small number of males. Developmental regression tends to start after a period of static developmental progress and usually between the ages of 6–18 months.

It is caused by mutations on the *MECP2* gene located on the X chromosome. In a small number of cases (<10%), mutations in other genes (*CDKL5* or *FOXG1*) can resemble features of Rett syndrome.

Clinical features include small hands and feet, deceleration in the rate of head growth leading to microcephaly in some girls and repetitive stereotyped midline hand movements, such as hand wringing. Children tend to have an increased incidence of gastrointestinal disorders and 80% have seizures. Girls tend to lose language skills and become non-verbal, and about half of girls do not walk.

There are clinical trials currently looking at the restoration of the *MECP2* gene function.

Males with *MECP2* mutations usually die within the first two years of life from complications of severe encephalopathy. Females with Rett syndrome can have a relatively normal life expectancy, although this tends to be dependent upon the complications of the disorder.

Metabolic or mitochondrial disorders

Some of the inborn errors of metabolism can be managed effectively and cause little in the way of disability if the damaging effects of accumulating poisonous metabolites is counteracted. A good example of this is glutaric aciduria type 1, which should be suspected and actively sought in children with macrocephaly, as a large head circumference can be one of the earliest signs. Another example is the autosomal recessive disorder Tay–Sachs disease, where deficiency of the enzyme hexosaminidase A leads to accumulation of gangliosides in neurons and cell death.

Once a child with an inborn error of metabolism has reached the stage of regression in their developmental progress, a degree of damage to the developing brain will already have occurred and management should focus on identifying the cause to minimize further damage.

Inborn errors of metabolism should be suspected in those with a family history, a history of neonatal encephalopathy, vomiting, unusual smell of the child or urine and where several systems are involved with acute symptoms. They tend to present in a wide variety of ways and a low threshold should be had for screening for these disorders, particularly in children with unusual presentations of illness or developmental regression (see Chapter 29, Metabolic medicine).

Dravet syndrome

Dravet syndrome or severe myoclonic epilepsy of infancy (SMEI) is caused by a mutation to the *SCN1A* gene in about 80% of affected children. This gene codes for proteins that regulate the function of sodium channels. Children typically present in the first year of life with intractable, severe epileptic seizures, which may initially manifest as atypical febrile seizures.

Developmental progress tends to follow a typical course prior to the onset of seizures and then follows a period of regression. The degree of eventual developmental impairment tends to correlate with the frequency of seizures, but most affected individuals have severe learning disabilities and difficult-to-treat epilepsy.

Specific developmental disorders

The specific developmental disorders which will be discussed in this section are: attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD) and developmental co-ordination disorder (DCD). These conditions all fit into a spectrum of severity, often overlap with one another, and must be manifest in more than one situation (e.g. present both at home and at school). Sometimes the term DAMP (Deficits in Attention, Motor control and Perceptual abilities) is used to describe children with difficulties in more than one category.

The multidisciplinary team is invaluable where there are concerns about a specific developmental disorder. For example, teachers will be able to provide useful information about a child's performance and difficulties in the classroom, a child's speech and language therapist may be able to provide insight into a child's use of language and highlight features consistent with an autism spectrum disorder, and physiotherapists and occupational therapists will be able to provide guidance on whether a child's coordination difficulties are likely to be suggestive of a developmental coordination disorder.

If the child does not yet have other professionals involved in their care, it can be helpful for the clinician to observe the child themselves in different settings so that a true picture of the child's difficulties can be ascertained.

Attention deficit hyperactivity disorder (ADHD)

Background

ADHD is a disorder that classically consists of hyperactivity, impulsivity and inattention. Depending on the diagnostic criteria used, the prevalence of the disorder amongst school-age children ranges from 1–2% to 3–9%. ADHD is three times more common in boys than in girls.

Risk factors

Although the exact aetiology of ADHD is not completely understood, there are a number of risk factors which seem to be associated with the disorder:

- Preterm birth or low birth weight
- Maternal illicit drug use, alcohol use or smoking during pregnancy
- Close family history of ADHD
- History of traumatic brain injury

- Exposure to some environmental toxins, particularly lead
- Psychosocial adversity
- High levels of family conflict
- Syndromic associations, e.g. neurofibromatosis type 1

Pathophysiology

A number of studies have been undertaken in the search for a genetic basis for ADHD, but have not identified any particular gene locus for the disorder. Twin studies, adoption studies and sibling studies have been carried out and there is a strong concordance between close family history of ADHD and risk of developing the disorder.

Studies have also focused on ascertaining whether the brains of children with ADHD are different from those of their peers. It has been postulated that there are differences, both at the structural level and at the molecular level, with differences in levels of neurotransmitters.

Imaging studies have suggested that a number of regions in the brain may contribute to the clinical manifestations of ADHD. These include the frontal and parietal cortex, basal ganglia, cerebellum, hippocampus and corpus callosum. The implication is that, in children with ADHD, there are alterations in the neural networks leading to symptoms of the disorder.

Children with ADHD tend to have a general reduction in brain volume, this being particularly marked in the prefrontal cortex. Pathways connecting the prefrontal cortex and the striatum have also been shown to differ in children with ADHD, which has led to the hypothesis that the manifestations of inattention, hyperactivity and impulsivity may be secondary to frontal lobe dysfunction.

It is possible that differences in the dopaminergic pathways in brains of children with ADHD differ from age-matched controls. Stimulant medications, often used in the management of ADHD, tend to increase dopamine levels in the brain and ease the symptoms of the disorder. However, the complex interactions of neurotransmitters in the brain and non-specific mechanisms of action of stimulant medications make it difficult to conclude that dysfunction of the dopaminergic pathways is the sole aetiological factor of ADHD.

Management

In all children with ADHD, behavioural management is an essential part of management, for example through parenting support groups and parenting courses. The child may be offered extra support in school, cognitive behaviour therapy (CBT) or social skills training. It is also important that the child's school is aware of the diagnosis and that appropriate strategies are put in place for managing the child within the school environment.

In children with ADHD causing severe impairment to daily activities and learning, medication may be commenced. Prior to medicating, children undergo a full mental health and social assessment, as well as physical examination, focusing particularly on cardiovascular risk factors and including the measurement of height, weight, heart rate and blood pressure. An ECG should be performed if there is a significant family or personal history of cardiac disease.

The three main drugs of choice for ADHD are:

a) Methylphenidate (which can be dispensed in immediate-release or modified-release preparations)
b) Atomoxetine
c) Dexamphetamine

Choice of medication will depend on a number of factors, some of which are described below:

- *Methylphenidate* remains the first-line drug therapy. It is a dopamine reuptake inhibitor. It acts by blocking both the dopamine transporter and the norepinephrine transporter centrally, which leads to increased concentrations of dopamine and norepinephrine in the synaptic cleft. It is generally tolerated but can affect sleep and appetite. Taken orally, it has a peak action around 2–4 hours for instant release, 3–8 hours for sustained release, and 8–12 hours for extended release preparations. The half-life of methylphenidate is 2–3 hours, depending on the individual. Dosing must begin in the morning and be tailored to cover symptoms during the day.
- *Atomoxetine* remains second line. It has a slightly smaller effect size than methylphenidate, and is useful in children where there is a risk of stimulant diversion by the family or where there is co-morbid tic disorder, Tourette's syndrome, anxiety disorder or history of stimulant misuse. However, it does not affect sleep or appetite as much, but has been associated with liver problems and suicidal thoughts. Atomoxetine acts primarily on the norepinephrine pathway, and differs from methylphenidate in that it acts as a longer term agent, altering the neuroendocrine environment of the brain over weeks. Not only does it take longer to work, but it also does not greatly matter when during the day it is taken.
- *Dexamphetamine* may be used where methylphenidate and atomoxetine have not been

tolerated, and is a first-line agent in some countries. Dexamphetamine is a stereoisomer of amphetamine. Amphetamines are sympathomimetic agents that cause release, and block the reuptake, of noradrenaline and dopamine from central neurons.

- In selected children, for example those unable to tolerate the above medications or those with tic disorder, clonidine may be used. It is a centrally acting alpha$_2$ adrenergic agonist and imidazoline agonist that is more commonly used as an antihypertensive agent. Other new treatments are under investigation, such as guanfacine hydrochloride (a non-stimulant selective alpha$_{2A}$ adrenergic receptor agonist).

The dose of medication should be slowly titrated upwards until there is no further improvement in symptoms, or stabilized sooner if side effects become troublesome. This titration should take 4–6 weeks in methylphenidate and atomoxetine.

Children taking medication for ADHD should be reviewed regularly, with attention paid to the potential side effects of the individual medication. In particular, weight loss and poor appetite, raised blood pressure, and sleep difficulties with methylphenidate. All of these should be assessed at each clinic appointment. Atomoxetine can lead to changes in behaviour, including self-harming behaviour and suicidal ideation.

Consideration of the ongoing effectiveness and suitability of the medication should also be made regularly.

Common co-morbidities

Other than developmental coordination disorder and autism spectrum disorders, there are a number of other common co-morbidities associated with ADHD. These include:

- Learning disabilities (20–30% of children with ADHD)
- Tourette's syndrome and tic disorders
- Oppositional defiant disorder (ODD) (50% of children with ADHD) and conduct disorder (CD) (20% of children with ADHD). Can lead on to antisocial personality disorder in adulthood in 50% of children with ADHD who also have either ODD or CD.
- Mood disorders, particularly bipolar affective disorder (in adulthood) and major depressive disorders
- Anxiety disorders
- Obsessive compulsive disorder
- Substance misuse
- Restless legs syndrome
- Sleep disorders

- Auditory processing disorders
- Language delay
- Persistent bed wetting.

Autism spectrum disorders (ASD)

Background

As the name suggests, autism spectrum disorders describe a range of disorders of varying severity but with a triad of impairments in common:

- Impaired social interaction
- Impaired verbal and non-verbal communication and impairment in imagination
- Restricted, repetitive or stereotyped behaviour

The prevalence of ASD amongst children in the United Kingdom is 0.9% and there has been a steady increase in prevalence over the last 20 years. It is difficult to know whether this is from increased awareness and identification of children with ASD or whether there has been a true increase in the number of children with ASD. It is five times more common in boys than in girls.

Associated learning disability is present in approximately half of children with ASD.

Risk factors

A single aetiological factor in the development of ASD has not been identified, but there are a number of factors which are known to be associated with an increased risk of ASD. These are:

- A family history of autism
- Preterm birth
- Parental mental health disorders (particularly schizophrenia and related disorders)
- Maternal use of sodium valproate in pregnancy
- Neonatal encephalopathy or epileptic encephalopathy, including infantile spasms
- Chromosomal disorders such as Down's syndrome
- Other genetic disorders such as neurofibromatosis, tuberous sclerosis, fragile X, Smith–Lemli–Opitz syndrome
- Muscular dystrophy

Diagnosis

In the assessment of ASD, attention must be paid to whether there is evidence of:

- Neurocutaneous markers of conditions such as tuberous sclerosis or neurofibromatosis
- Self-harm or child neglect or maltreatment
- Congenital anomalies or dysmorphic features
- Severe hearing or visual impairment

- Developmental regression (if present, Rett syndrome and epileptic encephalopathies should be considered)

Pathophysiology

There has been no one specific aetiological factor identified in children with ASD, but much research has been done looking into the genetics of the disorder, which have identified a number of proposed mechanisms.

The rate of success in identifying a specific aetiological diagnosis in children with ASD has been reported as being between 6–15%.

In particular, numerous cytogenetically detected deletions and duplications have been associated with ASD. However, this technology has been superseded by microarray-CGH, which, as discussed earlier in the chapter, detects copy number variants in the genome. About 10% of individuals with ASD have clinically significant copy number variants. If other clinical features in addition to ASD, such as microcephaly, epilepsy, congenital anomalies and dysmorphic features, are present, about 30% have copy number variants.

Management

Management of children with ASD is based upon clinical manifestations of the disorder and may include:

- Interventions for core features of ASD
- Interventions for mental health and medical co-morbidities
- Interventions for behavioural difficulties

Medications may be effectively used to treat specific co-morbidities, such as ADHD, but anti-psychotic, anti-depressant and anti-epileptic medications should not be used in the core management of autism spectrum disorder, nor should exclusion diets be recommended (e.g. gluten free, casein free).

Developmental coordination disorder (DCD)

DCD is associated with difficulties in forming ideas, motor planning and execution. The prevalence is around 5–6% of school-age children and is more common in boys than in girls. Up to 50% of children with ADHD also have DCD.

Diagnosis

Diagnosis is made on clinical history and examination providing evidence that a child's motor performance is significantly impaired relative to chronological age, and that it impacts upon daily functioning.

Management

Management is usually through occupational therapy or physiotherapy, along with adaptations in the school and home to aid motor function.

Co-morbidities

Other than ASD and ADHD, recognized co-morbidities of DCD include:

- Specific learning difficulties (e.g. dyscalculia, dysgraphia, dyslexia)
- Sensory processing disorder
- Specific language impairment.

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Lynn Sinitsky, Michael Marsh, David Inwald

Paediatric emergencies and critical care

Recognition and management of the seriously ill or injured child

The outcome of cardiac arrest in children is poor. To minimize the incidence of cardiac arrest and its consequent morbidity and mortality, a structured approach to children with serious illness or injury is required (Box 6.1). This also aids communication between health professionals and provides a safe and effective methodology for assessment of the seriously unwell child. The primary assessment systematically looks at respiratory, cardiovascular and neurological status and addresses problems as they are found. A secondary assessment is then performed, looking at each system in turn and instituting emergency treatment.

This approach, pioneered by the Advanced Life Support Group (ALSG) has been shown to be effective in reducing mortality. Following an ALSG education programme in Gambia, there was a 50% reduction in maternal mortality, a 32% reduction in infant mortality and a 94% survival rate in resuscitation.

Monitoring and post-resuscitation management

As part of recognition and management of critically ill children, whatever the underlying cause, the following physiological variables should be monitored:

- Respiratory rate
- Heart rate
- Blood pressure
- Oxygen saturation
- Electrocardiogram (ECG)
- Temperature
- End tidal carbon dioxide (if ventilated)

They provide important additional information to the clinical observations of ABCD.

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Box 6.1 Summary of the approach to a seriously ill child

Primary assessment

A (Airway):

Look for chest movement

Listen for additional sounds, e.g. wheeze, stridor, etc.

Feel for breath

B (Breathing):

Effort, e.g. rate, accessory muscles

Efficacy, e.g. oxygen saturation

Effect, e.g. heart rate, skin colour, conscious level

(N.B. In severe respiratory distress effort of breathing may be reduced due to exhaustion. This is a preterminal sign and requires prompt intervention.)

C (Circulation):

Heart rate

Pulse volume

Capillary refill time (CRT)

Blood pressure (N.B. Hypotension is a preterminal sign)

D (Disability):

Level of consciousness (AVPU/Glasgow Coma Score)

Posture

Pupils

Blood glucose

Where immediately life-threatening problems are identified then resuscitation should be performed during the primary survey before proceeding to a secondary assessment.

Secondary assessment

This comprises taking a focused history and instituting emergency treatment whilst developing a differential diagnosis. It requires a full physical examination from head to toe. If there is any clinical deterioration during this procedure, then the primary assessment must be repeated.

Box 6.2 Relative anatomical differences between infant and older child/adult airway

In an infant:

- Large head, short neck
- Tongue large
- Floor of mouth compressible
- Teeth (if present) may be loose
- Epiglottis large and prominent
- Larynx anterior
- Airway narrowest at the cricoid cartilage rather than larynx
- More prone to develop laryngospasm

Question 6.1

Airway of an infant

Which of the following statements BEST describes the anatomical and physiological differences between the airway of an infant and that of an adult or older child? Select ONE answer only.

In an infant, the airway:

A. Has an anterior larynx and this is where the airway is narrowest

B. Is maximally opened with the head fully extended, as the head is relatively large

C. Is more prone to laryngospasm

D. The epiglottis is relatively short and stiff

E. The tongue and soft tissues of the pharynx are relatively small and compressible

Answer 6.1

C. The infant larynx is more prone to laryngospasm. See Box 6.2 for further details.

They need to be related to normal age-appropriate values (see Chapter 3, History and examination). They also help to answer the important ongoing questions:

- Are things getting better or worse?
- If worse, do I need to escalate treatment and get senior involvement?

Although paediatric life support courses have been shown to improve health professionals' ability to recognize and provide initial management of critically ill children, regular reinforcement is required to maintain these skills.

The science of basic and advanced life support

The paediatric airway

There are many anatomical airway differences between infants, children and adults (see Box 6.2 and also Chapter 17, Respiratory medicine). The younger the child, the more pronounced the difference. This has relevance to emergency care, in particular airway opening manoeuvres, airway adjuncts and endotracheal intubation.

Life-threatening airway obstruction can develop rapidly in children as the airway is already narrow and further airway narrowing from any cause increases resistance according to Pouseuille's law (see Chapter 17, Respiratory medicine, for a detailed discussion). As resistance is inversely proportional to the fourth power of the radius, small reduction in their already small airway radius will result in a large increase in resistance.

Airway opening manoeuvres

Due to the relatively large head and short neck in infants, neck flexion or overextension can cause airway obstruction by tracheal compression. The relatively large tongue can also cause airway obstruction, especially if there is a reduced level of consciousness, as well as impede the view at laryngoscopy.

Airway opening manoeuvres, the head tilt/chin lift and jaw thrust manoeuvres, are used to improve patency of an obstructed or partially obstructed airway. Both manoeuvres apply anterior tension to the hyoid bone and draw the epiglottis away from the posterior pharyngeal wall, opening the pharynx. In addition, the jaw thrust manoeuvre pulls the tongue, which may cause airway obstruction, away from the palate and opens the oropharynx. Care must also be taken when positioning fingers for airway opening manoeuvres as the floor of the infant's mouth is easily compressible.

In the head tilt/chin lift manoeuvre, it is important to control the degree of head tilt to avoid airway narrowing due to overextension of the head and neck. In the infant, due to their large head and short neck, a neutral position is preferred. In the child, the sniffing position is used. This manoeuvre is contraindicated if there is history of trauma because it may exacerbate cervical spine injury. Therefore only jaw thrust is recommended in the airway management of paediatric trauma.

Use of airway adjuncts

An oropharyngeal airway adjunct or Guedel airway creates an open channel between the mouth to the posterior pharyngeal wall. They are only used in infants and children with a reduced level of consciousness as they may cause choking or vomiting if the gag reflex is present. They are sized according to length, by measuring the distance between the anterior nares and tragus of the ear. Airway adjuncts that are too small may be ineffective and those too large may cause laryngospasm.

A nasopharyngeal airway adjunct is often better tolerated than an oropharyngeal airway. However, insertion may cause haemorrhage from the vascular nasal mucosa and worsen airway obstruction. It is contraindicated in basal skull fracture.

Laryngeal mask airway

A laryngeal mask airway is a device for supporting and maintaining the airway without tracheal intubation (Fig. 6.1). It is designed to sit in the hypopharynx and cover the supraglottic structures, thereby allowing relative isolation of the trachea. In the emergency setting, it is helpful for airway obstruction caused by supraglottic airway abnormalities or if bag-mask ventilation is not possible. A laryngeal mark does not totally protect the airway from aspiration of secretions, blood or stomach contents, and with high pressure ventilation, gastric distension may occur.

Endotracheal intubation

Endotracheal intubation can be difficult in infants and should only be performed by trained health professionals. Unless the child is unresponsive, it should be preceded by induction of anaesthesia using drugs for sedation and neuromuscular blockade. There may be clues in the history or examination that suggest a child has a difficult airway (Box 6.3). Under these
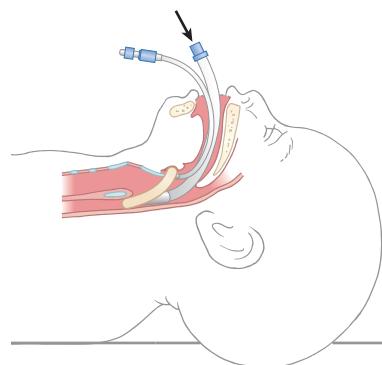
Fig. 6.1 Laryngeal mask airway. The cuff is deflated and inflated once in place above the oesophagus and laryngeal inlet.

Box 6.3 Clues to a difficult airway

- Presentation with airway obstruction or stridor, e.g. croup, retropharyngeal abscess
- Airway swelling or oedema, e.g. burns, anaphylaxis
- History of obstructive sleep apnoea
- Syndromes with facial malformations, e.g. short mandible, ear deformity, Pierre Robin sequence
- History of previous difficult endotracheal intubation
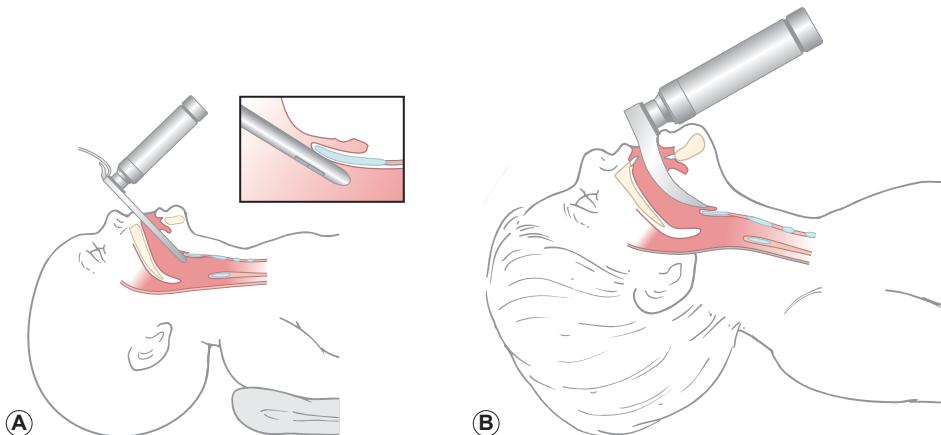
Fig. 6.2 A. Laryngoscopy in an infant using a Miller straight blade and 'Miller lift'. The epiglottis is scooped up by the blade allowing visualization of the larynx. B. Laryngoscopy in an older child using a Macintosh curved blade. The tip of the blade is inserted into the vallecula.

circumstances, senior anaesthetist and ENT surgeon should be present.

An understanding of the anatomy and appropriate preparation of equipment aids success. In infants, the epiglottis is horse-shoe shaped and relatively large. In addition, the larynx is high anterior (at C2/C3 in infants compared with C5/C6 in older children/adults). A straight blade laryngoscope ('Miller blade') is therefore more commonly used in infants, positioned posterior to the epiglottis, lifting it to allow visualization of the glottis and vocal folds (the 'Miller lift') (Fig. 6.2A). A curved blade laryngoscope ('Macintosh') is used in children and adults, and is positioned in the vallecula, anterior to the epiglottis, lifting it to visualize the larynx (Fig. 6.2B).

Question 6.2

Leak around endotracheal tube

A six-year-old child is intubated with a size 4.5 mm ID endotracheal tube. Following intubation, there is a large leak of air around the tube, audible at the mouth.

What is the most clinically significant effect of endotracheal intubation with a tube that is too small? Select ONE answer only:

A. Environmental pollution of anaesthetic gases

B. High gas flow consumption

C. Imprecise capnography

D. Increased risk of pulmonary aspiration

E. Unreliable ventilation and oxygenation

Answer 6.2

E. Unreliable ventilation and oxygenation.

An uncuffed endotracheal tube that is too small results in an air leak around the tube. While large air leaks cause all of the effects listed, it is unreliable ventilation and oxygenation that is immediately relevant to the patient. This is a particular problem when the airway resistance is high, e.g. in bronchiolitis, as high airway resistance tends to increase the size of the leak and makes adequate ventilation difficult.

Endotracheal tubes are sized by internal diameter in mm. Until the age of 12 years, the narrowest part of the airway is at the level of the cricoid cartilage. Therefore, an endotracheal tube that passes easily through the vocal cords may still be too large to pass through the cricoid ring. Too tight a fit at this level may damage the mucosa. Subsequent airway oedema and post-extubation stridor can occur and, rarely, tracheal scarring and stenosis may follow.

For many years, the use of cuffed tubes in children under 8 years old was considered inappropriate because of fears of mucosal damage at the level of the cricoid cartilage. However, over the last 10 years, studies have demonstrated that cuffed endotracheal tubes can be used safely in infants and young children providing correct tube size is used, tube position verified and cuff inflation pressure checked and limited. Consequently, cuffed endotracheal tubes are now first choice in paediatric critical care and are preferred in children with poor lung compliance or high airway resistance, or when precise ventilation and/or CO_2 control is needed. Uncuffed tubes are still used in newborn infants.

Cardiopulmonary arrest

Causes of cardiopulmonary arrest

Cardiorespiratory arrest in children is rare (incidence 1–20 per 100,000 children per year in developed countries). The majority occur in children under the age of one year. In adults, cardiac arrest is often due to primary cardiac disease, which occurs with near-normal function of the circulatory and respiratory systems until the moment of arrest. In contrast, in children, most occur secondary to hypoxia due to respiratory failure or circulatory failure due to fluid loss or fluid maldistribution. End organ damage is therefore often already present in children at the time of cardiac arrest and is responsible for their prognosis.

However, in up to 30% of children, there is a cardiac cause for cardiopulmonary arrest. This is becoming more common with improved survival in children with complex congenital heart disease. There are also children with sudden unexpected ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) who may have previously unrecognized cardiac disease, either a cardiomyopathy or an inherited channelopathy. Following an unexpected cardiac arrest or VF/VT arrest, referral to a paediatric cardiologist should be made. An identifiable cause may be found following detailed investigation, which may include genetic studies and pharmacological provocation tests, and treatment given. As family members of these children may also be at risk of sudden death, they should also be referred.

Treatment of cardiopulmonary arrest

Cardiac compressions and ventilation breaths

Cardiopulmonary resuscitation (CPR) is an emergency procedure to delay cell damage and death in the heart and brain by facilitating partial flow of oxygenated blood to these organs. This provides a brief window of opportunity to restore breathing and spontaneous blood circulation.

CPR comprises chest compressions and breaths, applied in a ratio of 15 compressions to 2 breaths (except in newborn infants, for whom a 3 : 1 ratio is required). Adequate chest compressions should be provided at a depth and rate that allow complete recoil of the chest after each compression. Experimental and mathematical studies have shown that the best compression rate at all ages is 100–120 per minute. The recommended depth is one third of the depth of the chest. There should be minimal interruption of compressions as coronary perfusion pressure has been shown to be greater with prolonged continuous compressions.

In adults, survival rates from out-of-hospital cardiorespiratory arrests are improved if bystander CPR is given, even if it is compression-only CPR. In children, bystander CPR also results in a more favourable outcome, but not if it is compression-only CPR. As most out-of-hospital arrests in children are hypoxic in origin, rescue ventilation remains the cornerstone of paediatric CPR.

Duration of resuscitation

Prolonged resuscitation is, in general, associated with a bad neurological outcome. However, a recent study of successful CPR in adults has shown neurological outcome is not directly correlated to the duration of CPR. Following this, the Resuscitation Council (UK) does not recommend a specific duration for CPR. Instead, clinicians are to determine duration on a case-by-case basis, continuing prolonged resuscitation where there is potential for a reversible cause.

Unfortunately, studies in children have not reported similar favourable outcomes in prolonged resuscitation, unless there is associated profound hypothermia (<30°C) or intermittent return of spontaneous circulation (ROSC). Survival is rare if resuscitation continues for longer than 20–30 minutes and any survivors are likely to have significant neurological deficits. However, there are cases of survival with reasonable outcome following prolonged in-hospital cardiac arrest in cardiac centres with ECMO (extra-corporeal membrane oxygenation). Although such specialist treatment is not feasible for all children following cardiopulmonary arrest, it raises an interesting question about the potential for treatments other than conventional CPR in the management of cardiopulmonary arrest.

Post-resuscitation care

Following return of circulation, children who survive cardiorespiratory arrest have significant multi-organ dysfunction. They should be transferred to an intensive care setting for specialist post-resuscitation care. Management focuses on achieving and maintaining homeostasis in order to optimize multi-organ recovery; initiating investigation of the underlying cause of the respiratory arrest; and treating any identifiable cause.

Oxygen

There is increasing evidence that hyperoxaemia can be detrimental. Excessive tissue oxygen concentrations may increase production of oxygen free radicals. Oxygen free radicals can damage mitochondria and so there is potential to compound neuronal damage. During resuscitation beyond the neonatal period,

100% oxygen is used. However, after return of spontaneous circulation, inspired oxygen should be titrated to achieve oxygen saturations of 94–98% using pulse oximetry.

Therapeutic hypothermia

In adults, mild therapeutic hypothermia has been shown to improve neurological outcome after ventricular fibrillation (VF) arrest. Therapeutic hypothermia of newborns with hypoxic–ischaemic encephalopathy has been shown to be associated with improved neurological outcome. Although the role of therapeutic hypothermia post cardiac arrest in children remains unclear, current guidelines suggest therapeutic cooling to 32–36°C for at least 24 hours. As increased core temperature increases metabolic demand by 10–13% for each degree centigrade above normal, as a minimum, hyperthermia should be avoided or, if present, treated with active cooling to achieve a normal core temperature. Shivering should be avoided as it increases metabolic demand. Sedation and neuromuscular blockade may be needed.

Blood glucose control

In all age groups, abnormal blood glucose levels (hyper- or hypoglycaemia) are associated with poor outcome following cardiorespiratory arrest. It remains unclear whether this is a causative or associated factor. Following the return of spontaneous circulation, plasma glucose levels should be monitored and hypo- and/or hyperglycaemia avoided. However, tight glucose control is not recommended as this increases the risk of hypoglycaemia without any survival benefit.

Resuscitation outcomes

For children who have a respiratory arrest without cessation of circulation, whether out-of-hospital or in-hospital, more than two thirds survive. The majority who get to paediatric intensive care (PICU) survive, most (over 90%) with a favourable neurological outcome.

However, outcome from cardiopulmonary arrest is poor. Only a third get to PICU. Of these, only a third survive to discharge from hospital, the majority (up to 90%) with moderate to severe neurological deficit due to hypoxic–ischaemic brain injury.

Discussion of withdrawal or limitation of life-sustaining treatment may be difficult and emotive. All health professionals have a duty to act in the best interests of the child. When treatment neither restores health nor confers any other benefit it may no longer be in the child's best interests. Sympathetic discussion between health professionals and parents usually allows a joint decision to evolve. Guidance is available from the General Medical Council (GMC), British Medical Association (BMA) and Royal College of Paediatrics and Child Health (RCPCH), which also addresses the uncommon situation when a joint decision cannot be reached. This is considered in more detail in Chapter 35, Ethics.

Question 6.3

Interpreting blood gases

Regarding blood gases, which of the following statements are TRUE and which are FALSE?

A. Bicarbonate is a buffer and if present in normal quantities will ensure pH is normal
B. In a compensated metabolic acidosis, pH is low
C. In a respiratory acidosis, pH is low and bicarbonate is usually normal
D. pH is directly proportional to the inverse of the hydrogen ion concentration
E. The base excess is low in metabolic acidosis

Answer 6.3

A. False; B. False; C. True; D. False; E. True. See below for discussion.

Blood gas abnormalities

Acid base disorders are very common in critically ill and injured children. A brief reminder of the principles is outlined below, and Table 6.1 summarizes common arterial blood gas patterns.
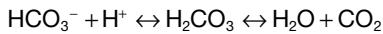
pH is defined as the decimal logarithm of the reciprocal of the hydrogen ion activity or concentration (aH^+) in a solution:

Table 6.1 Arterial blood gas patterns

Parameter	Normal	Respiratory acidosis	Compensated respiratory acidosis	Metabolic acidosis	Compensated metabolic acidosis
pH	7.34–7.44	↓	Normal	↓	Normal
CO_2	4.6–6	↑	↑	Normal	↓
HCO_3^-	22–26 mmol/L	Normal	↑	↓	↓
Base excess	−2–+2 mmol/L	Normal	↑	↓	↓

$$pH = -\log_{10}(a_{H^+}) = \log_{10}\left(\frac{1}{a_{H^+}}\right)$$

pH is maintained in range (7.34–7.44) by several buffering systems, the main one being the carbonic acid–bicarbonate system:

$$HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

The relationship between pH, HCO_3 and CO_2 is described by the Henderson–Hasselbalch equation:

$$pH = 6.1 + \log_{10}\left(\frac{[HCO_3^-]}{0.03 \times pCO_2}\right)$$

In hyperventilation, CO_2 is blown off and pH increases (respiratory alkalosis). In hypoventilation, CO_2 is retained and the blood becomes acidotic (respiratory acidosis). Respiratory changes have a rapid effect on the pH. HCO_3 is a base and a buffer of hydrogen ions (H^+), which are the product of normal cellular metabolism. When an excess of hydrogen ions are present due to excess acid production, the buffering effect of HCO_3 is overcome and the blood becomes acid (metabolic acidosis). Examples of excess acid are lactic acid in shock or ketones in diabetic ketoacidosis, acid administration (e.g. salicylic acid in aspirin poisoning) or bicarbonate loss (e.g. from the gut in gastroenteritis or in the urine in renal tubular disease). The kidneys can compensate for a respiratory acidosis in chronic respiratory failure by increasing the amount of HCO_3 in the blood and extracellular fluid (compensated respiratory acidosis). This results in a normal pH and a high CO_2 and HCO_3. This compensation takes several days. The respiratory system can compensate for a metabolic acidosis by blowing off CO_2 to normalize pH (compensated metabolic acidosis). This response is mediated via carotid chemoreceptors and results in normal pH, low CO_2 and low HCO_3.

The main limitation of the Henderson–Hasselbalch approach is that buffers other than HCO_3 exist, including haemoglobin and albumin. The consequence of this is that HCO_3 and CO_2 are not independent. In the dissociation equation below, a rise in CO_2 will cause formation of hydrogen ions:

$$CO_2 + H_2O \leftrightarrow H^+ + HCO_3^-$$

However, as hydrogen ions are buffered by haemoglobin and albumin, bicarbonate levels also rise. Thus, a rise in CO_2 results in a rise in HCO_3. This rise in HCO_3 could be mistaken for a metabolic alkalosis, when the cause was respiratory acidosis. The concept of base excess was developed to address this problem. Base excess is determined by equilibrating the sample to a normal pCO_2 (5.33 kPa) then titrating it to pH 7.4. The number of mmol/L required to do this equals the base excess, and is therefore a measure of how

Table 6.2 Common causes of metabolic acidosis and anion gaps

Increased anion gap (usually decreased Cl⁻)	Normal anion gap (usually increased Cl⁻)
Diabetic ketoacidosis	Diarrhoea
Alcohol poisoning	Parenteral nutrition
Starvation	Carbonic anhydrase inhibitors
Inborn errors of metabolism	Dilutional acidosis
Hyperosmolar non-ketotic coma	Ingestion of HCl or other acid
Lactic acidosis	Renal tubular acidosis
Methanol	Ileostomy
Ethylene glycol	Sodium chloride administration
Salicylate	

acidotic or alkalotic the sample is without any contribution of CO_2.

Finally, calculation of the anion gap ($= [Na^+] + [K^+]$) $- ([Cl^-] + [HCO_3^-])$ allows classification of a metabolic acidosis into those with a normal or increased anion gap. The anion gap is a measure of the concentration of unmeasured anions (e.g. plasma proteins, ketones, lactate) and is based on the theory of electrical neutrality (the sum of the positive ions must equal the sum of the negative ions). An increased anion gap (>16 mmol/L) suggests the presence of unmeasured organic acid, whereas a normal anion gap implies bicarbonate loss and/or increase in chloride concentration (Table 6.2; see Fig. 29.1).

Hyperchloraemic acidosis

Hyperchloraemic acidosis is common in patients given normal saline-containing fluids. There are two reasons for this. Firstly, normal saline (pH 5–6) is acidic and has little buffering capacity. The acidic pH of normal saline is due to the 'Grotthuss mechanism', whereby ions which dissociate when dissolved in water (e.g. Na^+ and Cl^- ions) cause disruption of the ionic bonding of H_2O, leading to greater dissociation and generation of $[H^+]$. Secondly, volume expansion causes plasma bicarbonate dilution. The importance of recognizing hyperchloraemia as a cause of acidosis is to avoid administration of further normal saline-containing fluids when further fluid therapy is unnecessary and will exacerbate the problem. The finding of a normal anion gap, raised chloride concentration and low bicarbonate should be the clue.

Scientific basis of respiratory support including mechanical ventilation

What is respiratory failure?

Respiratory failure may be defined as a syndrome of inadequate gas exchange, with the result that levels of

arterial oxygen, carbon dioxide or both cannot be maintained within their normal ranges (Box 6.4). A drop in arterial oxygenation is hypoxaemia; a rise in arterial carbon dioxide levels is hypercapnia. Classification into type I or type II relates to the absence or presence of hypercapnia, respectively.

Type 1 respiratory failure is defined as hypoxia without hypercapnia, and the $PaCO_2$ may be normal or low. It is typically caused by a ventilation/perfusion (V/Q) mismatch; the volume of air flowing in and out of the lungs is not matched with the flow of blood to the lungs. The basic defect in type 1 respiratory failure is failure of oxygenation characterized by:

- PaO_2 low (8.0 kPa)
- $PaCO_2$ normal or low (<6.7 kPa)

This type of respiratory failure is caused by conditions such as:

- Parenchymal disease (V/Q mismatch)
- Interstitial lung diseases: ARDS (acute respiratory distress syndrome), pneumonia, emphysema (V/Q mismatch)
- Shunts: right-to-left shunt

Type 2 respiratory failure is defined as hypoxia with hypercapnia. The basic defect in type 2 respiratory failure is characterized by:

- PaO_2 decreased (<8.0 kPa)
- $PaCO_2$ increased (>6.7 kPa)

Type 2 respiratory failure is caused by inadequate ventilation; both oxygen and carbon dioxide are affected. Causes include:

- Increased airway resistance (croup, bronchiolitis, asthma)
- Neurological hypoventilation (drug effects, brain stem lesion)
- Neuromuscular problems (Guillain–Barré syndrome, congenital myopathy)
- Decreased functional residual capacity (e.g. kyphoscoliosis, chest deformity, pneumothorax, flail chest)

Untreated, progressive respiratory failure can lead to end organ damage and death from hypoxia. The purpose of respiratory support is to prevent this progression.

Supportive therapy in respiratory failure

Respiratory support ranges from oxygen by face mask, to non-invasive respiratory support, endotracheal intubation and mechanical ventilation, nitric oxide (NO) and extracorporeal membrane oxygenation (ECMO). The purpose of supportive therapy is to maintain life while the underlying condition is treated.

Oxygen

In general, children with SpO_2 <92% in air should receive high flow oxygen via a tight-fitting mask. At SpO_2 below 92%, the oxygen haemoglobin dissociation curve becomes steep and delivery of oxygen to the tissues becomes compromised (see Fig. 17.5). Conversely, high concentration inspired oxygen can cause

direct cellular toxicity and reabsorption atelectasis. The amount of inspired oxygen should therefore be titrated according to pulse oximetry, aiming at SpO_2 of 92% and above in most cases. A fixed performance, high flow mask provides a fractional inspired oxygen concentration (FiO_2) within the range 0.24–0.6. FiO_2 is not known with the more common variable performance masks or with nasal cannulae but is usually <0.4. The maximum FiO_2 via face mask is 0.6 unless a reservoir bag is used. High flow oxygen (15 L/min) delivered by a face mask fitted with a reservoir bag will deliver an FiO_2 of up to 0.9.

Ventilatory support

Box 6.5 summarizes the main indications in respiratory failure for intubation and mechanical ventilation. While worsening hypoxaemia or worsening hypercarbia may confirm the imminent need for ventilation, blood gas analysis is not a substitute for clinical assessment.

Non-invasive

Non-invasive ventilation may be delivered via tight-fitting face mask, nasal masks, prongs and other devices or hood. The main advantage of non-invasive ventilation is that endotracheal intubation is avoided along with the complications of mechanical ventilation, such as ventilator-associated pneumonia. Also, sedative drugs are not needed. There are two main modalities of non-invasive ventilation: CPAP and BiPAP.

CPAP: Continuous positive airway pressure (CPAP) at +5 to +10 cm H_2O has a number of beneficial effects, including reduced alveolar collapse, improved oxygenation via alveolar recruitment and reduced work of breathing. Disadvantages include skin necrosis at the interface between the face mask and skin, stomach distension and risk of aspiration.

BiPAP: Biphasic positive airways pressure is a mode of ventilation in which two levels of pressure are set: inspiratory pressure (IPAP) and an expiratory pressure (EPAP – analogous to CPAP). Most modern ventilators will allow the patient to breathe spontaneously,

detecting inspiration and expiration via pressure or flow changes in the ventilator circuit. A fixed back-up respiratory rate is usually set in case of apnoea.

Invasive

The main modes of ventilation in paediatrics are intermittent mandatory ventilation (IMV), divided into pressure control and volume control ventilation, and high frequency oscillatory ventilation (HFOV). Unfortunately, manufacturers of intensive care ventilators have not agreed a uniform terminology for describing some of the pressure control and volume control modes. Despite this, the principles described below are universal.

Pressure control (PC) ventilation (Fig. 6.3): A peak inspiratory pressure (PIP) and a positive end expiratory pressure (PEEP) are set, along with inspiratory time (Tinsp), ventilator rate and inspired oxygen. While inspired breaths are delivered actively by the ventilator, expiration depends on the elastic recoil of the chest. The delivered tidal volume (TV) is a function of PIP, Tinsp and lung compliance. Pressure control ventilation can be delivered as a synchronized mode (synchronized intermittent mandatory ventilation – SIMV-PC), in which the ventilator delivers the PIP when the patient takes a breath. Synchronized modes are useful when ventilating non-paralysed patients and for weaning.

Volume control (VC) ventilation (Fig. 6.4): The patient is ventilated at a preset tidal volume (TV) and rate. PEEP and inspired oxygen concentration is also set. As tidal volume is fixed, the pressure required to deliver it varies depending on lung compliance. If the lungs are not compliant, this can result in high peak airway pressure and associated barotrauma – ventilator-associated lung injury (VALI). Consequently, volume
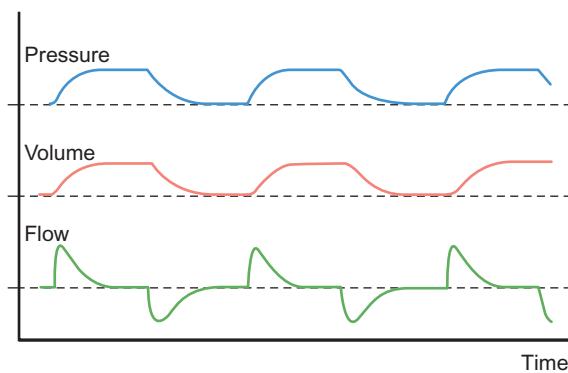
Fig. 6.3 **Pressure control ventilation. Changes in pressure at the airway opening, lung volume, and flow during pressure control ventilation (PCV). The rate is fixed and the patient cannot trigger additional breaths or breathe spontaneously between mandatory breaths; both tidal volume and minute ventilation can vary if the patient's lung–thorax compliance or airway resistance changes.**

Box 6.5 Indications for intubation and ventilation in respiratory failure

- Severe respiratory distress
- Tiring due to excessive work of breathing (may be indicated by progressive hypercapnia)
- Progressive hypoxaemia
- Reduced conscious level
- Progressive neuromuscular weakness – e.g. Guillain–Barré syndrome
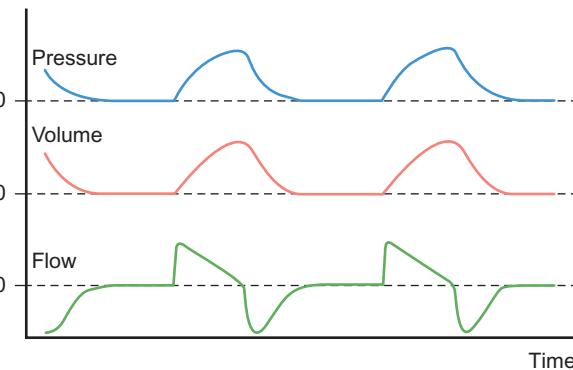
Fig. 6.4 Changes in pressure at the airway opening, lung volume, and flow during volume controlled mechanical ventilation. Note the decelerating flow pattern, in contrast to the fixed flow in pressure control ventilation.

modes of ventilation have not traditionally been favoured in paediatric intensive care. Spontaneous modes (SIMV-VC) are also available in volume control ventilation.

PEEP: PEEP is analogous to CPAP and provides the same advantages. Usually at least 4 cm H_2O of PEEP is applied to mechanically ventilated patients in intensive care, even if the lungs are normal, in order to prevent alveolar collapse during expiration and consequent atelectasis. In severe lung pathology, higher levels of PEEP, up to 15 cm H_2O, may be necessary to maintain lung volume. Very high levels of PEEP can cause cardiovascular compromise by impeding venous return to the heart. Very high PEEP can also cause CO_2 retention and barotrauma.

Support modes of ventilation: Synchronized modes of ventilation are used during weaning to allow the patient to begin to breathe spontaneously and to take over the work of breathing. Support modes may deliver pressure support (PS) or volume support (VS). In PS, each spontaneous breath is augmented with a preset positive pressure. In VS, augmentation is with a preset volume. Pressure or volume support can be combined with SIMV, so support is provided when the patient takes a spontaneous breath above the set SIMV rate.

Avoiding ventilator-associated lung injury (VALI): VALI is lung injury caused by high pressure (barotrauma) or high volume (volutrauma) ventilation. It may be limited by ensuring TV is 6–8 mL/kg and PIP is <35 cm H_2O. Permissive hypercapnia, aiming for an arterial pH of >7.25 rather than a specific CO_2 target, allows ventilation to be minimized. High levels of inspired oxygen can also be toxic, so FiO_2 should be titrated carefully to SpO_2, aiming for SpO_2 of no higher than 92% unless there are special circumstances. Judicious use of PEEP optimizes alveolar recruitment and results in lower FiO_2.

High frequency oscillatory ventilation (HFOV): HFOV delivers low tidal volumes, typically around 2 mL/kg (less than the anatomical dead space), at a rate of >150 breaths/minute. The tidal volume is delivered by a pressure sine wave oscillating around a mean airway pressure (MAP), which acts as a constant distending pressure. This constant distending pressure improves alveolar recruitment and ventilation/perfusion matching. Mechanisms of gas exchange are not clear, but probably include convection and molecular diffusion. HFOV is a mode of rescue ventilation which is often used when conventional ventilation fails. Such data as exist in paediatric critical care suggest that a trial of HFOV may be beneficial when the mean airway pressure is >16 and FiO_2 >0.6. Although there are theoretical reasons why HFOV may reduce barotrauma, it has not been proven to be more effective than conventional ventilation in clinical trials.

Gas exchange in mechanical ventilation

Respiratory failure is caused by failure to ventilate, characterized by increased arterial carbon dioxide tension, or failure to oxygenate, characterized by decreased arterial oxygen tension. Its treatment is to increase the patient's alveolar ventilation, that is, the rate and depth of breathing. Failure to oxygenate may occur as a result of decreased alveolar oxygen tension, reduced oxygen diffusion capacity or ventilation perfusion mismatch. The treatment for failure to oxygenate is restoration and maintenance of lung volumes, using recruitment manoeuvres and increased airway pressures.

In conventional forms of ventilation, arterial oxygenation depends on FiO_2 and airway pressure (PIP and PEEP) and in HFOV, oxygenation depends on FiO_2 and mean airway pressure (MAP). In conventional ventilation, carbon dioxide clearance is dependent upon alveolar ventilation, which in turn is dependent on minute volume (= tidal volume × respiratory rate). In HFOV, carbon dioxide clearance is also dependent on minute volume, which may be increased by increasing the amplitude of the sine wave (often referred to as deltaP) and by reducing the set frequency (Hz) of the oscillatory waveform.

Inhaled nitric oxide

Inhaled NO is a potent pulmonary vasodilator, which causes pulmonary arteriolar smooth muscle dilatation via a cGMP-dependent mechanism. There are no randomized controlled trials to support the use of inhaled NO outside the neonatal period, where it has been shown to be of benefit in meconium aspiration syndrome. However, older children with severe refractory hypoxaemic respiratory failure may benefit from inhaled NO. It may also protect patients whose

oxygenation might otherwise depend upon a potentially damaging ventilatory strategy.

Extracorporeal membrane oxygenation (ECMO)

ECMO is a modified form of cardiopulmonary bypass which can be used to provide respiratory or cardiovascular support. Deoxygenated blood, drained from the venous system, is heparinized and oxygenated outside of the body via a membrane oxygenator and pumped back into the body via a roller or centrifugal pump. In veno-arterial (VA) ECMO, this blood is returned to the arterial system, whereas in veno-venous (VV) ECMO, it is returned to the venous system. VV ECMO provides respiratory support and VA ECMO provides both cardiovascular and respiratory support.

The main indications for ECMO are shown in Box 6.6. Most contraindications are relative and include significant co-morbidities, age and size of patient and in neonates, presence of intraventricular haemorrhage (due to the risk of further bleeding). ECMO may be considered as a supportive therapy in the unventilatable child with respiratory failure ventilated for <7 days. This time limitation is to avoid offering ECMO to children with irreversible lung injury who are unlikely to recover. The benefit of ECMO for acute hypoxaemic respiratory failure outside the neonatal period is not proven in clinical trials.

Pathophysiology of shock and its management

Cardiovascular physiology is described in more detail in Chapter 18, Cardiology. A brief summary in relation to shock is given below.

Cardiac output

Cardiac output (CO) determines blood pressure and hence tissue perfusion. It is given by the formula:

$$\text{Cardiac output (CO)} = \text{HR (heart rate)} \times \text{SV (stroke volume)}$$

Box 6.6 Indications for ECMO

- Severe hypoxaemic respiratory failure
- Cardiogenic shock
- Cardiac arrest
- Failure to wean from cardiopulmonary bypass after cardiac surgery
- As a bridge to either cardiac transplantation or placement of a ventricular assist device

The heart needs to be able to respond to the changing demands of the body, whether they are physiological or pathological. Control of cardiac output can be divided into intracardiac and extracardiac mechanisms.

Intracardiac mechanism

This relies on the physical properties of the cardiac muscle. When cardiac muscle fibres are stretched, they respond with more forceful contraction until the sarcomeres become overstretched. This relationship is described by the Frank–Starling curve (Fig. 6.5). It ensures that the left and right ventricles perform equally and fluid does not accumulate in the lungs.

Extracardiac mechanism

This is the autonomic nervous system, described in detail below. The sympathetic nervous system increases heart rate and contractility, increasing cardiac output, and the para-sympathetic nervous system reduces heart rate and contractility.

Cardiac and circulatory physiology

Hormonal/neural control

The sympathetic nervous system causes release of adrenaline (epinephrine) from the adrenal glands and release of noradrenaline (norepinephrine) from sympathetic nerve fibres innervating the heart and blood vessels. Adrenaline and noradrenaline cause vasoconstriction of arterioles and veins and increase heart rate and contractility via stimulation of α and β adrenergic
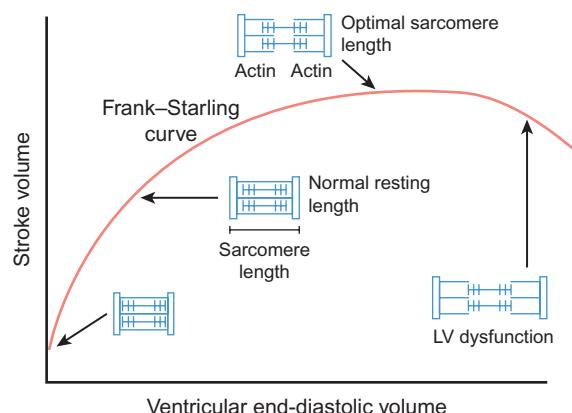
Fig. 6.5 **Frank–Starling curve. Initially, increases in ventricular end-diastolic volume result in an increase in stroke volume and hence cardiac output. This is the rationale for volume resuscitation in shock. However, beyond optimal sarcomere length, with progressive distension of the ventricle by overenthusiastic volume resuscitation, there is reduction in stroke volume. Assessing optimal volume status in critically ill children is very difficult.**

receptors. Parasympathetic fibres play less of a role through fibres that innervate blood vessels of the head, viscera and heart. These fibres release acetylcholine, which causes vasodilatation and reduction in heart rate and contractility via muscarinic M3 and M2 receptors, respectively.

Baroreceptors and chemoreceptors

Located in the carotid sinus and aortic arch, baroreceptors respond to stretch and send impulses to the autonomic vasomotor centre in the brainstem. Baroreceptor stimulation results in vasoconstriction and increases in heart rate, blood pressure and cardiac output via the sympathetic nervous system. Chemoreceptors in the carotid body and aortic arch respond to hypoxaemia, CO_2 and acidosis. These stimulate both the vasoconstrictor response to increase arterial pressure and the respiratory rate to provide respiratory compensation of metabolic acidosis. The vasomotor centre is an intense controller of blood pressure and the strongest response is seen when it is subjected to ischaemia (i.e. cerebral ischaemia).

Renin–angiotensin system

The juxtaglomerular cells of the kidney secrete the enzyme renin, in response to a fall in blood pressure. Renin then converts angiotensinogen to angiotensin I in the plasma (see Fig. 19.8). Angiotensin I is converted to angiotensin II in the lung; this is a vasoconstrictor and also causes the kidney to retain salt and water. Angiotensin II stimulates the adrenals to secrete aldosterone, causing more salt and water retention.

Aldosterone

This hormone is secreted in the adrenal cortex in response to angiotensin, leading to salt and water retention. Aldosterone takes 2–3 hours to be stimulated and almost a week to reach peak effect.

Antidiuretic hormone (ADH)

Secreted in the hypothalamus in response to reduced atrial stretch receptor response, ADH acts on the kidney to promote water reabsorption. In high concentrations it also causes strong vasoconstriction; hence its other name of vasopressin. The atrial stretch receptor is now known to produce a hormone called atrial natriuretic peptide (ANP), which promotes salt and water excretion and counteracts the effects of aldosterone and ADH.

What is shock?

Shock may be described as a clinical syndrome of inadequate tissue perfusion. Another more physio-logical definition of shock is DO_2 (delivery of oxygen) is less than VO_2 (tissue uptake of oxygen).

Some important relationships:

$$DO_2 \text{ (delivery of oxygen)} = CO \text{ (cardiac output)} \times CaO_2 \text{ (arterial oxygen content)}$$

$$CaO_2 = HbO_2 \text{ (oxyhaemoglobin)} + \text{dissolved oxygen}$$

Delivery of oxygen to the tissues is critically dependent on both cardiac output and the arterial oxygen concentration. Therapies designed to treat shock thus aim to improve cardiac output and oxygenation via a variety of different mechanisms. In shock, the final pathway is a state of acute cellular oxygen deficiency (Fig. 6.6). This in turn leads to anaerobic metabolism and tissue acidosis culminating in loss of normal cellular function, cell death, organ dysfunction and eventually death.

Shock may result from loss of fluid (hypovolaemia), defects of the heart pump (cardiogenic), abnormalities of vessels (distributive), flow restriction (obstructive) or inadequate oxygen-releasing capacity of blood (dissociative) (Table 6.3). In many cases of shock, several mechanisms may coexist, therefore treatment must be individualized. For example, in sepsis, hypovolaemia, distributive and cardiogenic mechanisms may co-exist. Shock may be compensated, uncompensated or irreversible.

Table 6.3 Causes of shock

Hypovolaemic	Haemorrhage Gastroenteritis, stomal losses Intussusception, volvulus Burns Peritonitis
Distributive	Septicaemia Anaphylaxis Vasodilating drugs Spinal cord injury
Cardiogenic	Arrhythmias Cardiomyopathy Heart failure Valvular disease Myocardial contusion
Obstructive	Congenital cardiac (coarctation, hypoplastic left heart, aortic stenosis) Tension pneumothorax Haemopneumothorax Flail chest Cardiac tamponade Pulmonary embolism
Dissociative	Profound anaemia Carbon monoxide poisoning Methaemoglobinaemia
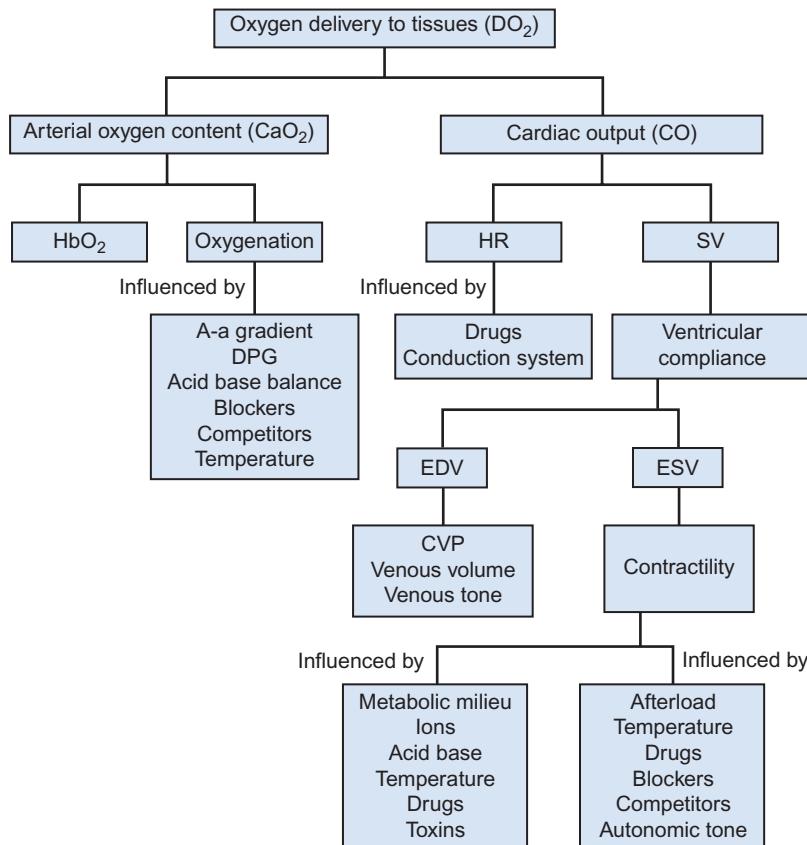
Fig. 6.6 Factors affecting oxygen delivery (DO$_2$) to tissues. A-a, alveolar-arterial; CVP, central venous pressure; DPG, 2,3-Diphosphoglycerate; EDV, end-diastolic volume; ESV, end-systolic volume; HbO$_2$, oxyhaemoglobin; HR, heart rate; SV, stroke volume.

Compensated shock

In compensated shock, vital organ function is maintained. The clinical signs are mild agitation, skin pallor, increased heart rate, cold peripheral skin with decreased capillary return and reduced urine output. The sympathetic nervous system increases systemic arterial resistance, diverts blood away from non-essential tissues, constricts the venous reservoir and increases heart rate to maintain cardiac output. Systolic blood pressure remains normal. Increased secretion of angiotensin and vasopressin causes the kidneys to conserve water and salt, while reduced renal perfusion leads to reduced urine output.

Uncompensated shock

In uncompensated shock, microvascular perfusion is impaired. Organ and cellular function deteriorate and anaerobic metabolism becomes the major source of energy. Anaerobic metabolism produces lactate, which causes lactic acidosis. Acidosis reduces myocardial contractility and impairs the response to circulating catecholamines. If recognized at this stage, shock may still be reversible if treated. In uncompensated shock, blood pressure is normal or low and there is tachycardia, prolonged capillary refill, cold peripheries, acidotic breathing, depressed mental state and reduced urine output.

Irreversible shock

In irreversible shock, tissue damage has already occurred and even if cardiovascular physiology is restored, the patient will still develop multiple organ failure and die as a consequence of this damage. Hence early recognition and treatment are vital.

Management of shock

Management strategies for shock vary according to the cause. In children, sepsis is the commonest cause of shock. Unless an alternative diagnosis is obvious, broad spectrum antibiotics should be given as soon as possible, ideally after doing a blood culture. Currently, third generation cephalosporins such as ceftriaxone are the antibiotics of choice in UK community-acquired sepsis outside the neonatal period. These antibiotics cover the most frequently encountered organisms in the UK, including pneumococcus and meningococcus, and with good penetration of the blood–brain barrier, can be used to treat both

meningitis and septicaemia. In septic shock, fluid resuscitation, inotropes and vasopressors may all be needed to treat hypovolaemia, myocardial depression and inappropriate vasodilation, respectively.

Exsanguinating haemorrhage in trauma should be treated by urgent replacement of circulating volume with blood and plasma and surgical management of the bleeding ('turning off the tap'). In cardiogenic shock due to a failing myocardium, some fluid resuscitation may be necessary but fluid should be given judiciously along with appropriate inotropic support. Arrhythmias should be treated with drugs or DC cardioversion. In the neonatal period, it is important to consider duct dependent congenital cardiac lesions and whether to give prostaglandin to maintain ductal patency. For anaphylaxis, intramuscular adrenaline, antihistamines and steroids should be given.

In all cases, however, an initial ABC approach is vital for a good outcome. It may be difficult to distinguish the underlying cause at the point of presentation and so management should initially prioritize physiological goals to maximize tissue oxygenation rather than focusing on the differential diagnosis to determine the specific cause. Oxygen delivery may be increased with supplemental oxygen therapy, blood transfusion given to maintain haemoglobin concentration within the physiological range and cardiac preload optimized with fluid therapy and cardiac pump function with inotropes. Oxygen demand may be decreased by intubation and mechanical ventilation to avoid the work of breathing, maintenance of normothermia and by treating the underlying cause of the problem.

Clinically, this usually translates into delivery of high flow oxygen and rapid volume expansion with 20 mL/kg boluses of crystalloid once intravenous or intraosseous access is obtained and appropriate monitoring attached to the patient. In sepsis, up to 200 mL/kg of fluid resuscitation may be necessary in the first 24–48 hours. In contrast, patients with cardiogenic shock may benefit from a cautious fluid bolus to optimize preload and 10 mL/kg fluid boluses are recommended. In patients with signs of raised intracranial pressure, hypotension is detrimental for cerebral perfusion, but excessive fluids may cause cerebral oedema; volume expansion should also be given cautiously as 10 mL/kg fluid boluses. Patients should be reassessed after each fluid bolus to look for signs of improvement such as fall in heart rate, improvement in skin perfusion and urine output, improved conscious level, increase in blood pressure and improvement in metabolic acidosis and lactate. Renal perfusion should be monitored with a urinary catheter and hourly urine output measured, as it is an important marker of renal perfusion.

Intubation and mechanical ventilation should be considered in patients who have received more than 40–60 mL/kg fluid and who still have signs of ongoing shock ('fluid refractory shock'). Mechanical ventilation, sedation and paralysis decrease tissue oxygen uptake, allow delivery of adequate concentrations of oxygen, reduce pulmonary oedema and facilitate placement of arterial and central venous catheters.

In fluid refractory shock, inotropic support should also be commenced (Table 6.4). Initially this may be dopamine given via a peripheral intravenous catheter. In cold shock, when myocardial depression and vasoconstriction predominate, adrenaline (epinephrine) may be added if dopamine alone fails to improve the situation. Milrinone is an inodilator that may also be useful in cold shock. In warm shock, when vasodilation is the predominant cardiovascular response, noradrenaline (norepinephrine) may be added.

Many intensivists continue to use the concept of 'goal-directed therapy' in septic shock, optimizing preload by titrating fluid bolus therapy to a central venous pressure (CVP) of 8–12 mmHg, aiming for a normal mean arterial pressure for age, urine output of ≥ 0.5 mL/kg/hour and central venous (superior vena cava) ($ScvO_2$) or mixed venous oxygen (SvO_2)

Table 6.4 Inotropes commonly used in paediatric critical care

Name	Mechanism	Action	Dose
Noradrenaline	α adrenergic receptor agonist	Increases SVR	0.05–1.0 µg/kg/min
Adrenaline	α/β adrenergic receptor agonist	Increase HR, SVR, contractility	0.05–1.5 µg/kg/min
Dopamine	DA (dopamine) receptor, α/β adrenergic receptor agonist	Low dose (2–5 µg/kg/min) increases renal and splanchnic blood flow (DA) Medium dose (5–12 µg/kg/min) increases HR (β) Higher dose (12–20 µg/kg/min) increases SVR (α)	2–20 µg/kg/min
Dobutamine	β adrenergic receptor agonist	Increases contractility, may reduce SVR	1–20 µg/kg/min
Milrinone	Phosphodiesterase 3 inhibitor in cardiac myocytes and vascular smooth muscle, increases intracellular Ca^{2+}	Increases contractility and vasodilator	0.3–1 µg/kg/min

HR, heart rate; SVR, systemic vascular resistance.

saturation of ≥70%. Central venous oxygen saturation reflects tissue uptake of oxygen from arterial blood into the tissues and values of <70% are suggestive of the inadequate oxygen delivery and excessive oxygen uptake which are the hallmarks of the shock state. Recently, three large trials in adults have failed to show benefit from such a strategy. Goal-directed therapy has not been assessed in large-scale clinical trials in children. In some cases, particularly cardiogenic shock due to cardiomyopathy or myocarditis, mechanical cardiovascular support with ECMO may be of benefit as a bridge to transplantation or recovery.

Neurointensive care and encephalopathies

'Neurointensive care' describes a strategy to prevent further damage ('secondary injury') to the brain and to allow the best possible recovery from the primary insult, irrespective of cause.

The physiological basis for neurointensive care is the Monro–Kellie doctrine. This sees the head as a 'rigid box' with a fixed volume made up of the brain, cerebrospinal fluid (CSF), arterial and venous blood. Expansion of brain volume may occur due to cerebral oedema or there can be 'new matter' that occupies space, e.g. expanding haematoma, tumour, obstructive hydrocephalus. There is a limited capacity for compensation by decreasing the amount of CSF or venous blood. Even when this compensation occurs, there will be some increase in the intracranial pressure (ICP) towards 20 mmHg from the normal value of 5–10 mmHg. When the capacity to compensate fails, the system becomes non-compliant and further small increases in volume will produce rapid rises in pressure (Fig. 6.7).
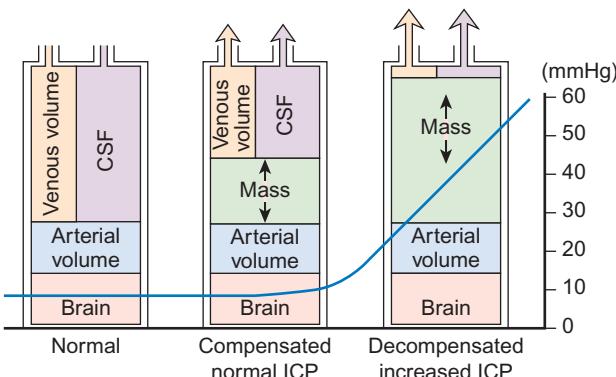
Fig. 6.7 Monro–Kellie doctrine showing the pressure (*y* axis)–volume (*x* axis) relationship between ICP, volume of CSF, blood, and brain tissue. *(From Nichols DG, et al. Rogers' textbook of paediatric intensive care, 4th edition, 1996 LWW; p.646.)*

This is the rationale for rapid management, including osmotherapy and the need to perform definitive surgery within 4–6 hours to remove expanding intracranial mass lesions such as haematoma in trauma (see Fig. 6.7) and CSF in obstructed hydrocephalus. Once ICP exceeds mean arterial pressure (MAP), cerebral perfusion becomes critically impaired and hypoxic–ischaemic brain damage may occur. Further increases in ICP may result in either transtentorial herniation of the innermost part of the temporal lobe, the uncus or cerebellar tonsillar herniation through the foramen magnum, resulting in brainstem compression and ultimately brain death. In tonsillar herniation, or 'coning', the cerebellar tonsils move downward through the foramen magnum causing compression of the lower brainstem and upper cervical spinal cord. Increased pressure on the brainstem results in dysfunction of the centres responsible for controlling respiratory and cardiac function.

All patients with encephalopathy must therefore have some neuroimaging to make an assessment of ICP. Consideration must also be given as to whether ICP monitoring is necessary. ICP monitoring is usually facilitated by neurosurgical insertion of a fine bore catheter into the substance of the brain through a small burr hole. ICP monitoring is a standard of care in traumatic brain injury requiring neurointensive care, although there is no evidence for the benefit of ICP monitoring in either traumatic or non-traumatic coma. However, the advantage of ICP monitoring is that an accurate assessment of cerebral perfusion pressure (CPP) can be obtained:

$$CPP = MAP - ICP$$

The control of CPP is used to prevent cerebral ischaemia, and normal values change with age (infant >50 mmHg, child >60 mmHg, adolescent >70 mmHg).

Blood flow also depends on the diameter of cerebral blood vessels, which is affected by $PaCO_2$, low levels causing vasoconstriction and high levels vasodilatation. Maintenance of normocapnia is therefore of critical importance. Once the patient is intubated, a formal blood gas should be measured to determine the $PaCO_2$. This should be correlated to an end-tidal CO_2 measurement, allowing adjustment of the ventilation constantly to avoid hyperventilation, which can induce ischaemia, and hypoventilation, which may lead to increased cerebral blood flow and exacerbation of raised ICP.

As pressure difference is dependent on arterial pressure, it is often necessary to maintain blood pressure to above normal levels, with inotropes if necessary.

Adequate oxygen delivery is maintained by ensuring physiologic haemoglobin levels, with transfusion if necessary. Cerebral oxygen demand can be reduced

by sedation and seizure control. Hypothermia may also have a role in reducing cerebral oxygen demand but as yet there is no definitive trial evidence to support its use in children. Steroids are not included in the treatment of raised ICP as there is limited evidence of beneficial effects, although they may have a role in meningitis or tumours. Osmotherapy (3% saline or mannitol) may provide benefit by reducing intracranial cellular oedema. In traumatic brain injury, osmotherapy should only be used on the advice of a neurosurgeon. Other strategies include fluid restriction, and maintaining the head at a tilt 30° upright in the midline to improve venous return. All the treatments of raised ICP are aimed at trying to decrease or limit cerebral oedema and acutely dropping the ICP by creating more space, hence limiting or preventing secondary brain injury.

Question 6.5

Cranial nerves in head injury

Tony, a previously fit and well 8-year-old boy, was brought into the emergency department by ambulance following a road traffic collision in which he was a pedestrian hit by a car driving at 40 mph. There was dried blood over his hair. He was intubated and ventilated and made no spontaneous respiratory effort. Oxygen saturations were 97% in FiO_2 100%. His heart rate was 70, capillary refill time 2 seconds and blood pressure 185/90. His Glasgow Coma Score was 3. On examination of his eyes, the right eye was deviated down and outwards with a fixed and dilated pupil; the left eye was in the midline position with a pupil that constricted to light.

Which ONE of the following cranial nerve(s) is involved in the localizing sign identified in the clinical examination?

A. Cranial nerve I
B. Cranial nerve I and III
C. Cranial nerve III
D. Cranial nerve IV
E. Cranial nerve IV and VI

Answer 6.5

C. Cranial nerve III

Uncal herniation commonly causes compression of cranial nerve III, which originates in the anterior aspect of the midbrain. Cranial nerve III compression results in:

- Parasympathetic paralysis and pupillary dilation of the eye on the affected side

- Loss of innervation of all ocular motility muscles except for lateral rectus (cranial VI) and the superior oblique (cranial nerve IV) resulting in the deviation of the eye to a 'down and out' position.

Pupillary dilation often precedes the somatic motor effects of cranial nerve III compression because the parasympathetic fibres surround the motor fibres of the nerve and so are compressed first. Initially pupillary dilation is ipsilateral to the side of the lesion (localizing sign). However, as intracranial pressure continues to rise, the contralateral cranial nerve III is also compressed and bilateral 'fixed and dilated' pupils are seen.

Acute non-traumatic encephalopathies

Acute encephalopathy may be defined as a sudden onset of diffuse brain dysfunction with or without an associated change in level of consciousness. Encephalopathies may be convulsive or non-convulsive. Convulsive status epilepticus (CSE) is defined as a generalized convulsion lasting 30 minutes or longer, or repeated tonic–clonic convulsions occurring over a 30 minute period without recovery of consciousness between each convulsion. Children presenting with non-convulsive acute encephalopathies may present with reduced conscious level, psychosis or confusion. These children may be in non-convulsive status epilepticus.

CSE in childhood is a life-threatening condition with a serious risk of neurological sequelae. These sequelae are due to a combination of (1) hypoxia due to airway obstruction and hypoventilation and (2) neuronal damage due to unmet increased cerebral metabolic demands. CSE in children has a mortality of up to 4%. Neurological sequelae of CSE, such as epilepsy, motor deficits, learning difficulties, and behavioural problems, are rare but occur in a minority of children.

The commonest cause of CSE in paediatrics is uncontrolled epilepsy with an underlying seizure disorder or febrile convulsion. Febrile convulsions only occur in children between the ages of 6 months and 6 years. In febrile cases, infective meningoencephalitis caused by bacteria (meningococcus and pneumococcus in particular) or viruses (herpes simplex and enteroviridae) are possible and must be treated until ruled out. However, other structural and non-structural causes should be considered in all cases of acute encephalopathy, including space-occupying lesions, autoimmune disease such as acute disseminated encephalomyelitis (ADEM) or anti-NMDA receptor

antibody encephalitis, vascular occlusion or bleeding, metabolic disorders, poisons and trauma including non-accidental injury.

Acute resuscitation and stabilization

Initial assessment and resuscitation should address, as always, the airway, breathing and circulation (A, B, C). High-flow oxygen should be given and the blood glucose level measured. A brief history and clinical examination should be undertaken to confirm genuine seizure activity. The initial resuscitation should involve stabilizing the airway, breathing and circulation whilst making an assessment of conscious level (GCS/AVPU). One of the major decisions that needs to be made is the need for artificial ventilation. The advantages of airway protection and controlling gas exchange are obvious but the disadvantage of artificial ventilation is that it reduces the ability to monitor conscious level.

Treatment of infection

Until a confirmed microbiological diagnosis has been made, patients should be started on high-dose antibiotic and antiviral treatment (usually a third generation cephalosporin, a macrolide and acyclovir to cover treatable infectious causes). Specimens must be taken to identify the cause and ideally should include CSF, but raised ICP must first be excluded because of the risk of coning. PCR is now routinely done for both bacterial and viral (herpes simplex) causes.

Seizure control

Unless effectively controlled, seizures result in further hypoxia and ischaemia due to a combination of airway obstruction and neuronal secondary energy failure. Seizure control should be part of the initial resuscitation but looking for further seizure activity is also vital. This can be done clinically but it is not always obvious when the patient is paralysed and sedated. Electroencephalography (EEG) may be used to identify continuing seizure activity. Whilst brief seizures may be managed with benzodiazepines (e.g. lorazepam), prolonged seizure activity often requires intravenous anticonvulsants (e.g. phenytoin) or barbiturate infusions (e.g. phenobarbitone, thiopentone). There are protocols for the management of status epilepticus, e.g. APLS (Advanced Paediatric Life Support).

Neurointensive care

If, 20 minutes after intravenous phenytoin or phenobarbitone has commenced, the child remains in CSE or the airway is not protected because of reduced conscious level, then rapid sequence induction of anaesthesia should be performed using thiopentone.

If neuromuscular paralysis is used, this should be short acting so as not to mask the clinical signs of the convulsion. Once ventilated, standard neuroprotective measures should be instituted as above, including good oxygenation, avoidance of hyper- or hypocapnia, maintenance of a good cerebral perfusion pressure, normothermia and adequate sedation. Lumbar puncture should be avoided until it is clear that intracranial pressure is not raised.

Dehydration and fluid management

Total body fluid is higher in children than adults. At birth, the body is made up of 80% water. By adulthood it is only 55–60%. Water is distributed two thirds in the intracellular space and one third in the extracellular space (divided 75% interstitial and 25% intravascular). The distribution of water between these compartments depends on the pressure and osmotic gradients between them.

Dehydration

Dehydration is loss of water and electrolytes. Children may become dehydrated from:

- Reduced oral fluid intake: reduced appetite due to illness, vomiting, sore throat
- Additional fluid losses: fever, diarrhoea
- Increased insensible losses: increased sweating, tachypnoea
- Loss of the normal fluid-retaining mechanisms: capillary leak, burns, the permeable skin of premature infants, increased urinary losses secondary to renal disease.

Infants and young children are more prone to dehydration than older children and adults because:

- Their body is made up of more water
- They have a high surface area in relation to their height or weight (high surface area : volume ratio)
- They have relatively high evaporative water losses
- They have a higher metabolic rate and so higher turnover of water and electrolytes
- They rely on others to give them fluids.

Dehydration itself does not cause death, but shock does. Shock occurs when there is rapid loss of at least 25% of the intravascular volume that is not replaced at a similar rate from the interstitial space (see above). Shock can occur in the absence or presence of dehydration, depending on the rate of fluid loss and fluid shifts between compartments. The treatment of shock requires rapid administration of intravascular volume of fluid that approximates in electrolyte content to

plasma. In contrast, the treatment of dehydration requires gradual replacement of fluids with an electrolyte content that relates to the electrolyte losses, or to the total body electrolyte content.

Weight is the only clinically available objective measure of total body fluid changes and enables an accurate assessment of fluid balance over time. If pre-illness body weight is known, then accurate percentage dehydration can be calculated:

$$\text{(weight before} - \text{weight after)}/\text{weight before} = \% \text{ dehydration}$$

However, pre-illness weight is rarely available in emergency situations. Therefore, clinical symptoms and signs provide an alternative, reasonable estimate of total body fluid losses.

Categorizing dehydration in this way aids assessment as well as appropriate fluid management. The 'red flag' symptoms and signs are important as they help identify children with severe dehydration at increased risk of shock. Clinical dehydration only becomes apparent after fluid losses of >25–50 mL/kg, that is, 2.5–5% dehydration and shock is seen with fluid losses over 10%.

Types of dehydration

There are three types of dehydration based on plasma sodium levels:

- Isotonic or isonatraemic – equal loss of water and electrolytes
- Hypotonic or hyponatraemic – primarily a loss of electrolytes and in particular sodium
- Hypertonic or hypernatraemic – primarily a loss of water.

Hyponatraemic (hypotonic) dehydration is defined as dehydration in association with a plasma sodium concentration <135 mmol/L. Extreme hyponatraemia (<125 mmol/L) or a rapid fall in serum sodium concentration is associated with cognitive impairment, seizures, brainstem herniation and death due to cerebral oedema. Hypotonic crystalloid fluids, for example sodium chloride 0.18% with glucose 4%, are no longer used in paediatrics because of the risk of associated hyponatraemia.

In hypernatraemic (hypertonic) dehydration (serum sodium concentration >145 mmol/L), there is excessive free water loss, or rarely, the administration of excess sodium. In healthy individuals, thirst and the stimulation of vasopressin (antidiuretic hormone, ADH) release protect against hypernatraemia. Therefore, sustained hypernatraemia predominantly occurs when thirst or access to water is impaired. The highest risk groups are infants, especially breastfed infants establishing lactation and infants with gastroenteritis.

In hypernatraemia, fluid shifts from the intracellular compartment into extracellular spaces result in cellular dehydration. Brain cells are especially vulnerable to complications resulting from cellular contraction. Severe hypernatraemic dehydration is therefore associated with cerebral haemorrhage, seizures, paralysis, and encephalopathy. In addition, rapid rehydration with hypotonic fluids may also cause cerebral oedema and central pontine myelinolysis, which can lead to coma, convulsions, and death. Therefore, if intravenous fluid therapy is required to treat dehydration, it is important to first check plasma electrolytes so that rehydration fluid choice and replacement rate is appropriate.

Maintenance fluid therapy

Maintenance therapy is the provision of fluid and electrolytes to replace anticipated losses from breathing, sweating and urine output. The maintenance fluid calculation is based on several assumptions: 100 kcal/kg/day of caloric requirement, 3 mL/kg/day of urine output and normal stool output. Fluid requirements are greatest for the first 10 kg of body weight, with a marked reduction of fluid required per kg after the first 20 kg of body weight (Table 6.5). The calculation by which daily fluid requirements are calculated (known as the Holliday–Segar formula) was devised in the 1950s based on these assumptions.

However, in critical illness or injury, losses may be profoundly disturbed. For example, in syndrome of inappropriate antidiuretic hormone secretion (SIADH) secondary to acute respiratory or neurological pathology, reduced renal fluid loss may reduce fluid requirements to as low as 30 mL/kg/day, whereas in severe diarrhoeal illness, fluid requirements may increase up to fourfold. It is therefore important to make individual regular assessments of all patients requiring intravenous fluid therapy.

Enteral feeds, by mouth or nasogastric tube, are in general used as maintenance fluid if tolerated. If intravenous maintenance fluid is required, isotonic crystalloid fluids are used, for example, sodium chloride

Table 6.5 **Maintenance fluid requirements**

Body weight	Fluid requirement per day (mL/kg)	Fluid requirement (mL/kg)
First 10kg	100	4
Second 10kg	50	2
Subsequent kilograms	20	1

Source: Advanced Paediatric Life Support, Fifth Edition. Edited by Martin Samuels, Sue Wieteska.© 2011 Blackwell Publishing Ltd. Published 2011 by Blackwell Publishing Ltd.

0.9% with dextrose 5%. In neonates, glucose 10% with added sodium chloride is used as neonates have a higher glucose requirement.

Rehydration fluid therapy

Rehydration therapy aims to replace fluid losses and correct any electrolyte deficits. When percentage dehydration is known accurately, the deficit volume to be replaced can be calculated:

$$\text{Water deficit volume (mL)} = \text{\% dehydration} \times \text{weight (kg)} \times 10$$

However, in clinical practice, the severity of dehydration is often determined and categorized by clinical features (see Box 6.7). These dehydration categories can be used to guide management.

In children with no clinically detectable dehydration, regular oral fluid intake, including breastfeeding and other milk feeds, should be encouraged. If a child is at risk of dehydration, oral rehydration solution (ORS) can be offered as supplemental fluid to prevent dehydration occurring.

In clinical dehydration, where there are no red flag symptoms or shock, the aim of management is to rehydrate via the oral route using a low osmolarity ORS (240–250 mOsm/L). A volume of 50 mL/kg of ORS is recommended for fluid deficit replacement over 4 hours in addition to a child's maintenance fluid volume. The ORS can be given orally or via a nasogastric tube.

Rehydration with intravenous fluids is only indicated if there are red flag symptoms, persistent vomiting despite nasogastric tube administration of ORS, or suspected/confirmed shock.

In cases of shock, a rapid intravenous fluid bolus of 20 mL/kg of 0.9% sodium chloride should be given. If features of shock persist and repeated fluid boluses are needed, then other causes of shock other than dehydration need to be considered (see above). Of note, the isotonic crystalloid 0.9% sodium chloride is currently the recommended first line fluid for resuscitation of all seriously ill children, though in practice other isotonic fluids such as Ringer's lactate are often used. There is currently insufficient evidence in the literature to support preferential use of one type of fluid over another.

Once shock has resolved, rehydration can start with intravenous fluids. The choice of fluid and the rate of deficit correction are dependent on serum electrolyte levels, in particular serum sodium levels.

In isonatraemic or hyponatraemic dehydration, an isotonic solution such as 0.9% sodium chloride or 0.9% sodium chloride with 5% glucose is used for fluid deficit replacement and maintenance. Current UK National Institute for Clinical Excellence (NICE) guidance recommends that for children who initially require rapid intravenous fluid boluses for suspected or confirmed shock, 100 mL/kg/day for fluid deficit replacement is added to maintenance fluid requirements. In children who are not shocked at presentation, 50 mL/kg/day for fluid deficit replacement may be added.

Rehydration with intravenous fluid therapy has traditionally been undertaken slowly, over 24 hours or longer. However, this is now an area of controversy, with recent guidance from the World Health Organization recommending that intravenous rehydration should be completed within 3–6 hours. Slow rehydration results in children remaining dehydrated for longer, delays restarting oral fluids and is associated with longer duration of hospital stay. Current NICE guidance also supports more rapid intravenous rehydration.

In hypernatraemic dehydration, an isotonic solution such as 0.9% sodium chloride, or 0.9% sodium chloride with 5% glucose, may be used for fluid deficit replacement and maintenance. However, the fluid deficit must be replaced slowly and typically over 48 hours. It is important that the serum sodium levels are reduced slowly, at a rate of less than 0.5 mmol/L per hour. Rapid correction is associated with cerebral oedema.

Consideration of electrolyte disturbances are also critical when managing diabetic ketoacidosis (DKA). Children presenting in DKA are often severely dehydrated, with abnormalities in serum glucose and sodium levels. Overhydration and/or rapid correction of blood sodium and glucose levels are risk factors for cerebral oedema. DKA management protocols therefore recommend treatment of shock with 10 mL/kg aliquots of 0.9% sodium chloride, limiting the total fluid deficit replacement to 8% dehydration or 30 mL/kg and rehydrating over 48 hours.

Electrolytes

Changes in serum sodium, potassium and calcium levels can be life-threatening. However, correction of these electrolyte disturbances, specifically rapid rates of change, can also result in serious complications. This is considered in detail in Chapter 19, Nephrology.

Box 6.7 How dehydration is graded

- No clinically detectable dehydration
- Clinical dehydration
- Clinical shock

Pathophysiology of sepsis

Sepsis is the systemic response to infection or, in the language of international consensus criteria, the systemic inflammatory response syndrome (SIRS) caused by infection (Table 6.6). SIRS has many causes, including infection, trauma, burns and pancreatitis and is defined by changes in temperature, heart rate, respiratory rate and white cell count. 'Septic shock' is inadequate organ perfusion in addition to the above changes. The characteristic pattern of worsening cardiovascular, respiratory and subsequently other organ system dysfunction is termed 'severe sepsis' when due to infection.

Since the early 1990s, the causative agents of septicaemia in children have dramatically changed due to the introduction of conjugate vaccines. There has been a major reduction in cases due to *N. meningitidis* (>99% decrease in serogroup C since vaccine introduction), vaccine serotypes of *S. pneumoniae* (98% decrease in vaccine types) and Hib (>90% reduction). Over the same period there has been a slight increase in rates of non-vaccine serotypes of *S. pneumoniae*, *E. coli*, *S. aureus* and Group A streptococcus. Toxic shock syndrome is an acute febrile illness caused by *S. aureus* or Group A streptococcus and is characterized by hypotension and multi-organ dysfunction caused by bacterial exotoxins that act as superantigens.

With improvements in public awareness and early recognition and management, the hospital mortality from meningococcal sepsis has fallen from over 90% in the mid 20th century to around 10% currently. An understanding of the pathophysiology is the key to successful management of children presenting with sepsis.

The systemic inflammatory response in bacterial sepsis

A large body of evidence now indicates that most of the pathophysiology of sepsis is caused by activation of host immune mechanisms, triggered by numerous bacterial factors. This activation may continue for days or even weeks after eradication of micro-organisms by appropriate antibiotic therapy. Activation is caused by bacterial cell wall components (particularly endotoxin in gram negative sepsis) binding to and stimulating inflammatory and vascular endothelial cells via a variety of mechanisms.

Stimulated monocytes produce a range of pro-inflammatory cytokines, including tumour necrosis factor α (TNFα). In general, cytokine levels are closely correlated with disease severity and risk of death. Stimulated neutrophils undergo a respiratory burst with the production of reactive oxygen species, as well as degranulation and the release of a range of inflammatory proteins, proteases, and other enzymes. Neutrophils probably contribute to the damage seen at the endothelial surface.

The microvascular injury in sepsis

The major pathophysiological event occurring in bacterial septicaemia is change in the vascular endothelial

Table 6.6 Definitions of SIRS, sepsis, severe sepsis and septic shock

SIRS	The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:
	• Core temperature of >38.5°C or <36°C
	• Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs or painful stimuli; or otherwise unexplained elevation over a 0.5–4-hour time period OR children <1 year old; bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blocker drugs or congenital heart disease, or otherwise unexplained persistent depression over a 0.5-hour time period
	• Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anaesthesia
	• Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils
Infection	A suspected or proven (by positive culture, tissue stain or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, or laboratory tests (e.g. white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash or purpura fulminans).
Sepsis	SIRS in the presence of or as a result of suspected or proven infection.
Severe sepsis	Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions.
Septic shock	Sepsis and cardiovascular dysfunction.

SIRS, systemic inflammatory response syndrome.
Source: Goldstein B, et al. Pediatr Crit Care Med 2005;6:2–8. Organ dysfunction may include cardiovascular, respiratory, neurological, haematological, renal or hepatic.

surface, which normally regulates vascular permeability and presents a thromboresistant, non-reactive surface to circulating blood cells. These properties are lost. The complex physiology of sepsis is thus explained by four basic processes affecting the microvasculature:

- Increased vascular permeability
- Pathological vasoconstriction and vasodilatation
- Loss of thromboresistance and intravascular coagulation
- Myocardial dysfunction

These events are responsible for the development of shock and multi-organ failure in sepsis.

1. Increased vascular permeability

Hypovolaemia is the most important cause of shock and is a result of increased vascular permeability. Loss of circulating plasma is initially compensated for by homeostatic mechanisms, including vasoconstriction of both arterial and venous vascular beds. However, as capillary leak progresses, venous return to the heart is impaired and cardiac output falls. Although restoration of circulating volume is the most important component of resuscitation, it is also associated with a risk of increasing oedema in all tissues and organs as a result of persistent capillary leak. Fluid may accumulate in tissues and muscle compartments, peritoneal and pleural spaces, and in alveoli. Pulmonary oedema is the consequence of increased vascular permeability.

2. Vasoconstriction and vasodilatation

Compensatory vasoconstriction is an early protective mechanism to maintain tissue and organ perfusion in the face of diminished cardiac output. Most children with septic shock have intense vasoconstriction, which may persist after resuscitation. Severely affected patients may develop cold, pale, and ischaemic limbs, so-called 'cold shock'. In contrast, some patients, usually older children, develop profound vasodilatation following resuscitation, with bounding pulses, warm peripheries and hypotension, so-called 'warm shock'. 'Warm shock' usually responds to fluid resuscitation and vasopressors such as noradrenaline, which causes peripheral vasoconstriction. Between these two extremes of vasomotor response there are patients who have a mixture of vasoconstriction in some vascular beds and dilatation in others.

3. Intravascular thrombosis

The hallmark of severe meningococcal sepsis is widespread purpura fulminans with thrombosis and haemorrhagic necrosis in skin and, in extreme cases, infarction and gangrene of limbs and digits. This occurs due to disruption of the normal antithrombotic properties of the vascular endothelial surface and impairment of natural anticoagulant pathways and fibrinolysis. Platelets and clotting factors are consumed as clot is formed in small vessels, resulting in profound thrombocytopenia and prolonged coagulation. Sluggish capillary circulation and intense vasoconstriction further increases the likelihood of thrombosis in the skin and the peripheries.

4. Myocardial dysfunction

Hypovolaemia caused by the capillary leak and loss of circulating volume is the major contributor to the low cardiac output seen in sepsis. However, there is also a profound defect in myocardial contractility, which persists even after correction of circulating volume. In meningococcal sepsis, the development of myocardial dysfunction is thought to be caused by the negative inotropic effect of proinflammatory mediators, particularly IL-6. Furthermore, hypoxia, acidosis, hypoglycaemia, hypokalaemia, hypocalcaemia, and hypophosphataemia are common in all forms of sepsis and may adversely affect myocardial function. Although some patients require very high doses of inotropes, the impairment of myocardial function seen in sepsis usually recovers without any long-term sequelae.

Question 6.6

Fever

A 5-year-old boy presents with a 24-hour history of fever, reduced oral intake and progressive lethargy. He is previously well and fully immunized. Initial assessment: T 39.6°C, HR 158/min, RR 40/min, SaO$_2$ 95% (air), BP 70/40, central CRT 4 seconds. He is lethargic but opens his eyes in response to his mother's voice. On examination, he has a purpuric rash on his trunk, and there are no other specific abnormal findings. After two 20 mL/kg boluses of normal saline, he remains clinically unchanged. Which ONE of the following statements best describes the next treatment he should be given?

A. He should be given activated protein C

B. He should be given IV hydrocortisone

C. He should be given inotropes if central IV access has been obtained

D. He should be given inotropes through peripheral or central IV access

E. He should continue to be given boluses of normal saline until there is a clinical response

Answer 6.6

D. He should be given inotropes through peripheral or central IV access.

This child is most likely to have meningococcal septicaemia and is in fluid-refractory shock. Initial management is assessment and resuscitation. Broad-spectrum antibiotics (in this age group, a third generation cephalosporin) should also be given.

In a child who remains shocked after 40 mL/kg of fluid resuscitation, a further bolus should be given. The child should be urgently discussed with a PICU specialist and further management be guided by them, in conjunction with the local anaesthetist. The child should be intubated and ventilated (even in the absence of respiratory indications) as pulmonary oedema can be anticipated due to capillary leak caused by sepsis. In addition, inotropes should be commenced at this stage. Dopamine can be administered peripherally and adrenaline can be given via IO or central IV access. Noradrenaline can also be given

via central IV access. Giving continuing fluid boluses without additional support will not be sufficient to maintain tissue perfusion.

Cohort studies show that a delay in the use of inotropic therapies is associated with major increases in mortality risk. Inotrope therapy may be required to sustain perfusion pressure, even when hypovolaemia has not yet been resolved. Choice of agent depends on the clinical assessment of the child, type of IV/IO access available and local PICU expertise. While steroids may also be used in children with fluid-refractory shock, they may also be given in those who remain in shock after inotropic support has been given, particularly if there is any evidence of adrenal insufficiency. Randomized-controlled trials of activated protein C and other biological therapies show no benefit in children or adults. Current management of sepsis therefore consists of basic ABC management, organ-specific support (e.g. ventilation, inotropes, renal support), antibiotics and source control.

Further reading

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National Collaborating Centre for Women's and Children's Health. Bacterial meningitis and meningococcal septicaemia in children: the management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. London: RCOG Press; 2010.

Mark Anderson, Eleanor Dawson

Accidents and poisoning

Accidents

Traumatic injury is the leading cause of death in children and young people aged 1–19 years. For every child who dies as the result of an accident, a significantly greater number are hospitalized, a proportion of whom will acquire permanent disability or disfigurement. In England and Wales, the mortality rate due to accidents has fallen markedly over the last 20 years (Fig. 7.1). This has resulted in more children aged 1–14 years now dying from malignant disease than injury. However, in 2011, 143 children died from an unintentional injury and 68 of these were under five years of age. The rate of admission to hospital of children and young people aged 0–17 years in England due to unintentional and deliberate injuries remains steady at about 120 per 10,000 population.

Worldwide, injuries are a leading cause of death and disability in children and young people, with much higher mortality rates in low- and middle-income countries (Table 7.1), with road traffic injuries and drowning featuring very commonly.

Accidents are particularly common in children and young people:

- Young children do not perceive situational danger and are unaware of the potential dangers in their environment.
- Older children and young people indulge in risk-taking behaviours and often underestimate their potential dangers.

Anatomical and physiological differences between young children and adolescents influence the pattern of injuries seen and have implications for the assessment and management of injured children and young people:

- Young children have less fat and a more elastic skeleton protecting tightly packed internal organs. This, combined with their smaller size, means that impact force is distributed widely through the body, resulting in a higher incidence of multisystem trauma than adolescents and adults.
- The larger body surface area to mass ratio in young children predisposes them to greater heat and insensible fluid loss.
- Blood pressure is often maintained in children even following more than 20% loss of circulating volume, so careful attention has to be paid to other physiological parameters when assessing perfusion status.

Road traffic collisions (RTCs) account for the highest number of accidental deaths in children. Child pedestrians are the most vulnerable individuals in RTCs, followed by cyclists and then vehicle passengers. Most accidents occur in built-up areas rather than higher speed dual carriageways and motorways. Over 2000 children were killed or seriously injured as a result of road accidents in the UK in 2012. Burns and scalds, drownings, falls and poisonings complete the top five causes of childhood accidental deaths.
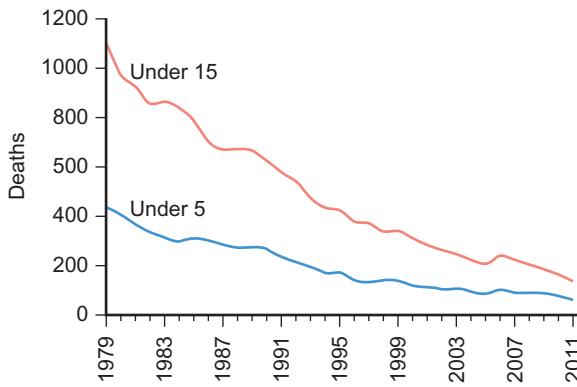
Fig. 7.1 Deaths due to unintentional injuries in England and Wales in children from birth to 14 years. ONS, Office for National Statistics.

Table 7.1 Unintentional injury death rates per 100,000 children by age and country income level 2004

	Age				
	<1 y	1–4 y	5–9 y	10–14 y	15–19 y
HIC	28.0	8.5	5.6	6.1	23.9
LMIC	102.9	49.6	37.6	25.8	42.6
World	96.1	45.8	34.4	23.8	40.6

HIC, high-income countries; LMIC, low- and middle-income countries. (Source: WHO (2008), Global Burden of Disease: 2004 Update.)

Table 7.2 Examples of causes of primary and secondary injury

Primary	Secondary
Extradural haemorrhage	Cerebral oedema
Subdural haemorrhage	Infection
Subarachnoid haemorrhage	Hypoxia
Cerebral contusion/laceration	Hypotension
Axonal stretching/shearing	Seizures

Accident prevention is a major public health issue. The variety of causes and multitude of factors involved in accident causation render a blanket approach to their prevention ineffective. Small targeted strategies and campaigns, which can be scaled up once efficacy has been proven, are likely to be successful. There are three main strategies to accident prevention:

- Child and parent education
- Altering the child's environment to be safer
- Enforcing environmental change through the law

Box 7.1 lists some specific examples of successful accident prevention strategies.

Trauma

Head injury

Head injury is the commonest cause of death in injured children. Severity of the injury is therefore the

principal determinant of outcome in multisystem trauma. In young children, falls are the commonest cause of severe injury, whereas in the older age groups, road traffic collisions, particularly from cycle accidents, are more common. Non-accidental (inflicted) head injury must be considered in infants.

Damage to the central nervous system (CNS) as a result of head injury can be divided into primary and secondary causes (Table 7.2).

Primary injury

This is sustained as a direct consequence of the impact, causing disruption of the intracranial contents, including neuronal injury, such as diffuse axonal injury and vascular trauma.

Diffuse axonal injury (DAI) is one of the most serious forms of primary neuronal injury and is associated with high mortality and neurodisability. It results in widespread injury in the brain, not in just one specific area, and occurs as a result of traumatic shearing forces due to rapid acceleration, deceleration and/or rotation of the brain (Fig. 7.2). As the brain moves rapidly backwards and forwards within the skull, the axons are disrupted, particularly at the grey–white matter junction. The clinical manifestations of this will depend on the site and severity of axonal damage, but loss of consciousness is a predominant feature. DAI is typically not demonstrated by computerized tomography (CT) but requires magnetic resonance imaging (MRI).

The force of impact may cause injury to intracranial blood vessels, leading to bleeding within the skull. Traumatic extra-axial bleeds (those occurring outwith the brain) are usually extradural and subdural haematomas. In extradural haematomas, blood accumulates between the dura mater and the skull. This type
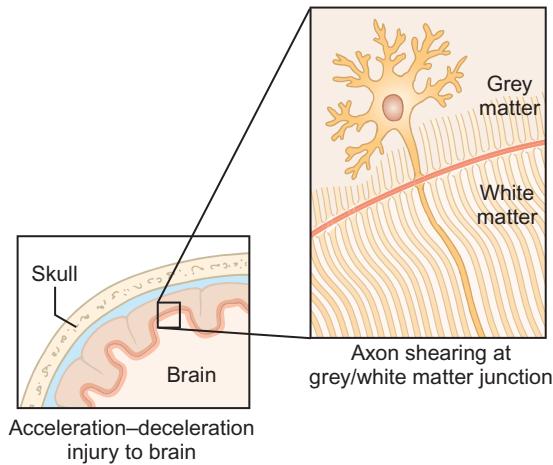
Fig. 7.2 The mechanism of diffuse axonal injury.

of bleed is usually due to arterial breach, particularly of the middle meningeal artery, and as such, develops rapidly. Subdural haematomas involve bleeding between the dura mater and the arachnoid mater and, in contrast to extradural haematomas, are usually venous in origin, so develop at a slower pace. Bridging veins in the dural regions are the most common source of bleeding. Both types of haematomas can cause raised intracranial pressure as the bleed enlarges, causing mass effect and compression of the brain tissue. Subdural haematomas can also be seen in non-accidental head injury. An incidental finding of these or a finding inconsistent with the history given, should raise suspicion and consideration of non-accidental injury.

Traumatic subarachnoid haemorrhages can also occur and usually develop in close proximity to cerebral contusions or skull fractures.

Secondary injury

Secondary injury is further damage to the brain that can occur minutes to days after the original injury. It is often either preventable or treatable, and failure to minimize its effects results in a poorer overall outcome. Patients with significant traumatic brain injury need extremely close monitoring, especially in the initial period after injury, with the main aim of early management being the prevention and treatment of complications which may give rise to secondary injury.

Management

Mild head injury

Despite the seriousness of paediatric head trauma, the vast majority of head injuries in children are mild. Determining which children require neuroimaging is difficult. Various criteria, related to both the history and examination, are used to try to predict the likelihood of intracranial pathology. The current

> **Box 7.2 NICE indications for CT scan following traumatic head injury in children (2014)**
>
> Any of:
> - Suspicion of non-accidental injury
> - Post-traumatic seizure
> - Glasgow Coma Score (GCS) <14 on arrival at emergency department (<15 for <1 year of age)
> - GCS <15 two hours after injury
> - Suspected open or depressed skull fracture
> - Evidence of basal skull fracture
> - Focal neurological deficit
> - Presence of bruise or swelling >5 cm in diameter in children aged <1 year
>
> More than one of:
> - Witnessed loss of consciousness >5 minutes
> - Abnormal drowsiness
> - >2 discrete episodes of vomiting
> - Amnesia of >5 minutes
> - Dangerous mechanism of injury

recommendations from the National Institute for Health and Care Excellence (NICE) are found in Box 7.2. These criteria display excellent sensitivity but poor specificity and result in a significant number of normal scans.

Severe brain injury

The aim of resuscitation of the child with severe head injury is to maximize cerebral perfusion while minimizing the effect of raised intracranial pressure. This is described in Chapter 6, Paediatric emergencies and critical care.

Outcome

Although children sustaining a severe traumatic brain injury are likely to have a very long period of recovery, with intensive rehabilitation therapy they can make good progress and recover some function. Cognitive, behavioural and psychiatric problems are the most common long-term sequelae. Cognitive problems result in difficulty with memory, learning and language, while behavioural and psychiatric complications include personality changes, lack of inhibition and depression. These outcomes vary according to the severity of the injury, the age of the child and the pre-morbid condition.

Spinal cord injury

Spinal cord injury is rare in the paediatric age group, occurring most commonly as the result of road traffic collisions. The most common cervical fracture involves

the first two vertebrae. In addition, spinal cord injury without radiologic abnormality (SCIWORA) is almost exclusively a paediatric problem. This occurs as a result of the elasticity of the cervical spine allowing significant cord injury in absence of X-ray changes.

Thoracic injury

The most common causes of thoracic injury in children are road accidents and falls. Chest injuries are mostly caused by blunt trauma with only a very few due to penetrating injury, and usually occur in conjunction with trauma to other body parts. The chest wall of children is much more compliant than adults, leading to transfer of impact energy to underlying organs and structures with minimal, if any, external sign of injury or fracture. The presence of rib fractures or mediastinal injury indicates very significant and high energy impact. Common underlying injuries include lung contusions, which develop as energy is transferred rapidly to the lungs causing haemorrhage and oedema in the lung tissue, and pneumothoraces. Great vessel trauma is very rare.

Abdominal injury

Children are more vulnerable to major abdominal injuries as a result of pliable rib cages, which provide little protection to solid organs, which are proportionally larger than in adults. In addition, their abdominal wall is thin and provides less impact absorption.

Most abdominal injuries are caused by blunt trauma, often due to road traffic collisions, seat belt restraint and handlebar injury. The pancreas is particularly at risk from handlebar injury. Intra-abdominal organs bleed readily, resulting in hypovolaemia and circulatory collapse. Acceleration and deceleration forces cause injury to organs, which are moved rapidly and may come into contact with the spine. Abdominal injury can be life-threatening and difficult to diagnose quickly in the absence of external signs. Injury to organs such as the spleen and liver manifest themselves rapidly, while bowel or pancreatic injuries may not become clinically evident for several days. A proactive approach to identifying abdominal injury is needed, especially in high mechanism injuries. Although focused abdominal sonography for trauma (FAST) is a useful tool, it can miss major solid organ injury and it must be combined with clinical judgement.

Burns and scalds

Burns are injuries to tissues usually caused by heat, but also by friction, electricity, radiation (from the sun, for example) or chemicals. Scalds are caused by contact with hot liquid or steam. They are among the most common of childhood accidents. The vast majority of childhood burns and scalds occur within the home.

Risk factors

Children in low- and middle-income countries are most at risk from fatal burn injuries. Cooking on an open fire is a major risk factor and children with underlying medical conditions, such as epilepsy, are at particular risk when near fires. In high-income countries such as the UK, children in lower socio-economic groups are at increased risk.

Pathophysiology

The severity of burns and scalds is determined by two main factors – the length of contact and the temperature:

Contact temperature (°C)	Duration of contact required to result in epidermal injury
44	6 hours
54	30 seconds
70	<1 second

Burns are classified according to the depth and severity of the tissue damage and extent of body surface area. Previously, burns were described as first, second or third degree, but this has been replaced with the classification shown in Table 7.3.

Question 7.1

Burns

When calculating fluid requirements in children with burns, which ONE of the following statements is correct?

A. 4 mL/kg × % of total body surface area affected should be given within the first 8 hours

B. 0.9% sodium chloride is the preferred intravenous fluid

C. Maintenance requirements are given in addition to resuscitation fluid

D. The volume of resuscitation fluid required is determined by the depth of the burn

E. Urine output is a poor way to monitor adequacy of fluid replacement

---

Answer 7.1

C. Maintenance requirements are given in addition to resuscitation fluid

Table 7.3 Burn classification

Type of burn	Description
Superficial – simple erythema	Painful, reversible redness of the skin, such as in milder cases of sunburn. Only affects the epidermis so there is no blistering of the skin. Takes several days to heal and may result in peeling over the following days.
Superficial – partial thickness	Involves only the upper layers of the skin (epidermis and into the dermis) and usually heals within two weeks with minimal or no scarring. It appears as erythema with blistering and is painful.
Deep – partial thickness	Extends into the deeper layers of the dermis. The burn will be more yellow or white in colour and there may be blistering. These burns may require surgery such as skin grafting to aid healing. Without surgery, they will usually be associated with delayed healing and risk of significant scarring.
Full thickness	Involves all layers of skin and extends through the entire dermis. As the nerve endings have been fully damaged, these burns are painless and white or brown in colour. Healing takes many months and there is a high risk of complications such as contractures if the burn occurs across a joint. Surgery is usually indicated.

Burn injuries produce both local and systemic reactions. In small burns, the body's response is localized to the site of the burn. In larger burns affecting over 30% of the total body surface area, and also in deeper dermal burns, a systemic inflammatory response is seen with inflammatory mediators such as cytokines, prostaglandins, histamine and complement being released into the circulation. Capillary leak increases, leading to oedema in the soft tissues and intravascular fluid depletion. Hypovolaemia then results in hypoperfusion. Myocardial contractility can be reduced by the presence of tumour necrosis factor alpha. Intra-abdominal vasoconstriction occurs, potentially compromising blood flow to organs such as the spleen, kidneys and bowel. Fluid, including electrolytes, is also lost through evaporation from the burn itself and all these changes combine to produce systemic hypotension and end organ hypoperfusion. Catabolism is marked after major burns and early nutritional input is necessary to aid recovery. Infection risk is increased significantly due to direct entry of micro-organisms through the damaged area and because the local immune response is compromised.

As intravascular fluid depletion is a major complication of burns, adequate fluid resuscitation is important. Shock in burn is the result of a combination of factors, including hypovolaemia, microcirculatory injury and the release of local and systemic

Box 7.3 Sample criteria for referral to specialist burns unit

Burns greater than 5–7% total body surface area
Burns to face, hands, feet, genitalia, perineum, across major joints
Full thickness burns
Electrical burns
Chemical burns
Inhalation burns
Circumferential burns
Suspicious burns

inflammatory mediators. The foundation of early burn management is the treatment and prevention of shock with intravenous fluid resuscitation.

The heterogeneous nature of children with burns, in terms of their varying size and burn area, has led to the exploration of a number of formulae to guide fluid resuscitation. The most widely accepted version is the Parkland formula:

$$\text{Volume required over first 24 hours in mL} = 4 \times \% \text{ body surface area of burn} \times \text{body weight}$$

50% of this volume is administered over the first 8 hours with the remainder administered over the subsequent 16 hours. This mimics the physiological situation as plasma losses are greatest in the first 6–8 hours after a burn with ongoing slower capillary leakage thereafter. As a corollary, the 24-hour period therefore begins from the time of the burn, not the time of initiation of fluid resuscitation. The recommended fluid is crystalloid and, in general, Hartmann's solution is used as this has the closest electrolyte composition to plasma. Maintenance fluid requirements should be administered in addition to these volumes. The Parkland formula, and others like it, provide only a guide to fluid requirements and clinical response is the final arbiter of adequacy of fluid resuscitation. In particular, maintenance of urine output of 1.0 mL/kg/hour is generally accepted as evidence of euvolaemia in patients with burns.

Adequate analgesia is an essential element of the acute and ongoing management of burns with intravenous opiates often required for most significant burn injuries.

It is generally accepted that burns involving more than 5–7% of the body surface area and certain other burns should be cared for in a specialist burns unit (where possible) (Box 7.3), as these burns are more likely to require surgical input (e.g. skin grafting) and/or specialist monitoring of longer term complications (e.g. contractures).

Inhalation injury

The management of respiratory complications of burns sustained as a result of house fires is relatively common. Inhalation injury is the commonest cause of death in burns patients from smoke inhalation, and in combination with cutaneous burns has a mortality of 30–90%.

Upper airway injury resulting in obstruction in the first 12 hours after exposure is caused by direct thermal injury as well as chemical irritation. Lung parenchymal injury associated with inhalation, by contrast, is not a result of direct thermal injury – only inhaled steam, which has a heat-carrying capacity significantly greater than dry air, is capable of overcoming the heat dissipation mechanisms of the upper airways. Damage to the distal airways is caused by the incomplete products of combustion, in particular aldehydes, nitrogen and sulphur oxides, and carbon monoxide.

Whilst inhalation injury mostly results in proximal airway damage and oedema, it also inactivates surfactant leading to reduced pulmonary compliance and in severe cases to adult respiratory distress syndrome (ARDS).

Carbon monoxide poisoning

Carbon monoxide is a colourless, odourless and tasteless gas, which is produced as a result of incomplete burning due to insufficient oxygen. This can occur in older or poorly maintained gas appliances or when solid fuel is burned in enclosed areas with inadequate ventilation, for example using a cooking stove within a tent. Carbon monoxide exerts its toxic effect as a result of its extremely high affinity for haemoglobin, 230 times greater than that of oxygen. The binding of carbon monoxide to one of haemoglobin's four oxygen binding sites increases the affinity of the other three sites for oxygen. This has the effect of shifting the oxygen dissociation curve to the left and impedes the release of oxygen to body tissues. Carbon monoxide also binds to other haem-containing molecules, such as myoglobin and mitochondrial cytochrome oxidase, which may disrupt their function.

Symptoms of early carbon monoxide poisoning, such as headache, nausea, malaise and dizziness are non-specific and easily attributed to common causes such as colds and flu-like illnesses. As poisoning progresses, symptoms such as confusion and drowsiness occur, eventually leading to loss of consciousness and subsequent death.

In hospital settings, detection of carboxyhaemoglobin levels can be carried out by a using a pulse CO-oximeter or by blood gas analysis. Standard pulse oximetry is often normal even in the presence of significant carbon monoxide poisoning as carboxyhaemoglobin is misrepresented as oxyhaemoglobin. Symptoms of carbon monoxide poisoning may persist after blood carboxyhaemoglobin concentrations have returned to normal.

Treatment of carbon monoxide poisoning is to give high flow oxygen via a non-rebreathe mask which hastens the dissociation of carbon monoxide from carboxyhaemoglobin. Hyperbaric oxygen may reduce the half-life of carbon monoxide further but there remains controversy over whether it offers significant clinical benefit over standard high flow oxygen.

Depending on the extent of poisoning, long-term effects such as irreversible hypoxic brain damage may occur, although many patients make a full recovery. As carbon monoxide poisoning can present with non-specific symptoms, many milder cases are thought to go undetected. Carbon monoxide detectors are now widely available and are recommended for use at home to detect high levels at an early stage.

Drowning

Drowning is defined (by WHO) as the process of experiencing respiratory impairment from submersion or immersion in liquid, regardless of outcome. Drowning outcomes are classified into three categories: death, morbidity or no morbidity. This terminology replaces the previously used 'drowning and near-drowning'. Drowning is the third highest cause of accidental death in children in the UK. Once submerged, asphyxia with or without aspiration occurs. Hypoxia and ischaemia rapidly develop causing multisystem failure. Key factors affecting outcome after drowning are the duration of hypoxic–ischaemic injury, the temperature of the liquid and the adequacy of resuscitation. Immediate action and effective resuscitation can prevent death.

In 2011, 46 individuals aged 0–19 years died as a result of drowning in the UK. Drownings were most common in summer months and during weekends. At all ages, boys were at least five times more likely than girls to die in water-related incidents. Preschool-aged children and teenagers were at higher risk than other age groups. The most common location for drowning was in swimming pools. In younger children, baths and ponds were incriminated, while in older children, canals and rivers were more predominant. Young children are particularly at risk of drowning due to their inquisitive nature and lack of sense of danger.

Following immersion, once water enters the airway, through gasping and aspiration, hypoxia may occur through two mechanisms, either by large volume aspiration or by laryngospasm. Ongoing hypoxia rapidly

leads to loss of consciousness, bradycardia and ultimately cardiorespiratory arrest. This can occur within minutes of the initial water entry. Hypoxia and ischaemia may affect multiple organ systems, with the brain particularly vulnerable. Irreversible neurological damage can occur within a very short period of time. The diving reflex – bradycardia followed by peripheral vasoconstriction to preserve blood supply to vital organs – triggered by facial contact with cold water is likely to be one of the protective mechanisms allowing a longer survival time in cold water drowning. There is a case report of a child surviving neurologically intact after submersion in cold water for 66 minutes.

The type of water (saltwater or freshwater) was once thought to be relevant to the outcome of drowning but is now known not to make a difference. If the water is particularly dirty or contaminated with chemicals, this may cause further respiratory complications.

Sudden unexpected death in infancy

Sudden unexpected death in infancy (SUDI) is said to have taken place when an apparently healthy baby dies suddenly, unexpectedly and without an obvious cause identified prior to investigation. Approximately 300 infants in the UK die suddenly every year, with peak incidence between 2 and 4 months of age. Boys are twice as likely as girls to be affected and deaths are more common in winter months.

An identified cause is not found in the majority of cases of SUDI. Where a cause is found, the most common diagnoses are infection, cardiovascular abnormalities, metabolic or genetic disorders and non-accidental injury. In all cases, extensive investigations are carried out to look for an underlying cause. It is extremely important to search for a possible diagnosis for a number of reasons. Firstly, it can be of great help and comfort to the parents to know why their baby died suddenly. Having a diagnosis can also be helpful in future pregnancies, especially if there is opportunity for antenatal diagnostic testing. In the small number of families who experience a second sudden infant death, this information can be crucial in the clearly more complex investigation which has to take place.

Investigations to be carried out soon after death are blood and CSF samples, together with microbiological swabs. These samples must be taken at the earliest opportunity after death as delay reduces yield of positive results.

Sudden infant death syndrome

Question 7.2

Sudden infant death syndrome

Which ONE of the following is not a recognized risk factor for sudden infant death syndrome (SIDS)?

A. Male gender

B. Parents who smoke

C. Prematurity

D. Previous SIDS in a sibling

E. Use of a dummy (pacifier)

Answer 7.2

E. Use of a dummy (pacifier).

Sudden infant death syndrome (SIDS) is a cause of SUDI. It is a diagnosis of exclusion and is defined as the sudden death of an infant that cannot be explained after thorough investigation including a post-mortem and examination of the scene of death. No single cause has been elucidated, but several associated risk factors have been identified from large case-control studies (Fig. 7.3). The relative contribution of each of the risk factors is difficult to ascertain, but the most important appear to be:

- Environmental factors
  - Sleeping position – placing an infant to sleep in the prone position is a major risk factor. This observation is supported by physiological evidence demonstrating that infants who sleep on their back have lower arousal thresholds and less slow-wave sleep compared with prone sleeping infants. It is theorized that this 'deeper' sleep interferes with the infant's physiological response to overcome other normally minor environmental triggers, resulting in life-threatening consequences.
  - Exposure to tobacco smoke – SIDS is more common in children of parents who smoke.
  - Co-sleeping – sharing a bed with the infant increases the risk for SIDS and is compounded when the co-sleeper has used alcohol or drugs. A number of these deaths may in fact be due to unintentional overlying rather than SIDS.
  - Overheating – from elevated room temperature and/or wrapping in too many clothes and/or blankets.
  - Not breastfeeding – some evidence that breastfeeding reduces the risk.
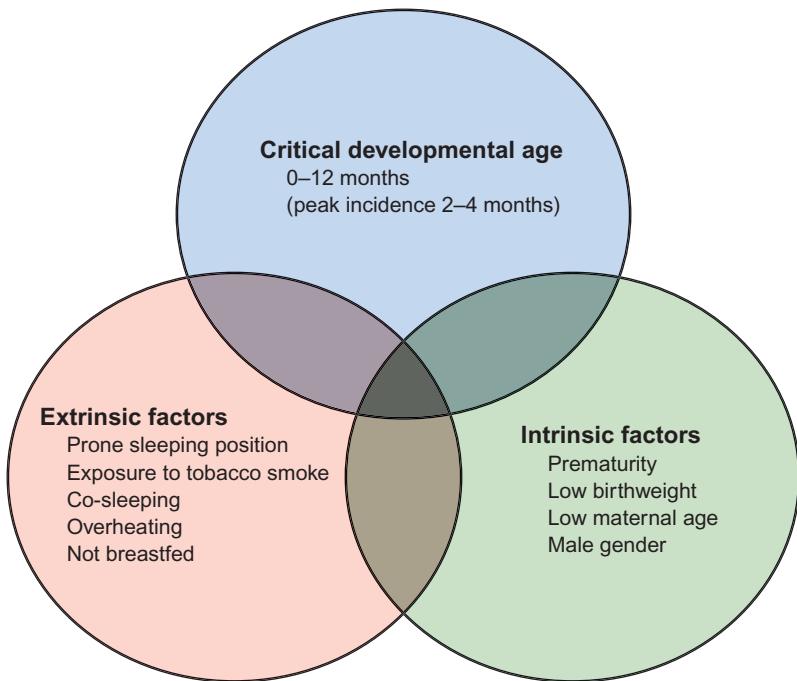
Fig. 7.3 Risk factors for sudden infant death syndrome.

- Intrinsic factors
  - Maternal age – SIDS rates decrease with increasing age of the mother
  - Low birth weight
  - Preterm birth

Although previously known as 'cot deaths', this term is now obsolete and indeed sudden infant death can occur in any place a baby is sleeping, such as a cot, crib, car seat or pram.

Parental advice to reduce the risk of SIDS is as follows:

- The 'Back to Sleep' campaign, which promotes positioning babies on their backs when sleeping with their feet to the foot of the cot or crib
- Safe sleep environment, including the baby sleeping in the same room as its parents for the first six months of life (possibly due to heightened awareness of the baby)
- An ambient room temperature of 16–20°C is recommended as the optimum range
- Dummies or pacifiers, if used consistently at nap or bed times
- Breastfeeding

Multiple SIDS

Although very rare, it has been shown that in families who have had a baby die from SIDS, there is an increased risk of future babies being affected. There have been several high-profile cases in the UK in recent

> **Box 7.4 Multiple SIDS – the danger of incorrect interpretation of statistics**
>
> In 1999 in the UK, a mother was convicted of the murder of her two sons who had died suddenly within weeks of their births in 1996 and 1998. An expert medical witness gave evidence that the chance of two children dying in the same family from SIDS was 1 in 73 million, a figure which was arrived at by squaring 1 in 8500 – the accepted probability of SIDS at the time. The conviction was overturned on appeal in 2003. The statistical analysis was severely criticized for two main reasons:
>
> - The expert witness's calculation was based on the assumption that two SIDS deaths in the same family would be independent of each other, and did not take into account that there may be a common, unidentified, genetic or environmental predisposition.
> - The court did not take into consideration that, although 1 in 73 million is a very rare occurrence, rarer still is the occurrence of double infant murder. This is a statistical error known as the prosecutor's fallacy.

years of families affected by two or more cases of SIDS, where parents have been prosecuted on suspicion of homicide. This approach has now been discredited (Box 7.4).

Poisoning

Poisoning, or potential poisoning, is a common presenting condition in paediatric practice, with ingestions in children aged under 5 years accounting for around 2% of that age group's attendances at emergency departments. Around a third of all calls to the UK National Poisons Information Service involve young children. In the United States, such calls account for about 50% of contacts with the Poison Control Center network.

The age distribution of presentation of poisoning in children is bimodal. Young children, aged under 5 years, are curious, explore their environment using all of their senses and are particularly prone to putting things in their mouths. Combined with a lack of sense of danger, they present with unintentional poisoning. By contrast, adolescents and young adults usually present with deliberate ingestion of substances from deliberate self harm or the result of exploratory behaviour with recreational drugs. Poisoning in middle childhood (age 6–11 years) is rare.

As expected, the substances most commonly ingested by young children are those found directly accessible in their own environment – household products, such as bleach, and commonly used over-the-counter medicines, such as paracetamol suspension. The same is true of young people – paracetamol and ibuprofen, both widely available without prescription, are by far the commonest substances taken in attempts at self harm. Poisoning is, of course, not limited to ingestions. Dermal exposure and, in particular, inhalation can cause significant problems, with carbon monoxide poisoning a significant cause of accidental death in children.

Serious harm to a child or young person from poisoning is fortunately an unusual event. The majority of children and young people attending healthcare provision for potential poisoning suffer little in the way of adverse effects and do not require active management. Some substances, listed in Box 7.5, however, are extremely toxic following ingestion and can result in death, particularly to young children. For these medications, one or two adult dose units can result in severe harm to a small child. Safe storage of these medications is paramount to avoid tragic unintentional harm.

Recent scientific advances which have improved clinical practice

Study of the epidemiology of childhood poisoning led to legislation for child-resistant containers for medicines, leading to a significant reduction in harm from accidental poisoning in young children.

Box 7.5 Medications that can be fatal in a small dose (1 or 2 tablets) to children weighing <10kg

Tricyclic antidepressants
Antimalarials
Beta blockers
Calcium channel antagonists
Oral hypoglycaemics
Opioids
Antiarrhythmics
Theophylline
Clozapine

Recognition and evaluation of the poisoned child

The majority of children and young people in whom poisoning is suspected present with a clear history of a potentially toxic exposure. Young children are usually found in possession of a packet of tablets or a bottle of medicine or household cleaning product. Following attempts at deliberate self harm, young people frequently admit the ingestion and the substance to a third party, often a relative or friend. Management is then guided by a risk assessment of the potential harm, taking into account a number of factors including:

- Toxicity of the substance
- Toxicity of co-ingested substances
- Dose ingested and the reliability of the history
- Presence of symptoms
- Time since ingestion
- Other co-morbidities

In a minority of cases, the substance responsible for poisoning is not clear, either due to an unwillingness on the part of the patient to reveal what they have ingested or where they do not actually know its identity. Both situations are most common in young people experimenting with illicit substances. One must remember that poisoning represents an important differential diagnosis for a number of non-specific presentations, in particular reduced conscious level and altered or peculiar behaviour.

In these cases, careful questioning of family and friends as well as a search of the patient's clothing may help to identify the causative agent. Physical examination can also be useful in the identification of the potential class of substances, aiding further investigation and management. The term 'toxidrome' has been coined to describe the constellation of physical findings that result from the excessive effect of specific classes of drugs. Table 7.4 details the features of a number of these with examples of the drugs that may cause them. Toxidromes can be useful in narrowing

Table 7.4 'Classic' toxidromes

Type of poisoning	Common agents	Toxic symptoms and signs
Anticholinergic	Antihistamines, tricyclic antidepressants, carbamazepine, phenothiazines	Tachycardia, hyperthermia, mydriasis, warm and dry skin, urinary retention, agitation
Cholinergic	Carbamates, organophosphate insecticides, some mushrooms	Salivation, lacrimation, urination, diarrhoea, bronchorrhoea, bronchospasm, bradycardia, vomiting
Hallucinogenic	Amphetamines, cocaine, MDMA (ecstasy)	Hallucinations, panic, seizures, hypertension, tachycardia, tachypnoea
Opioid	Morphine, codeine, methadone	Hypoventilation, hypotension, miosis, sedation, bradycardia
Sedative/hypnotic	Anticonvulsants, benzodiazepines, ethanol	Ataxia, blurred vision, sedation, hallucinations, slurred speech, nystagmus
Sympathomimetic	Cocaine, amphetamines, MDMA	Tachycardia, hypertension, mydriasis, agitation, seizures, hyperthermia, diaphoresis

the diagnosis but physical findings can be confounded by co-ingestion of other medications and inter-individual variability.

There are few specific laboratory tests that add significantly to thorough history and examination. A few quantitative serum drug assays, in particular paracetamol, salicylate, iron and digoxin, can be useful in guiding acute management if they are rapidly available. Blood gas analysis is frequently useful, both when considering poisoning as a cause of an unusual presentation, or in the patient with a reduced conscious level, and to assess poisoning severity for certain more dangerous substances. If a metabolic acidosis is present, the anion gap should be calculated using the formula:

$$([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$$

Abnormal > 16 mmol/L

A high anion gap indicates that there are elevated serum concentrations of anions, which are not part of the anion gap calculation, resulting in a loss of buffering $HCO3^-$ to maintain electroneutrality.

The classical mnemonic for the aetiology of an elevated anion gap metabolic acidosis, 'MUDPILES', includes six toxicological causes: Methanol, Propylene glycol, Iron and Isoniazid, Ethylene glycol and Salicylates (to accompany Uraemia, Diabetic ketoacidosis and Lactic acidosis), though cyanide and toluene poisoning also result in an elevated anion gap. The finding of an elevated anion gap metabolic acidosis should result in a search for the excess anions, which include the toxins listed above. This is discussed further in Chapter 29, Metabolic medicine.

Toxicologic screens of urine and blood typically test for drugs of abuse and, without clinical suspicion or known access to illicit drugs, are not useful in guiding acute treatment. They may, however, provide forensic evidence indicating safeguarding concerns. In these cases, it is vital that 'chain of evidence' procedures are followed when transferring samples to the laboratory.

Management

The clinical management of the poisoned child can be broadly divided into:

- Achieving and supporting physiological and biochemical homoeostasis
- Reduction of further absorption of the poison
- Enhancement of elimination of the poison or its toxic metabolites

Most mildly poisoned children require little more than supportive care. The clinical challenge of toxicology is the identification of children in whom the poison or their clinical status requires further intervention and active treatment.

Reduction of absorption and enhancement of elimination

In the past, an aggressive gastric decontamination regimen was advocated for all poisonings. Routine use of this approach is no longer advised due to limited evidence of benefit and the possibility of significant harm. The need for gastric decontamination should be tailored to the individual child or young person taking into account:

- The type and amount of poison ingested
- The time since ingestion
- An assessment of the risks of treatment versus non-treatment.

There are a number of strategies for reducing absorption or enhancing elimination that may be effective for a number of different ingested poisons. Table 7.5 contains a list of substances with more specific therapies or 'antidotes', some of which are discussed in more detail in the case histories.

Activated charcoal

Controlled burning of high-carbon substances, such as sawdust or nutshells, results in the production of charcoal, which can be activated by heating it in an oxidizing atmosphere. This results in a highly porous particle with an exceptionally high surface area – one

Table 7.5 Examples of antidotes

Poisoning agent	Antidote(s)	Mechanism of action
Paracetamol	N-acetylcysteine	Augments glutathione reserves and binds toxic metabolites
Iron	Desferrioxamine	Binds free iron and enhances renal elimination
Opioids	Naloxone	Competitive antagonist at the opioid receptor
Ethylene glycol, methanol	Fomepizole, ethanol	Competitive inhibitors of alcohol dehydrogenase preventing toxic metabolite production
Digoxin	Digoxin-specific antibody fragments	Binds digoxin preventing interaction with target sites
Cyanide	Hydroxycobalamin, dicobalt diedetate Sodium thiosulfate	Cobalt compounds chelate cyanide; cobalt cyanides are less toxic than free cyanide Enhances endogenous cyanide elimination through sulfur donation
Warfarin	Cryoprecipitate vitamin K	Replaces vitamin K-dependent clotting factors
Benzodiazepines	Flumazenil	Competitive antagonist at benzodiazepine receptor site
Beta blockers, calcium channel antagonists	Glucagon	Probably activates cardiac adenylate cyclase and increases intracellular cAMP leading to positive inotropic and chronotropic effects
Organophosphates	Pralidoxime	Reactivates acetylcholinesterase
Lead	Sodium calcium edetate	Binds divalent and trivalent metal ions – calcium is displaced leading to formation of water-soluble chelate

gram of activated charcoal may have a surface area of 950–2000 m^2. Activated charcoal administered into the stomach, either by swallowing or nasogastric tube, has the ability to adsorb potentially poisonous substances, reducing their bioavailability and hence toxicity. To maximize efficacy, the activated charcoal needs to be in direct physical contact with as much of the poison as possible. To allow this, activated charcoal is formulated as a powder dispersed in water, rather than as a tablet or capsule, and administration needs to occur as soon as possible after ingestion. In general, administration more than one hour after ingestion of a poison is unlikely to result in a significant reduction in systemic absorption. In addition, there is considerable debate in relation to whether activated charcoal improves outcomes when used in clinical practice, as demonstration of efficacy is based upon volunteer studies involving therapeutic drug ingestions.

Administration of activated charcoal should be considered when all the following criteria are met:

- Type and amount of substance ingested implies significant potential toxicity
- Substance ingested known to be adsorbed by activated charcoal
- Less than 1 hour has elapsed since ingestion
- No contraindications to administration of activated charcoal (e.g. unprotected airway, gastrointestinal obstruction)

Iron, lithium, potassium, toxic alcohols and pesticides are the main substances known not to be effectively adsorbed by activated charcoal.

For some drugs with a small volume of distribution and a prolonged elimination half-life, multiple doses of activated charcoal administered enterally may enhance elimination. Theoretically, this occurs as a result of adsorption of the drug from the enteric circulation by the charcoal in the intestinal lumen. Volunteer studies demonstrate that, in particular, carbamazepine, dapsone, phenobarbital, quinine and theophylline may have their elimination enhanced by using multiple doses of activated charcoal. Studies demonstrating clinical benefit in poisoned patients remain limited.

Gastric lavage

Gastric lavage, or 'stomach pumping' was once widespread practice for the initial treatment of poisoning. It is now very rarely used. Large volumes of 0.9% saline are administered via a large bore nasogastric tube into the stomach with the recovery of gastric contents via the same route. Concerns regarding aspiration, fluid and electrolyte imbalance, as well as a lack of proven clinical benefit, have led to almost complete withdrawal of the technique.

Induced emesis

The induction of vomiting using syrup of ipecac was once standard treatment, in particular for accidental poisoning in young children. There is no clinical evidence that it is of benefit and it may reduce the efficacy of activated charcoal. As a result, induced emesis is no longer recommended.

Whole bowel irrigation

Following the ingestion of sustained release drug preparations, which are formulated to exhibit delayed absorption, prolonged administration of large volumes of osmotically-balanced polyethylene glycol with electrolytes may be beneficial. Theoretically, this leads to a reduction in gut transit time, reducing the potential for drug absorption; effectively 'washing' the toxic substance through the gut. There is little clinical evidence,

but whole bowel irrigation is considered for the ingestion of toxic quantities of sustained release or enterically coated medications, especially where presentation is delayed. In addition, whole bowel irrigation is appropriate for children who have ingested toxic quantities of iron preparations, as there are few other strategies for reduction of absorption.

Whole bowel irrigation should be continued until the rectal effluent is clear. Fluid and electrolyte balance should be monitored during therapy.

Urinary alkalinization

The administration of intravenous sodium bicarbonate to increase urinary pH may enhance the excretion of certain drugs and toxic compounds. These substances are renally excreted and exist as weak acids. As a result, an alkaline urine favours the presence of the substance of the ionized form in the urine. The glomerulus filters both ionized and unionized forms but only unionized molecules can be reabsorbed. As a result, ionized molecules are 'trapped' in the tubular lumen, enhancing excretion. This may also generate a concentration gradient facilitating further passage of the toxic substance into the urine.

Urine alkalinization appears to increase the renal excretion of salicylate, phenobarbital, methotrexate, fluoride and chlorophenoxy herbicides. Urinary alkalinization is standard therapy for moderate to severe salicylate poisoning that does not meet the criteria for haemodialysis.

Intravenous lipid emulsion therapy

Intravenous lipid emulsion is a well-accepted treatment for local anaesthetic-induced cardiovascular collapse. Theoretically, administration results in the creation of an enlarged intravascular lipid phase. This results in enhanced retention of the implicated drug within the lipid phase, preventing its toxic effects. It has been proposed that administration of intravenous lipid emulsion may also ameliorate the toxic effects in overdose of other lipid-soluble drugs, such as beta blockers and calcium channel blockers. Clinical evidence is currently limited to case reports only.

Antidotes

A number of antidotes exist for the treatment of overdose of specific drugs and toxins. These are listed in Table 7.5, along with brief notes regarding their mechanism of action. Further details of some are included in the illustrative cases.

Poisoning prevention

The incidence of childhood poisoning was markedly reduced in the 1970s and 1980s in the UK and worldwide, following the introduction of child-resistant packaging. Commenting on its 2008 world report on child injury prevention the World Health Organization (WHO) considered child-resistant packaging to be '…one of the best documented successes in preventing the unintentional poisoning of children.'

Child-resistant packaging is designed to be significantly difficult for young children to open, or gain access to the contents, within a reasonable time and not difficult for normal adults to open. Child-resistant is not synonymous with child-proof. Safe storage and parental supervision are essential components of an environment that seeks to eliminate the risk to young children from unintentional poisoning.

Child resistance in packaging of medicines is achieved by creating a barrier of either dexterity or cognition. Examples of barriers of dexterity include the need to undertake two physical actions at the same time, e.g. the push down and turn caps on most medicine bottles. Examples of barriers of cognition generally have the need to understand an instruction, either explicit or implicit, e.g. the need to line up two arrows, one on the cap and one on the container, prior to attempting the opening manoeuvre.

At present, legislation in the UK regarding child-resistant packing is limited to aspirin, paracetamol and certain iron preparations. Other countries have more stringent legislation. There is a need for international agreement on standards.

Paracetamol

Question 7.3

Paracetamol

A 14-year-old girl reports that she has taken an overdose of paracetamol. Which ONE of the following statements is correct?

A. For maximum effect, treatment with *N*-acetylcysteine must be started within 4 hours of ingestion

B. Serum paracetamol concentrations should be measured within 4 hours of ingestion

C. The toxic metabolite *N*-acetyl-*p*-benzoquinoneimine is produced by glucuronidation

D. Toxicity occurs because of saturation of the glutathione-mediated inactivation of toxic metabolites

E. Treatment with the antidote *N*-acetylcysteine should not be started until the serum paracetamol concentration is known

Fig. 7.4 Metabolism of paracetamol.

Case history

A 14-year-old girl attends the emergency department with vomiting and abdominal pain. She reveals to her mother that she took 16 paracetamol tablets (500 mg) the previous day following an argument with her boyfriend. Blood tests reveal an alanine transaminase (ALT) concentration of 1200 U/L and a prothrombin time of 18 seconds. Her paracetamol concentration is undetectable. She receives treatment with intravenous N-acetylcysteine in view of evidence of hepatotoxicity due to paracetamol. Regular blood test monitoring demonstrates gradual normalization of her prothrombin time and she makes a full recovery.

With wide over-the-counter availability, paracetamol is the most common medication taken in overdose, either deliberately or inadvertently, by children in developed countries. The toxic dose of paracetamol is very variable, although higher doses are associated with a greater risk of adverse effects. A single dose of over 200 mg/kg is considered to have a reasonable likelihood of causing toxicity, but lower single doses can result in significant problems, as can multiple smaller doses, which cumulatively exceed this threshold taken within a 24-hour period.

Classically, paracetamol toxicity is divided into three phases:

0–24 hours	Nausea, vomiting, excessive sweating
24–72 hours	Right upper quadrant pain, liver dysfunction, possible renal impairment
72–120 hours	Hepatic necrosis leading to liver failure, renal failure, cerebral oedema and death

Biochemical evidence of paracetamol-induced liver damage includes elevated blood concentrations of aspartate and alanine transaminase and a prolongation of the prothrombin time. A metabolic acidosis ensues in severe cases. Acute kidney injury occurs as a result of hepatorenal syndrome or multi-organ failure, although renal failure may sometimes be the primary manifestation of paracetamol toxicity.

The metabolism of paracetamol (Fig. 7.4) explains both its toxic effects and the mechanism of action of the antidote, N-acetylcysteine. Paracetamol is primarily metabolized by glucuronidation and sulfation in the liver. At therapeutic doses, a small proportion (approximately 5%) undergoes hydroxylation by cytochrome P450 (CYP450) enzymes to the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI). The small amount of NAPQI is easily detoxified by conjugation with glutathione to produce cysteine and mercapturic acid conjugates. In overdose, however, the glucuronidation and sulfation pathways become saturated and a much higher proportion of paracetamol is converted to NAPQI. Hepatic stores of glutathione are depleted rapidly and NAPQI remains in its active toxic form causing acute hepatic necrosis.

Administration of N-acetylcysteine (NAC) within 8 hours of ingestion of a toxic dose of paracetamol helps to limit hepatotoxicity and prevents death. It is progressively less effective the longer administration is delayed after this time. NAC acts primarily by augmenting glutathione reserves, thus enhancing ability

to detoxify NAPQI. Need for administration of NAC is guided by measurement of plasma paracetamol levels at least 4 hours after overdose and the use of a nomogram to assess risk of toxicity.

Certain factors may put individuals at greater risk of paracetamol toxicity:

– Starvation/malnutrition – probably a result of depleted hepatic glutathione stores
– CYP450-inducing drugs, such as carbamazepine and phenytoin
– Neonates – the sulfation pathway is the primary metabolic pathway for paracetamol in the neonatal period because of low glucuronidation activity, although the CYP450 pathway also displays a significantly lower activity than in later life, which may be protective.

Paracetamol toxicity may be irreversible and result in fulminant hepatic failure. King's College criteria show good operating characteristics to identify those patients in whom liver transplantation should be considered. A poor prognosis suggesting referral for consideration of transplant is indicated by:

• Arterial pH <7.3
• All 3 of:
  – International normalized ratio >6.5
  – Serum creatinine >300 μmol/L
  – Grade III/IV hepatic encephalopathy

Recent scientific advances which have improved clinical practice

The elucidation of the biochemical mechanism of hepatocellular necrosis in paracetamol poisoning paved the way for trials of glutathione precursors, such as *N*-acetylcysteine, for the treatment of paracetamol overdose.

Aspirin

Case history

A 13-year-old boy presents to his general practitioner with nausea and dizziness. He is diagnosed with viral labyrinthitis and sent home. Several hours later, he presents to the emergency department agitated and confused with a high temperature. Blood gas analysis reveals an elevated anion gap metabolic acidosis. Plasma salicylate concentrations are measured and found to be 850 mg/L. His mother later finds his grandmother's empty aspirin bottle in her son's bedroom.

Although aspirin poisoning in children is much rarer than it once was, it remains a very dangerous drug in overdose, particularly for young children. Severity of toxicity is related to dosage. Doses of 150 mg/kg or less generally result in only mild toxicity with no symptoms or only nausea and vomiting. Doses of 150–300 mg/kg result in nausea and vomiting, tinnitus, headache, confusion and fever. Doses over 300 mg/kg are potentially fatal. Plasma salicylate concentrations are useful for the diagnosis of aspirin toxicity and peak concentrations provide a guide to the extent of toxicity. Concentrations of 30–300 mg/L are usually seen after therapeutic doses, with concentrations of greater than 700 mg/L typically seen in overdose. Concentrations should be measured four hours after ingestion and repeated at two-hourly intervals to determine the peak concentration, as aspirin tablets can form concretions in the stomach leading to delayed absorption.

Classically, acute aspirin overdose initially causes a respiratory alkalosis as salicylate directly stimulates the respiratory centre in the brain. A raised anion gap metabolic acidosis follows. This is the result of uncoupling of oxidative phosphorylation leading to lactic acid accumulation. In addition, the reduction in ATP production leads to fatty acid oxidation generating ketone bodies. In older children and adults, the metabolic acidosis occurs 12–24 hours after ingestion. However, in infants the metabolic acidosis may occur much sooner (4–6 hours after ingestion) with no evidence of a respiratory alkalosis.

Haemodialysis or diafiltration is very effective at removing salicylate from the circulation and should be considered in all cases of severe or life-threatening toxicity. Urinary alkalinization enhances the excretion of salicylate and should be considered in cases of moderate toxicity and while awaiting the initiation of extracorporeal methods of elimination. It is achieved by administration of significant amounts of sodium bicarbonate intravenously. Salicylates exist as weak acids and are excreted in urine. Increasing the pH of urine in the renal tubular lumen leads to increased ionization of salicylates favouring excretion over passive diffusion back into the blood. A 10- to 20-fold increase in renal salicylate clearance is associated with an increase in urinary pH from 5 to 8. It would appear that enhanced clearance is much more dependent upon urine pH rather than urine flow and, as a result, a forced diuresis is not required.

Ethylene glycol and other toxic alcohols

> **Case history**
>
> A three-year-old boy is brought to the emergency department having ingested an unknown quantity of antifreeze solution he found in his grandfather's garage. He appears intoxicated. He is treated with fomepizole and makes a full recovery.

Ethylene glycol is an odourless sweet-tasting liquid that carries significant toxicity if ingested, even in small amounts (<5 mL in a 20 kg child). The signs and symptoms classically follow a three-stage progression and are best appreciated from an understanding of the metabolic pathway (Fig. 7.5):

0.5–12 hours	Intoxicated appearance: dizziness, incoordination, slurred speech, confusion and nausea/vomiting – due to unmetabolized ethylene glycol
12–36 hours	Tachycardia, hypertension, raised anion gap metabolic acidosis with compensatory hyperventilation – due to accumulation of glycolic and oxalic acid
24–72 hours	Signs and symptoms of renal failure – probably due to deposition of calcium oxalate crystals in the kidney

The mechanism of action of the antidotes to ethylene glycol (and methanol) poisoning can also be better understood from the metabolic pathway. Alcohol has a much higher affinity for alcohol dehydrogenase than ethylene glycol; fomepizole is a potent inhibitor of this enzyme. Both act to prevent the formation of toxic metabolites while ethylene glycol is gradually excreted unchanged in the urine. Fomepizole has significant advantages over alcohol in that it does not cause intoxication or hypoglycaemia; it is, however, significantly more expensive.
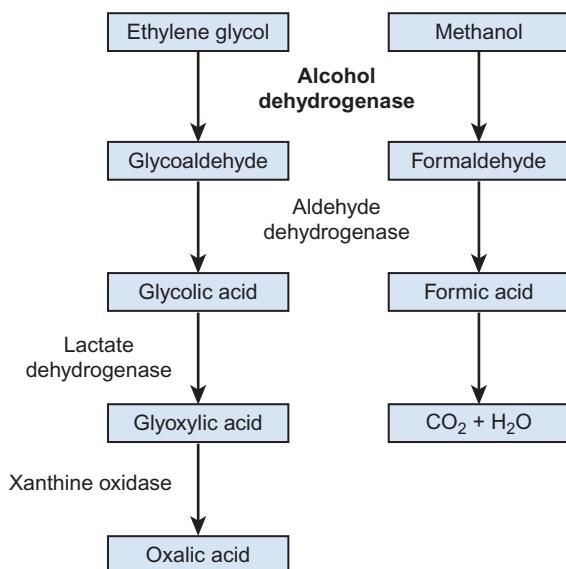
Iron

> **Case history**
>
> A two-year-old girl ingests an unknown quantity of her pregnant mother's iron medication. She is brought to the emergency department but is asymptomatic. A serum iron concentration, measured approximately 4 hours after the ingestion, is found to be 71 µmol/L. She is observed for a further 4 hours and her repeat serum iron concentration is 45 µmol/L. She remains well and is discharged.

Iron poisoning is a significant cause of toxicological mortality in young children due to its presence in the environment as a result of supplementation for pregnant and breastfeeding mothers. The amount of elemental iron ingested is broadly related to the severity of toxicity. In general, toxic effects follow ingestion of 10–20 mg/kg with severe effects and potential death following ingestion of 50–60 mg/kg.

In overdose, total iron binding capacity is saturated and free ferric iron (Fe^{3+}) is present. This leads to production of hydroxyl free radicals causing lipid peroxidation, which results in local tissue injury, primarily in the gut and liver. Initial symptoms are those of nausea, vomiting and possible haematemesis, abdominal pain and diarrhea. Following this, there may be an improvement in symptoms. However, this may mask evolving raised anion gap metabolic acidosis as a result of disturbance of mitochondrial function. Multi-organ failure may then supervene. The liver is often the first organ to be affected as a result of early exposure during first pass metabolism. In survivors of severe iron poisoning, intestinal mucosal injury may lead to the formation of strictures. These typically occur in the pylorus of the stomach.

Serum iron concentrations 4 hours after ingestion can be useful in predicting toxicity in asymptomatic patients. A measurement of less than 60 µmol/L following ingestion of an immediate release preparation makes significant toxicity very unlikely. Measurement of serum concentrations after 4 hours may underestimate toxicity due to redistribution of iron to tissues

Fig. 7.5 Metabolism of ethylene glycol and methanol.

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and binding to ferritin. Serial serum iron concentrations are, however, useful in monitoring asymptomatic patients or those who have ingested slow release or enteric coated formulations.

Iron is not adsorbed by activated charcoal. Whole bowel irrigation may be effective in reducing absorption and is recommended for ingestions of >60 mg/kg of elemental iron. Desferrioxamine is a bacterially-derived iron chelating agent that binds free iron and enhances its elimination in urine. It is indicated in all cases with signs of systemic intoxication, especially those with a raised anion gap metabolic acidosis. Treatment should not be delayed in symptomatic patients while serum iron concentration is awaited. Treatment should be continued until the acidosis is reversed and the patient is asymptomatic. Desferrioxamine interferes with most laboratory assays for serum iron and therefore this measure cannot be used to monitor response to therapy.

Question 7.4

Poisons

The following (A–J) is a list of possible ingested substances:

A. 3,4-methylenedioxy-*N*-methylamphetamine (MDMA)

B. Amitriptyline

C. Amphetamine

D. Atenolol

E. Cocaine

F. Diazepam

G. Ethanol

H. Methadone

I. Organophosphate

J. Paracetamol

Choose the most likely poison in each of the following cases. Select ONE answer only for each question. (Note: Each answer may be used once, more than once or not at all.)

1. A 3-year-old boy has been playing in a field with his sister. Several hours later, his mother finds him unwell and brings him to the emergency department. He is sweaty, with a pulse rate of 85 bpm. He has vomited, is drowsy and has increased work of breathing.

2. A 2-year-old girl has been found unconscious with a respiratory rate of 10 and miosis evident on examination.

3. A 14-year-old girl who has been on a night out with her friends complains of feeling unwell then collapses. She is very agitated, has a pulse rate of 170 bpm and is tachypnoeic.

Answer 7.4

1. I. Organophosphate
2. H. Methadone
3. A. 3,4-methylenedioxy-*N*-methylamphetamine

See Table 7.4 for explanation

Lead

Case history

Since 2008, in the Nigerian province of Zamfara, over 400 children have died and many more suffered severe neurodisability following open cast mining for gold. Artisanal miners crush and grind ore to find gold, releasing dust highly contaminated with lead. Children were affected because they worked in the process, because their relatives return home covered in the dust and because the groundwater is contaminated by the mining process. Children under five have been targeted for monitoring and treatment, though removal of the source of the lead poisoning is essential for success.

In developed countries, exposure to lead in children can occur from environmental sources in the home, such as leaded paint, lead-contaminated dust and soil and water contaminated by lead pipes, but significant toxicity is now rare. In the developing world, lead is a much more significant public health problem. Sources vary from country to country, but lead-glazed ceramics are a common cause, particularly as their production is often a home-based industry in which children are actively employed. Other sources include leaded petrol, groundwater contamination from mining, smelting and battery factories, as well as exposure to other occupational sources via parents.

The toxic effects of lead are dose-related (Fig 7.6). The potential for adverse effects of environmental lead in children is higher than in adults for several reasons:

- Smaller body size leads to greater per unit body weight exposure
- Young children are orally exploratory, making them more likely to ingest lead-containing dust and soil
- Physiological uptake rates of lead are higher in children than adults
- There is the potential for adverse developmental effects
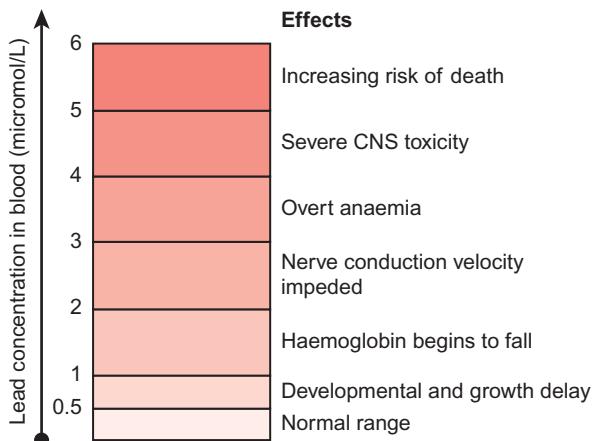
Fig. 7.6 Concentration–effect relationship of lead.

Lead distribution in the body comprises three pools:

- Blood – mostly bound to the erythrocyte membrane (2% of total)
- Skin and muscle (2–3% of total)
- Bone and dentine (95% of total with biological half-life of 20–30 years)

The toxic effects of lead span several different systems:

- Haematological – Lead inhibits the enzymes 5-aminolaevulinic acid dehydratase (ALAD) and ferrochelatase, which are essential for the production of haem. This results in a microcytic, hypochromic anaemia with elevated plasma concentrations of 5-aminolaevulinic acid (ALA) and zinc protoporphyrin (ZPP).
- Neurological – Children may present with cognitive impairment as a result of chronic low-level lead exposure or an acute encephalopathy. The mechanism of neurotoxicity is not known.
- Renal – Acute severe lead exposure may give rise to proximal tubular dysfunction resulting in glycosuria and aminoaciduria. Chronic exposure leads to interstitial nephritis.

The most important initial aspect of the management of lead poisoning is removal of the child from the source of exposure. A comprehensive environmental assessment is therefore essential.

Chelating agents can be used to enhance the elimination of lead. These form water-soluble complexes with lead, preventing its binding to cell components. The complexes are subsequently excreted in the urine. The most widely used agents are intravenous sodium calcium edetate (EDTA) and oral succimer (2,3-dimercaptosuccinic acid, DMSA). The decision to treat is based upon clinical symptoms, duration of exposure and blood lead concentrations.

Further reading

Cullen PM. Paediatric trauma. Contin Educ Anaesth Crit Care Pain 2012;doi:10.1093/bjaceaccp/mks010.

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Kerry Robinson, Alice J Armitage, Deborah Hodes

CHAPTER

8

Child protection

Child abuse exists in all cultures across the world. In the twenty-first century there is increasing international recognition that child maltreatment needs to be a high priority, requiring active prevention and legislation enforced by governments. This stance has been enshrined in article 19 of the United Nations Convention of the Rights of the Child (UNCRC), which states that 'all children have a right to protection from all forms of physical and mental violence, injury or abuse, neglect and maltreatment or exploitation, including sexual abuse while in the care of parent(s), legal guardian(s) or another person who has the care of the child'.

Currently, 193 countries are party to the UNCRC and once a country has ratified the treaty they are bound to its terms by international law.

Maltreatment worldwide
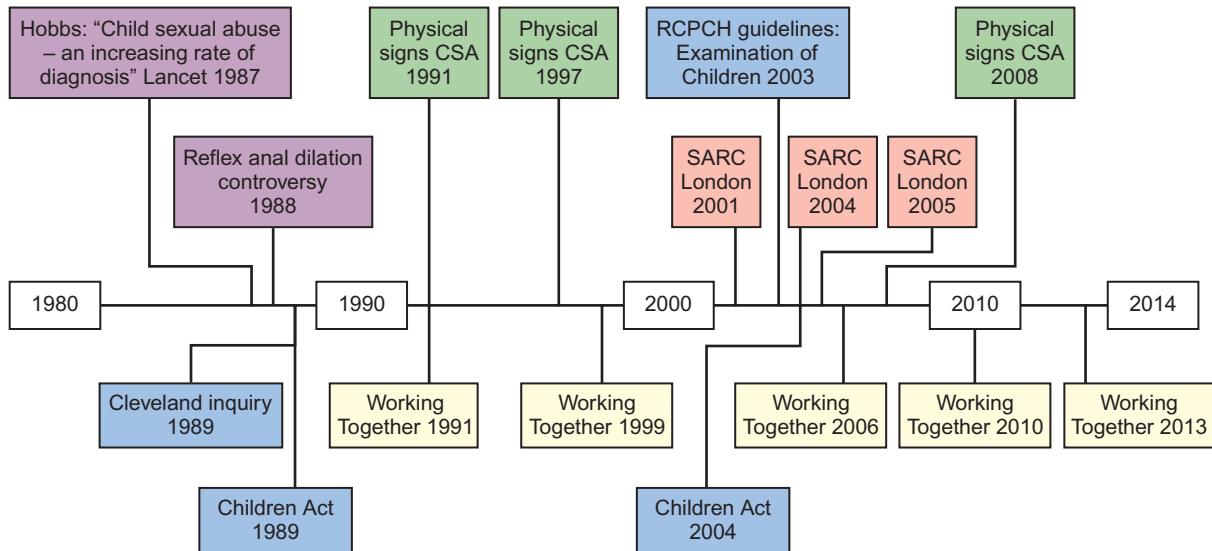
Although there is international condemnation of child maltreatment, it remains a universal problem defined by culture and tradition. The lack of standardized data collection and variation in definitions of child maltreatment make worldwide comparisons difficult to draw. The UN Secretary General's report on violence against children estimates that in 2002 almost 53,000 children were murdered worldwide. The report also highlights the lack of governance and funding in poverty-stricken, fragile countries that provide the setting for widespread and serious forms of abuse and

exploitation. Hundreds of millions of children are subject to child labour, sexual exploitation, female genital mutilation (FGM), honour-based violence and trafficking. Other abuses include child soldiers, feticide, abandonment, begging and orphans who are often institutionalized. A global action plan will address the determinants of abuse, which include poverty, family violence, culture and tradition, institutional care, discipline, armed conflict and treatment of girls.

Maltreatment in England

In England, a series of high-profile child deaths have shaped attitudes and legislation around child protection. Nomenclature is different in the other three countries of the UK, but the underlying principles are the same. Two particular cases were the tragic deaths of Jasmine Beckford and Victoria Climbié. Jasmine Beckford's death in 1984 shocked the nation and led to the Children Act of 1989. This established the principle that the welfare of the child (as opposed to the rights of the parents) is paramount in decisions made regarding their upbringing. Victoria Climbié's death in 2000 resulted in the Children Act 2004, which augmented established legislation emphasizing the integration of local services based around the needs of the child.

Since the inception of the first Children Act, there has been complex and frequently changing guidance

Hobbs: "Child sexual abuse – an increasing rate of diagnosis" Lancet 1987

Reflex anal dilation controversy 1988

Physical signs CSA 1991

Physical signs CSA 1997

RCPCH guidelines: Examination of Children 2003

SARC London 2001

SARC London 2004

SARC London 2005

Physical signs CSA 2008

1980 | 1990 | 2000 | 2010 | 2014

Cleveland inquiry 1989

Working Together 1991

Working Together 1999

Working Together 2006

Working Together 2010

Working Together 2013

Children Act 1989

Children Act 2004

SARC: Sexual Abuse Referral Centre

RCPCH: Royal College of Paediatrics and Child Health

Fig. 8.1 Timeline of key events with a focus on the management and investigation of the child in whom there is a suspicion of sexual abuse (CSA). It shows the many changes in guidance and legislation since 1980. *(From: The Child Protection Companion 2013, 2nd edition; Royal College of Paediatrics and Child Health.)*

Child protection plan (43,000)

Looked after children (67,000)

Children in need (3–400,000)

Vulnerable children (4 million)

All children <18 years (11 million)
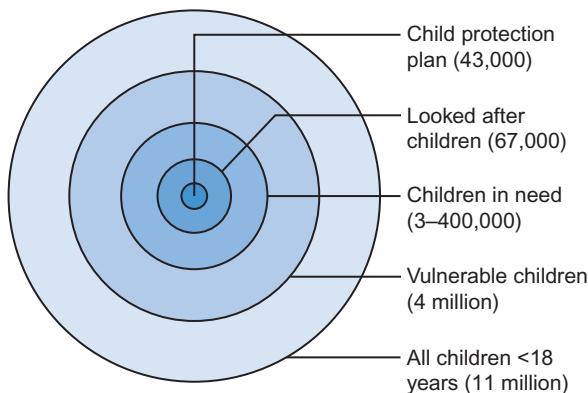
Fig. 8.2 Professional efforts are directed towards the relatively small number of children subject to a Child Protection Plan and 'looked after children'.

published around child maltreatment, which is often challenging for the professionals involved (Fig. 8.1).

Of approximately 11 million children across the UK, professional efforts are directed towards those subject to a Child Protection Plan and 'looked after children'. As shown in Figure 8.2, this represents only a small proportion of the 'children in need' and those defined as vulnerable, which includes disabled children and those living in poverty. Sadly, high-profile cases continue, with Peter Connelly in 2007 and Daniel Pelka in 2012 representing two of approximately 85 child deaths per year attributed to child maltreatment.

Case history

Daniel Pelka

Date of birth: 15.7.07

Date of death: 3.3.12

Daniel was murdered by his mother and stepfather in March 2012. For a period of at least six months prior to this, he had been starved, assaulted, neglected and abused. His older sister Anna was expected to explain away his injuries as accidental. His mother and stepfather acted together to inflict pain and suffering on him and were convicted of murder in August 2013, both sentenced to 30 years' imprisonment.

Daniel's mother had relationships with three different partners whilst living in the UK. All of these relationships involved high consumption of alcohol and domestic violence. The police were called to the address on many occasions and in total there were 27 reported incidents of domestic abuse.

Daniel had a spiral fracture of the humerus at the beginning of 2011 and abuse was suspected but the medical evidence was inconclusive. A social worker carried out an assessment concluding that there was need for intervention.

In September 2011, Daniel commenced school. He spoke very little English and was generally seen as isolated, though he was well behaved and joined in activities. As his time in school progressed, he began to present as always being

hungry and took food at every opportunity, sometimes scavenging in bins. His mother was spoken to but told staff that he had health problems. As Daniel grew thinner, his teachers became increasingly worried and, along with the school nurse, help was sought from the GP and the community paediatrician.

Daniel also came to school with bruises and unexplained marks on him. Whilst these injuries were seen by different school staff members, they were not recorded, nor were they linked to Daniel's concerning behaviours regarding food. No onward referrals were made in respect of these injuries. At times, Daniel's school attendance was poor and an education welfare officer was involved.

Daniel was seen in February 2012 by a community paediatrician, but his behaviours regarding food and low weight were linked to a likely medical condition. The differential diagnosis of maltreatment, i.e. emotional abuse or neglect as a possible cause, was not considered.

The paediatrician was unaware of the physical injuries that the school had witnessed.

Three weeks after the paediatric assessment, Daniel died following a head injury. He was thin and gaunt. Overall, there had been a rapid deterioration in his circumstances and physical state during the last six months of his life.

(Extract above taken from Coventry Safeguarding Children's Board Serious Case Review.)

In child protection today, there is an emphasis on the importance of multi-agency information-sharing and communication along with early intervention. This is a change that has taken place over the last 30 years. According to the multi-agency document *Working Together 2013*, the approach to child protection should be underpinned by two key principles:

- Safeguarding is everyone's responsibility
- A child-centred approach - 'Think Family' is a recent directive from the Department of Children, Schools and Families which emphasizes the importance of a whole family approach to safeguarding.

Why recognition and response is important

We all know that children may die from abuse. Less well recognized are the long-term sequelae in adulthood, that spare only the resilient minority. Outcomes include long-term health problems with poorer physical health, more risk taking, more medically unexplained symptoms and an increase in mental health problems including depression and suicide. Victims have lower educational attainment and difficulty parenting and thereby perpetuate the abusive cycle.

Sequelae have been shown to be both structural and functional. There is evidence from MRI studies that child maltreatment in the first two years of life, when brain growth is maximal, affects the developing brain. Persistent psychological maltreatment is a potent source of anxiety and stress, which disrupts the development of the neuroendocrine system. There is dysregulation of the hypothalamic–pituitary–adrenal axis, and parasympathetic and catecholamine responses which persist, so that the child either continues with a heightened response to stress or dissociates and withdraws.

During the first two years, there is also both synaptogenesis and synaptic pruning prior to myelination of the brain pathways. Studies have also shown that severe maltreatment can lead to alterations in this process and an overall reduction in brain volume. So, there is now increasing evidence that abuse and neglect, particularly in early infancy, can be extremely harmful, resulting in damage to the development and function of the child's brain, which later in life may lead to problems including aggression, depression, poor attention and concentration, social communication and relationship problems and anti-social behaviour. The importance of early intervention and attention to the chronicity of environmental adversity may indicate the need for permanent alternative caregivers, in order to preserve the development of the most vulnerable children.

The relatively new scientific field of epigenetics is also relevant to the cycle of child abuse and neglect. Its premise is that external influences can alter the way our DNA is expressed, and that this variability in expression is passed on in each generation.

Ever since the existence of genes was first suggested by Mendel in the 1860s and Watson and Crick described the double helix in 1953, science has developed the belief that DNA is nature's blueprint. Chromosomes passed from parent to child form a detailed genetic design for development. Recent research revolutionizes this idea and suggests that genes can be altered. There are millions of markers on your DNA and on the proteins that sit on your DNA. These have been termed the epigenome (literally 'upon genetics'). DNA itself might not be a static predetermined programme, but instead can be modified by these biological markers. Chief among them are methyl groups, which bind to a gene and say 'ignore this bit' or 'exaggerate this part'.

Methylation is how the cell knows it needs to grow into, say, an eyeball rather than a toenail. There are also 'histones' controlling how tightly the DNA is spooled around its central thread and therefore how

'readable' the information is. And it is these two epigenetic controls – an on–off switch and a volume knob – which give each cell its orders.

Darwin's central premise is that evolutionary change takes place over millions of years of natural selection, whereas this new model suggests characteristics are epigenetically 'memorized' and transmitted between individual generations.

Research on rats has identified changes in genes caused by the most basic psychological influence – maternal love. A 2004 study showed that the quality of a rat mother's care significantly affects how her offspring behave in adulthood – rat pups that had been repeatedly groomed by their mothers during the first week of life were subsequently better at coping with stressful situations than pups who received little or no contact.

You might think this is nothing new; that we already know from Bowlby and Rutter's work that a loving upbringing has positive psychological effects on children. But the epigenetic research suggests the changes are physiological as well as psychological. Epigeneticists also think socio-economic factors like poverty might 'mark' children's genes to leave them more prone to drug addiction and depression in later life, regardless of whether they are still poor or not.

This all bears weight when considering the outcome for the future generations of children exposed to traumatic life events and fits in well with the intergenerational cycle of abuse that is well documented.

Prevalence and relationship with medical conditions

Surprisingly, maltreatment is more common than many other medical conditions (Table 8.1), but even these numbers are likely to be significant underestimates of the true prevalence. From interviewing adults, an NSPCC study found that 25% reported being subject to maltreatment in childhood. The changes in the number of children with a Child Protection Plan are shown in Table 8.2.

Table 8.1 Prevalence (per 10,000 children) of vulnerable children and medical conditions

Child protection plan	4.6
Looked after children	6
Child in need	64.6
Cerebral palsy	1.5–4
Fetal alcohol syndrome	2
Severe learning disability	3.7
Sensorineural hearing loss	1–2
Down's syndrome	0.5

The relationship between medical conditions and abuse is complex. Recent studies found that as many as 30–60% of maltreated children will have a coexisting medical condition. Therefore, as many abused children will be seen either routinely or for a medical condition, it should be part of the differential diagnosis for any childhood presentation.

In summary, recognition and response to maltreatment is important to prevent the psychological and physiological changes at structural, functional and genetic levels. This may go some way to preventing poor outcomes for the child in question and also to stop the intergenerational cycle of abuse and neglect.

Why is recognition and response difficult?

Historically, child protection has been taught as a separate topic in paediatrics, but no such separation exists. Child maltreatment is a differential diagnosis for every medical condition discussed in this textbook. Protecting children requires thinking of the possibility of maltreatment in any child who presents and having it on the list of differential diagnoses. Serious case reviews highlight the failure to 'think the unthinkable' when professionals accept parents' explanations too readily.

Although easy in theory, there are many barriers that prevent the professional from recognizing the possibility of abuse, including:

- Busy looking for rare medical condition to explain the symptoms
- Not wanting to open a can of worms
- Fear of being reported to the General Medical Council
- Fear of being wrong and missing a medical cause
- Reluctance to consider abuse
- Fear of parents' reaction to possibility
- Fear of loss of relationship with parents or carers.

Table 8.2 Changes in the numbers of children on the child protection register (1999 and 2008) or with a Child Protection Plan (2013) in England and Wales

Category of abuse	1999	2008	2013
Neglect	13,400	13,400	17,930
Physical abuse	9,100	3,400	4,670
Sexual abuse	6,600	2,000	2,030
Emotional abuse	5,400	7,900	13,640
Multiple	–	2,500	4,870
Total	**35,630***	**29,200**	**43,140**

*Includes 630 children with no category available
(Data from Department of Health.)

Risk, vulnerability and resilience

We know that there are factors that impact on the likelihood of abuse occurring, such as drug and alcohol misuse, psychiatric illness in the parents and domestic violence. However, none of them have a causal link and there will be families who provide excellent parenting despite very difficult circumstances. It is therefore helpful to consider the risks, vulnerability, and resilience factors in a non-judgemental fashion.

Risk

Using data from serious case reviews, risk factors identified in the child's caregiving environment are shown in Table 8.3.

Vulnerability

The common assessment framework (Fig. 8.3) is a tool used initially by social workers but now by all professionals, and forms the basis of the Common Assessment Framework (CAF) form used to make referrals to social care. It is a shared assessment and planning framework for use across all children's services and all local areas in England. It aims to help the early identification of children and young people's additional needs and promote coordinated service provision to meet them. By looking at the themes listed, vulnera-

Table 8.3 Risk factors in serious case reviews

Risk factor	Frequency mentioned 2007–2009 (n = 268)*
Parent characteristics	
Domestic violence	91 (34%)
Mental health problems – parent	73 (27%)
Drug misuse – parent	60 (22%)
Alcohol misuse – parent	58 (22%)
Child of teenage pregnancy	19 (7%)
Parent has history of being in care	19 (7%)
Child characteristics	
More than one child abused	50 (19%)
Serious illness	18 (7%)
Drug or alcohol misuse – child	18 (7%)
Mental health problems – child	17 (6%)
Factors related to case	
Physical abuse	147 (55%)
Long-standing neglect	67 (25%)
Recent neglect	48 (18%)
Sexual abuse	38 (14%)
Shaken baby syndrome	22 (8%)
Emotional abuse	30 (11%)

*The numbers add up to more than 268 as more than one risk factor may apply to each case.
(Data from a two-year analysis of child protection database notifications (2007–2009), Department of Education by Marian Brandon et al.)

ASSESSMENT FRAMEWORK

Health
Education
Emotional and behavioural development
Identity
Family and social relationships
Social presentation
Self-care skills

Child's development needs

Basic care
Ensuring safety
Emotional warmth
Stimulation
Guidance and boundaries
Stability

Parenting capacity

CHILD Safeguarding and promoting welfare

Family and environmental factors

Community resources
Family's social integration
Income
Employment
Housing
Wider family
Family history and functioning

Fig. 8.3 **The common assessment framework.** *(From: Working together to safeguard children. DFES publications Crown © 2013. Contains public sector information licensed under the Open Government Licence v3.0.)*

Table 8.4 Vulnerability factors

Child's developmental needs
Premature and low birth weight
Separated from mother/primary caregiver
Disabled and/or chronic ill health, including physical and mental health
Unwanted/unplanned or different to expectations, for example the 'wrong' sex
Parenting capacity
Drug and alcohol misuse
Domestic violence
Mental health problems
Learning disability
Personal history of abuse and neglect
Family and environmental factors
Frequent moves, homelessness
Social isolation, weak supportive networks of family and friends
Socio-economic problems, such as poverty and unemployment
Living in a gang-associated area
Strong cultural beliefs leading to: • Female genital mutilation • Forced marriage • Honour killing

bility factors can be identified and a thorough medical history will usually elicit them. They are listed in Table 8.4.

Resilience

As well as factors that make children vulnerable to abuse, there are factors that are generally protective. A child may be resilient against abuse taking place, and when children are abused, some will have more resilience in terms of the outcomes. A strong relationship with a parent or significant other adult, an easy temperament and high cognitive ability are a few examples.

Practical guidance in the assessment of a child with suspicion or allegation of maltreatment

General approach

The child should be assessed in a rigorous and systematic way irrespective of whether there is an allegation of abuse, unexplained injury or the incidental discovery of abuse and/or neglect during any medical consultation. The only difference from the diagnostic process in any other disorder is that when

maltreatment is diagnosed or suspected, the management occurs within a multi-agency context of assessment and planning for the child.

Timescales

All child protection assessments should be carried out within timescales appropriate to the type of abuse and the requirement for collection of evidential samples:

• Physical injury – within 24 hours and where police investigation or protection from harm is required.
• Acute sexual assault – as soon as possible to obtain forensic evidence and prevent pregnancy and infection.
• Historic sexual abuse, neglect or emotional abuse – the referral should be assessed according to clinical need and requirement of the safeguarding process. Children should not be kept waiting for more than 10 working days from the point of referral, unless there are clear mitigating factors agreed by all parties.

Consent

Consent should be sought from both child, where understanding allows, and the parent with parental responsibility (PR). If the child is brought without their parent, establish the reason. Request the parent to be present unless this would lead to distress for the child or a delay and loss of important acute signs. If there is no parent, then obtain consent from the person with parental responsibility; this maybe the local authority.

History-taking

Additional care should be taken in documenting time, place and people present during history-taking and examination, and record from whom you have taken a history. Talk to the child alone if there is no police interview (see ABE interview, below) and ask only open questions including those pertinent to the medical history and examination so that you can draw a conclusion regarding the presentation and allegation. The details of the story will be taken by the police in this situation. Asking leading questions prior to the ABE interview can lead to stories changing and important evidence being lost.

Use quotations and explicit descriptions when possible and distinguish between the history, observations, suspicions and interpretations. You should also consider risk factors and vulnerabilities for abuse (as listed above) in the history, remembering that cycles of abuse and neglect often repeat themselves through generations.

Documentation

Always document all findings fully, as any consultation may be subject to legal scrutiny; make clear, precise and contemporaneous notes; sign, date and print your name legibly under your signature. Use body maps whether the injury is accidental, non-accidental or uncertain, or draw diagrams. Comment on site, size, colour, cause of each lesion/injury as given by child and/or parent. Ensure you sign and date your body maps too. Include birthmarks and scars. Increasingly, there is a role for photography to supplement and be kept as part of the medical record. Consent must be obtained specifically for this.

Always conclude by linking the reason for the referral and the diagnosis you have made so that it is clear for social care and police.

It is important to establish whether the child has unmet health needs, such as outstanding immunizations, dental caries or chronic urinary tract infections, which could indicate medical neglect. Behavioural and emotional problems, including symptoms of post-traumatic stress, may be a consequence of maltreatment.

Examination

Conduct a thorough general physical examination to include height, weight and head circumference and plot them on a growth chart. Note the pubertal stage using the Tanner classification. Examine the whole body, including hair, nails, mouth, teeth, ears, nose, head, skin and hidden areas behind ears and neck.

Evaluate demeanour, response to carer, play, attention and behaviour during the time you spend with the child. Record whether or not the child was able to cooperate. If the examination is incomplete, explain how and why. Comment on developmental milestones, cognitive ability and school attainment (and attendance), all of which can be relevant to the diagnosis.

With the child's permission, it is important to examine the buttocks and genitalia of all children whether or not there is a suspicion of sexual abuse; it is thought that in 1 in 7 physically abused children there is associated sexual abuse. Ensure the child or young person has a clear explanation of the process; that they understand that it is only doctors, with their and their parent's permission, who can look, and this is part of starting to teach 'keeping safe'.

Initially view the buttocks, anus and external genitalia. In boys, look for injury to the urethra, penis and scrotum, comment on the testes and presence of circumcision. In girls, look for any injuries to the external genitalia (including FGM) and note any vaginal discharge. Examine the anus and surrounding area for any injury, including lacerations (previously termed fissures) or scars.

If sexual abuse is suspected, a more detailed examination of the anogenital area with a colposcope should be undertaken by an expert (see below for more details).

Investigations

The need for medical investigations will be indicated by examination findings and any allegations. You will need to consult your local guidelines and the Child Protection Companion published by the RCPCH and available online. Some specifics are listed later in this chapter.

Diagnosis/opinion – coming to a conclusion

There are a range of diagnoses which may coexist:

- Clear medical diagnosis – lesion not the result of inflicted injury, for example Mongolian blue spot
- Newly identified health needs – may need follow-up/referral for ongoing assessment and management
- Normal physical examination – could be consistent with the allegation but neither supports nor refutes it, for example child sexual abuse
- Physical findings on examination consistent with the history – for example, bruising on upper arm on a mobile toddler with an allegation of being pinched four days ago
- Physical findings on examination consistent with a clinical diagnosis of physical abuse on the balance of probability (more likely than not) – for example, unexplained bruising on the buttocks of a three-year-old girl; further investigation may be required, such as taking history from other parties and excluding coagulation disorder
- Physical findings on examination that provide strong evidence of physical or sexual abuse – for example, DNA findings as evidence to support a sexual assault in an 11-year-old girl, pattern of the implement used, such as an iron

Give an opinion on whether the findings are consistent with the allegation/history given. If there is uncertainty and/or no diagnosis, say so and outline the next steps, i.e. investigations, further referrals, etc.

Comment on other findings from history and examination, such as growth or language development, medical co-morbidities or unmet medical needs.

For clarity, use bullet points when listing the other factors elicited in history contributing to maltreatment, for example:

• Brother has degenerative neurological condition.

Management and communication

Give clear information with an opinion on the outcome of the assessment to parents, child, police and social care. Consider the immediate safety of the child and any siblings. In complex cases, ongoing responsibilities include obtaining past records and completing a medical chronology. Consider follow-up and/or referrals, such as child and adolescent mental health services. Write reports and participate in strategy meetings and child protection conferences and, if needed, for care proceedings or witness statement for the criminal court. Sharing of reports is part of written communication.

Verbal information to the child's social worker and the police should be followed up in writing with a report if possible, within three working days of an assessment.

Types of abuse and neglect – overview

Although a useful framework, in practice there is usually coexistence and overlap between the types of abuse. For simplicity, we will use the following categories:

• Physical abuse
• Sexual abuse
• Neglect
• Emotional abuse
• Fabricated illness

Evidence is increasingly moving away from the idea of certain injuries being classical or pathognomonic of child abuse. Instead, child maltreatment should be part of your differential diagnosis in any child presenting to medical services. However, an abused child can have a normal physical examination at any given time.

As children get older, the categories and perpetrators of abuse become less clear-cut and the young person thought to be a perpetrator may also be a victim of abuse and/or exploitation.

The WHO defines exploitation as a category of abuse, incorporating slavery, child labour and sexual exploitation. In the UK, we are increasingly recognizing the importance of sexual exploitation and trafficking as a child protection issue.

Physical abuse

This is defined as a form of abuse which may involve hitting, shaking, throwing, poisoning, burning or scalding, drowning, suffocating or otherwise causing physical harm to a child. Physical harm may also be caused when a parent or carer fabricates the symptoms of, or deliberately induces, illness in a child.

Where physical signs are present, certain characteristics in the history should alert you to suspicion of child abuse. These include:

• A significant injury where there is no explanation
• An explanation that does not fit with the pattern of injury seen or motor-developmental stage of the child
• Injuries in infants who are not independently mobile
• An explanation that varies when described by the same or different parents/carers
• Unusual/inappropriate interaction between child and carer
• Aggression towards staff or the child or other relative/carer
• An inappropriate time delay in seeking appropriate medical assessment or treatment
• A history of inappropriate child response (e.g. did not cry, felt no pain)
• Presence of multiple injuries
• Child or family known to children's social care or subject to a Child Protection Plan
• Previous history of unusual injury/illness, e.g. unexplained apnoea
• Repeated attendance with injuries that may be due to neglect or abuse.

Bruising

Bruising is a very common finding in children and is the commonest injury seen in physical abuse. The Cardiff Child Protection Systematic Review Group (CORE INFO updated 2013) showed that the majority of school-aged children will have bruising at any given time; in 2 to 9-year-olds, 60–90% have a bruise. Accidental bruising tends to be over bony prominences and on the front of the body and is generally small (1–6 mm). The distribution of accidental bruising varies with the developmental age of the child – crawling babies typically injure their chin, nose and forehead, while older children have bruises to their knees and shins.

Abusive bruising can occur anywhere and is commonly found on soft tissue areas and on the head, cheeks, neck, ears, trunk, arms, buttocks and genitalia. Multiple bruises or bruises in clusters are suspicious. Only less than 1% of babies under 6 months have bruises and any bruising in a non-ambulant child is highly suspicious. Bruises inflicted with significant force may have surrounding petechiae and this finding is strongly correlated with abuse. Abused children

tend to have more and larger bruises. Inflicted bruises may bear the imprint of a hand or implement. Evidence from the Cardiff Child Protection Systematic Reviews (CORE INFO) suggests that in physical abuse, additional injuries and being known to social care are both more likely.

Ageing of bruises

Evidence suggests that paediatricians are unable to age bruises with any certainty. Recommendations are now that this should not be commented on.

Differential diagnosis of bruising

One needs to remember child maltreatment is more common and may coexist with any medical condition, as well as being a cause of the features. Exclude a

> **Case history**
>
> A 3-year-old girl is referred to social care. Concerns have been raised by her nursery regarding bruises on her back (Fig. 8.4A) and unusual marks on her arm (Fig. 8.4B). When questioned, the girl had said her mum 'hit her with something in the kitchen'. The family are from Korea and have recently moved to the UK. What are the lesions on her back and arm?
>
> The lesions on her back are Mongolian blue spots, which can be anywhere on the body. The lesions on the upper arm are not fork marks but lesions following BCG immunization as carried out in Korea.

family history of bleeding disorders (see below). Mongolian blue spots, and traditional practices such as coining (rubbing the edge of a coin on the skin in a linear fashion to cause subcutaneous bleeding, often along the spine and ribs) and cupping (placing heated glass vessels on the skin) need to be included in the differential.

Investigations to exclude a bleeding disorder

There are rare medical causes for bruising and bleeding, which may need to be excluded before a diagnosis of non-accidental injury is made. They include Von Willebrand disease, idiopathic thrombocytopenic purpura, inherited disorders of platelet function (e.g. storage pool disorder, Glanzmann's thrombasthenia) and coagulation disorders (e.g. Factor VIII deficiency, Factor XIII deficiency), vitamin K deficiency and drugs (warfarin, heparin).

Bite marks

A human bite mark is always an inflicted injury and adult bite marks are highly suspicious for abuse. It leaves an oval or circular mark, consisting of two symmetrical, opposing, U-shaped arches separated at their base by an open space. The arcs may include puncture wounds, indentations or bruising from the marks of individual teeth. It is difficult to distinguish child from adult bites, as factors such as the amount of skin and fat in the victim and the force of the bite will influence these measurements. If necessary, it can be helpful to refer bite marks and possible bite marks to a dentist or a forensic odontologist, who may be able to gather

Fig. 8.4 A. Suspected bruises on the back. B. Marks on the upper arm.

dental imprints and DNA. They are also able to give expert advice distinguishing child bites, adult bites and animal bites.

Burns and scalds

Burns are a common cause of emergency presentation in children and can be associated with abuse of all types. Assessing the likelihood that the burn is non-accidental should take into account the alleged mechanism of injury and developmental stage of the child. Abuse is recorded in an estimated 1–14% of children in a hospital setting with a burn or scald.

Accidental burns are usually from flowing water or spills. They are characteristically asymmetrical and more likely to involve the head, neck, trunk and upper extremities. Accidental contact burns are caused by grabbing hot objects, e.g. an iron or hair straighteners, and tend to involve the fingertips and the palm of the hand. Although not usually inflicted burns, these may indicate a lack of supervision and safety precautions.

Evidence shows the most common type of intentional burn is an immersion injury in hot water. These burns typically have clear margins and a symmetrical distribution. They may show a 'glove and stocking' distribution or skin sparing in buttock creases (the 'hole in doughnut' effect). They are more frequently found on the buttocks and lower extremities. Features that should increase suspicion include coexistent unrelated fractures or injuries, a history incompatible with the examination findings, for example a history of a burn from flowing water when the examination findings indicate immersion, and a sibling being blamed for the burn. Inflicted contact burns may show the imprint of whatever is used, e.g. iron burns. Intentional cigarette burns cause symmetrical round, well-demarcated burns of uniform thickness.

Table 8.5 Conditions which need to be considered when fractures are diagnosed

Normal variant – especially skull sutures
Birth injury – especially clavicle
Infection
Osteomyelitis
Osteogenesis imperfecta (see Chapter 27, Musculoskeletal disorders)
Malignancy
Caffey disease – infantile cortical hyperostosis
Metabolic bone disease of prematurity
Vitamin D deficiency
Copper deficiency
Vitamin A deficiency
Vitamin C deficiency

Fractures

Fractures have been recorded in as many as 55% of young children who have been physically abused, 18% of whom have multiple fractures. Large-scale studies have enabled a revised meta-analysis by age group, which is of value in determining probability of abuse for a child presenting with unexplained fractures. Other conditions which need to be considered when fractures are diagnosed are listed in Table 8.5.

Question 8.1

Fall of 4-week-old baby

A 4-week-old baby is brought to the emergency department by her parents. They report that she had fallen off their bed approximately 12 hours previously. She had cried immediately but has been irritable since. They have brought her to be checked. The mother is a doctor and the father works in IT. The doctor does a CXR because of concern about the fall from the bed and some faint bruises over the chest. It shows three posterior rib fractures on the left side.

What is the most appropriate action to take? Select ONE answer only:

A. Check whether the family are known to social care

B. Explain to the family that the baby will need to stay in hospital for further investigations

C. Give the baby oral paracetamol and reassess

D. Perform an urgent brain CT scan

E. Reassure parents, explaining that the baby is crying because she has healing rib fractures

Answer 8.1

B. Explain to the family that the baby will need to stay in hospital for further investigations.

This is laid out in best practice guidelines – RCPCH/Working Together. Good, honest, clear communication will help in the long term. When difficult (and it always is), it is helpful to say words such as 'when we find unexpected injuries – after all, she only fell off the bed – we want the best for the child and we really want to get to the bottom of this'. This puts the emphasis on the health of the child and we expect caring parents to be pleased with this approach.

Steps A, C and D must also be done subsequently.

Patterns of fractures

The characteristics of a fracture alone cannot be used to distinguish between accidental and non-accidental injury. The evidence increasingly suggests that many types of fracture previously classically associated with child abuse can also result from accidental injury; therefore, the history and developmental age of the child are key to making a diagnosis.

A systematic review by Kemp et al in 2008 found fractures resulting from abuse were recorded throughout the skeletal system, more commonly in infants (<1 year) and toddlers (1–3 years old). This data is supported by the Cardiff Child Protection Systematic Review Group (CORE INFO updated 2013) who reviewed 505 studies; eight studies compared abusive and non-abusive fractures in the 0–12 year age group.

Summation of both Kemp and CORE INFO shows:

- 85% of accidental fractures occur in children over five years of age
- 80% of abusive fractures occur in children under 18 months of age, with the highest incidence of abusive fractures in children under four months of age. No gender difference was noted in children aged less than one year.
- Multiple fractures were more common in abuse. Rib fractures have the highest probability of abuse (70%). Evidence suggests that chest compressions in resuscitation very rarely cause rib fractures, and when present these were anterior or anterolateral.

The probability of abuse for a *humeral fracture* was approximately 50% in all groups. A child under 3 years with a humeral fracture has a 50% chance of being abused. Mid-shaft fractures of the humerus are more common in abuse than in no-abuse, whereas supracondylar fractures are more likely to have non-abusive causes. The commonest abusive humeral fractures in children aged less than five years are spiral or oblique. Humeral fractures in those aged less than 18 months have a stronger association with abuse than those in older children.

Femoral fractures resulting from abuse are more likely to be seen in children who are not yet walking. Mid-shaft fracture is the commonest fracture in abuse and non-abuse (analysed for all age groups).

Metaphyseal fractures are more commonly described in physical child abuse than in non-abuse. They will only be found if rigorous radiological techniques are applied. Metaphyseal fractures have been frequently described in fatal abuse.

Imaging

Abusive fractures are frequently occult; it is for this reason that guidelines suggest a skeletal survey with follow-up radiology or nuclear medicine bone scan in children under two years with unexplained or suspicious fractures. The Royal College of Paediatrics and Child Health Guidance (Child Protection Companion, 2nd Edition) states that a single skeletal survey will miss fractures, particularly acute rib and metaphyseal fractures. It suggests a second radiological investigation (skeletal survey after 11–14 days or a contemporaneous nuclear medicine bone scan) is required, particularly if the skeletal survey is negative. Conditions which need to be considered when fractures are diagnosed are listed in Table 8.5.

Skeletal imaging allows one to:

- Detect and describe any fractures
- Estimate the age of any fractures 'in broad terms'
- Check bones are normal and identify any underlying skeletal disorder (e.g. osteopenia, osteogenesis imperfecta)
- Detect any other bony injury.

Skeletal survey should also be considered in:

- Severe inflicted injury in a child older than two years
- A child with localized pain, limp or reluctance to use limb where abuse is suspected
- A child with previous history of skeletal trauma and suspected of abuse
- A child with unexplained neurological presentation or suspected acute head trauma
- A child dying in suspicious or unusual circumstances (request specimen radiography as part of post-mortem to maximize detection of rib and metaphyseal fractures)
- A twin of an infant (or sibling less than two years old) with signs of physical abuse; consider screening siblings if there is any suspicion of abuse
- Older children with a disability and suspected physical abuse.

Fractures in physical child abuse denote severe assault and it is essential that they are identified if present. Radiological dating has been facilitated by the publication of new primary data providing a timetable of fracture healing. Estimating the age of a fracture can:

- Inform inconsistencies between the appearance of the fracture and the timing of an injury described
- Determine whether multiple fractures are of the same or different ages, thereby indicating one or more episodes of trauma.

Police and lawyers often seek detailed information about the exact timing of injuries to identify or exclude potential perpetrators. The evidence suggests that radiologists are able to estimate the age of a fracture in broad time frames of acute (<one week), recent (one

to five weeks) and old (more than five weeks of age) based on the signs of healing on a radiograph.

Skull fractures

An infant or a toddler with a skull fracture has a 1 in 3 chance of being abused. Parietal and linear skull fractures are the most common type of skull fracture seen in both abuse and non-abuse.

No clear difference exists in the distribution of complex skull fractures between the two groups (abused/non-abused).

Fractures resulting from accidental domestic falls rarely result in intracranial injury. Skull fractures do not heal by developing callus and cannot be dated from the radiographic appearances. If soft tissue
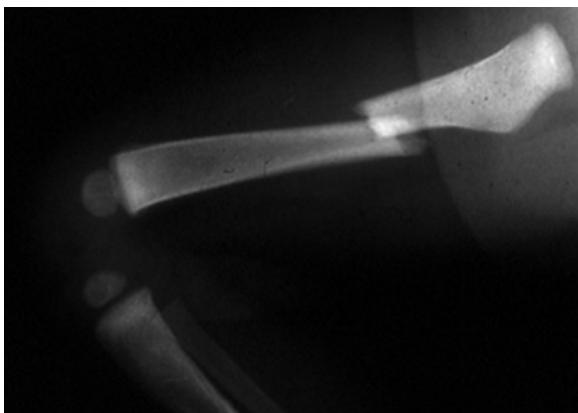
Fig. 8.5 X-ray of right leg showing a displaced mid-shaft fracture of the femur.

swelling is present overlying the fracture, it is likely to have occurred within the previous seven days.

Abusive head trauma (AHT)

'Shaken baby syndrome', first described in the 1970s, is predominantly seen in children under the age of two; most commonly in those under six months of age. There is an estimated prevalence of 1 in 3000 in babies of less than six months. The inflicted head injuries cause injury to the brain or bleeding within the structures around the brain, most often subdural haemorrhage or intraocular bleeding. Survivors may be left with long-term brain damage; half the survivors have residual disability of variable severity. The mortality is up to 30% and is the leading cause of death in abused children.

Intracranial injury can be caused by impact, shaking or a combination of both. Presentation may be as a result of the identification of an overlying soft, boggy swelling or obvious bruising. Trauma to the head should be part of the differential diagnosis in any child presenting with a low Glasgow Coma Scale (GCS), new onset of seizures or unexplained drowsiness or irritability. In the infant with an open fontanelle, the signs may be less obvious and the parent may only report poor feeding or excessive crying.

The presence of apnoea in the child with brain injury is highly correlated with inflicted injury. This has only recently been appreciated. The presence or absence of apnoeas should be recorded in every child with brain injury. The presence of retinal haemorrhages is strongly associated with inflicted brain injury (see Chapter 30, Ophthalmology).

Investigations

Where there is a high clinical suspicion of AHT, the following are suggested:

- Day of presentation: head CT, as soon as child stabilized after admission
- Day 1–2: skeletal survey, including skull films if the child is well enough; if the child is too unstable, the survey should be done as soon as is possible
- Day 3–4: if initial CT head scan abnormal, perform head MRI or, if not available, repeat CT head scan; the MRI should include the spine, to exclude coexisting injury to the spinal cord
- Follow-up CT or MRI, if an earlier abnormality was detected; this may be required at around 10 days and possibly two to three months after the initial injury

Appearance on neuroimaging is poorly correlated with probability of abuse.

Sexual abuse

Sexual abuse involves forcing or enticing a child or young person to take part in sexual activities, not necessarily involving a high level of violence, whether or not the child is aware of what is happening. The activities may involve physical contact, including assault by penetration (for example, rape or oral sex) or non-penetrative acts such as masturbation, kissing, rubbing and touching the outside of clothing. They may also include non-contact activities, such as involving children in looking at, or in the production of, sexual images, watching sexual activities, encouraging children to behave in sexually inappropriate ways, or grooming a child in preparation for abuse (including via the internet). Sexual abuse is not solely perpetrated by adult males. Women also commit sexual abuse, as can other children.

Incidence

Although sexual abuse accounts for a minority of child protection registrations in the UK, it is often unrecognized and therefore frequently missed. Some 4% of all children in the UK are subject to sexual abuse at some time, usually perpetrated by those close to the child. This is in contrast to the NSPCC survey of 18–24-year-olds, where 11% considered they had been sexually abused.

Sexually abused children may not manifest any signs or symptoms, and they may not allege it is happening for fear of not being believed. These children are more likely to grow up into adults who are more vulnerable to further sexual abuse, are promiscuous, are more likely to have a teenage pregnancy, suffer mental ill health, drug misuse, difficulties with relationships and protecting their own children.

Presentation

Child sexual abuse (CSA) may present in a variety of ways.

Allegation

This may be in the acute period when the child or young person alleges acute sexual assault/rape and forensic evidence must be gathered as a matter of urgency. More often the child, especially in cases of intra-familial abuse, will make allegations of abuse that happened weeks to years previously.

Physical symptoms

A wide range of physical symptoms may be linked to sexual abuse, some may be detected incidentally by a carer, some may be reported by the child and some may be found on examination. Symptoms include: constipation, dysuria, enuresis and recurrent urinary tract infections, vaginal discharge or vulvovaginitis, recurrent itching or soreness. Medical causes need to be excluded, such as lichen sclerosus et atrophicus, rectal lacerations/fissures and bleeding. One needs to be clear if the bleeding is from the vaginal tract, gastrointestinal (including anus) or renal tract.

Emotional/behavioural changes

Sudden changes in behaviour may be a pointer, especially if associated with other changes, such as new stepfather moving in. It is helpful to ask the child alone if there is anything worrying them or if they have a bad secret. Other non-specific symptoms include:

- Sleep disturbance or nightmares
- Anxiety, depression, withdrawal
- Aggression, attention seeking and/or poor concentration
- Sexualized behaviour – repeated, coercive or persistent
- Encopresis (soiling)

  Symptoms in older children/adolescents include:
- Self-harm
- Suicidal ideation
- Running away

Psychosomatic

This includes recurrent headaches, changes in eating behaviour and abdominal pains.

Investigations

Children presenting acutely, within the forensic time frame, should have intimate body swabs for forensic evidence (semen, saliva, hair and other substances) and clothing examined for semen and DNA, which needs to be carried out in a sexual abuse referral centre (SARC). If abuse is suspected, irrespective of time frame, then serum and urine samples can be tested for sexually transmitted diseases and pregnancy testing should be considered.

Case history

Deterioration in concentration

A teacher asked the mother why her 7-year-old daughter's concentration had deteriorated. On questioning, her mother says her new boyfriend has just moved in. He is very helpful bathing her daughter and looking after her when she goes to work. On talking to the child alone, she says he gets onto her bed at night and 'white stuff' goes on her leg.

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Recent onset of nocturnal enuresis

A 7-year-old girl presents with nocturnal enuresis. It emerges that she is wetting because she is frightened to go to the shared toilet in their temporary accommodation. She admits an older man sometimes waits outside and on one occasion had exposed his penis when she came out of the shared toilet.

Question 8.2

Recurrent vaginal discharge

A 10-year-old girl is seen in clinic with a history of recurrent vaginal discharge. She has also had multiple ear infections over the last six months requiring six courses of antibiotics. On asking more of the family history, it turns out she is the oldest of four children, all born to different fathers, and that her biological father was shot dead last year. When you ask her mother if you can talk to the child on her own, the mother refuses to let you.

What is the next course of action? Select ONE answer only:

A. Examine the child in the presence of her mother and take a low vaginal swab for MC&S

B. Insist that in your role as a paediatrician you are legally obliged, if you deem it necessary, to see children on their own and that you would not be doing your job properly if you did not

C. Phone the GP to gather more information

D. Prescribe a stat dose of oral fluconazole and arrange to see the child and mother next week

E. Request that she is seen by another doctor.

Answer 8.2

A. Examine the child in the presence of her mother and take a low vaginal swab for MC&S

Wait for the results before treating with any antimicrobials.

You should gather as much information as you can, as this is a complex presentation. Recurrent vaginal discharge in any child should alert you to consider sexual abuse.

The next course of action would be C, and you would also want to know if she was known to social care.

Rape and sexual assault

Teenagers and children represent 35% of reported accounts of rape and sexual assault. Children presenting acutely must be seen urgently in an SARC for intimate body swabs, and for medical evaluation for signs of trauma, risk of pregnancy and infection. Later psychological assessment and treatment is offered for this vulnerable group.

Achieving best evidence interview

Following an allegation, the child is interviewed by a trained police officer and social worker in a purpose-built suite with video-recording. This is known as the 'achieving best evidence' (ABE) interview, when the police and social worker will hear details of what happened without asking direct questions. On occasions, the ABE interview will occur after urgent medical examination, in which case the health professionals should only ask questions pertinent to the examination so as not to contaminate the verbal evidence.

Examination

Always seek the child and care giver's permission and remind the child of how to keep safe.

An experienced senior doctor (see the guidelines written by the Faculty of Forensic and Legal Medicine (FFLM) and the RCPCH) should carry out the examination of the anogenital area. In acute assault, intimate body swabs are taken and each exhibit labelled carefully and given to the police officer in the case. A colposcope should be used enabling detailed examination of the genitalia and anus with photo documentation, having had written consent from the parent/carer with parental responsibility and the child, if old enough. The descriptions of markings around the hymen and anus are likened to that of a clock face. There is much variation in normal anatomy and the size and appearance of the hymen changes from birth to puberty.

In girls, the genitalia are examined in the frog-legged position and, if tolerated, also in the knee–chest position. Acute genital injury can cause erythema, bruising, or lacerations. Vaginal penetration may result in a laceration to the hymen, typically between 3 and 9 o'clock. In non-acute allegations of penetration, notches in the hymen and transections which are healed lacerations can be demonstrated with a swab or Foley catheter and are found in only a small percent of victims.

The anus is examined in the left lateral position. The actual or attempted application of a blunt penetrating force to the anus, which may be digital, penile or instrumental, may cause erythema, bruising,

or lacerations acutely. Lacerations may be seen non-acutely, as may reflex anal dilatation (RAD), which occurs when the anus dilates to reveal the rectum after separating the buttocks for up to 30 seconds. The latter is seen in up to a third of children with a history of anal abuse, although it can also be seen in small numbers of children selected for non-abuse. Constipation must always be excluded as a possible cause.

Following an acute allegation, there may be other injuries to the body, such as bruising, scratches or bite marks.

At the conclusion, it is essential to draw the findings on a body map. The resulting DVD is taken for peer review and court proceedings. Approximately 90% of children alleging historic abuse have normal physical findings. This does not refute the allegation, but explanation of this to the child and parents is necessary and always a great relief.

Neglect

Neglect is the persistent failure to meet a child's basic physical and/or psychological needs, likely to result in the serious impairment of the child's health or development. Neglect may occur during pregnancy as a result of maternal substance abuse. Unlike other forms of abuse, it results from omission rather than an act.

Neglect is increasingly used as a category for making children subject to a Child Protection Plan. Actual

Question 8.3

Speech delay

You are asked to see a three-and-a-half-year-old boy because he is not yet talking. When you see him, he has about 15 single words, but his mother assures you he has good comprehension and will follow two-stage commands. He has limited eye contact. On examination, his clothes are grubby and he has multiple bruises on his shins and body. He has several cuts on his forearms and a circular bruise on his forehead.

What is the most appropriate initial management option? Select ONE answer only:

A. Check if he is known to social care

B. Refer him for a hearing test

C. Refer him for an autism assessment to the local child development team

D. Reassure his mother that he is within normal limits and see him again in three months

E. Tell his mother that you are concerned about him and want to keep him in hospital to do further tests

Answer 8.3

A. Check if he is known to social care

He may have autism spectrum disorder, but the most immediate concern is that he is neglected/abused. The grouping of factors – lack of eye contact/cuts and bruises – are the alerting factors.

incidence is difficult to measure and it frequently coexists with other forms of abuse. A series of serious case reviews have highlighted the prevalence of neglect where severe maltreatment is present. Neglect is harmful and can be life-threatening; it needs to be taken as seriously as the other types of abuse.

Clinical features of neglect

It is possible to categorize the types of neglect in various ways. These are not fixed but can be a helpful framework within which to consider presenting features and extra considerations.

Emotional neglect: See section below.

Abandonment: Child is found unattended in the home by social worker, housing officer or neighbour – the law in England says it is an offence to leave a child alone when doing so puts him or her at risk.

Medical neglect: Failure to immunize, missed clinic appointments and failure to comply with medical treatment, e.g. refusing to give anti-epileptic drugs.

Nutritional neglect: May have many underlying causes, but presents to health professionals as poor growth, which is why plotting all children's weight, length/height and head circumference routinely is essential. Food maybe inadequate for growth for many reasons and includes being withheld as punishment, poverty, parental drug misuse and not attending to the child, inappropriate food for the child's age or medical condition.

Educational neglect: Poor school attendance (less than 95%). Medical conditions may be used as an excuse by the parent as a reason for not attending school. Paediatric consultation may clarify the extent of the condition for the educational welfare officer.

Physical neglect: Unkempt and dirty appearance/failure to provide supervision and guidance, recurrent accidents (e.g. falls, scalds, road traffic accidents).

Dental neglect: Persistent failure to meet a child's basic oral health needs, which is likely to result in the serious impairment of the child's oral or general health and development. As a consequence, these children may present with dental pain, and many need dental extractions. The Welsh Systematic Reviews found these children had a higher number of caries compared with controls.

In assessing neglected children and when there is a suspicion of maltreatment a detailed history, including social and family history, is paramount. Risk factors for neglect should be considered, which include poverty, parental mental health problems and history of domestic violence. Ensure that the child's educational attainment and school attendance is asked about in the history.

Examination should specifically identify poor clothing, dirty hair and skin, poor dentition and recurrent skin infections (including nappy rash in babies). Signs of physical and sexual abuse should be identified in the examination, as different types of abuse frequently coexist.

Case history

Nutritional neglect

Daniel Pelka, whose death was described above, had a growth chart as shown in Fig. 8.6. It shows growth failure, which included nutritional neglect.
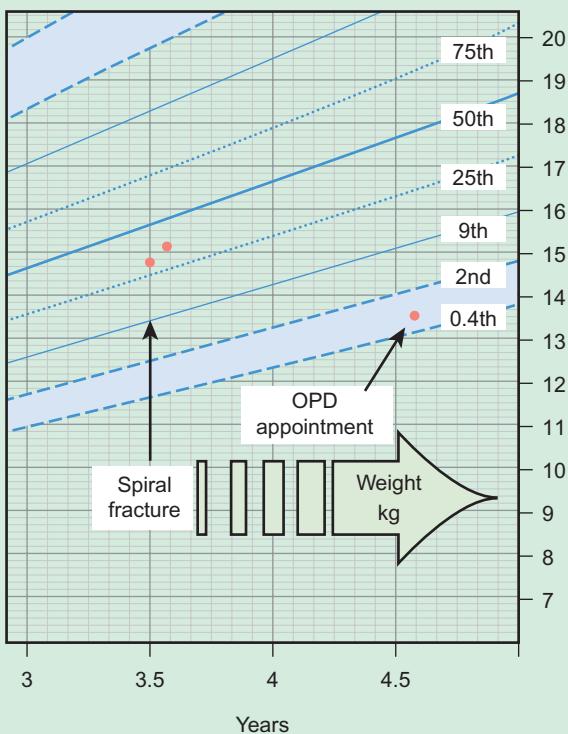
Fig. 8.6 Daniel Pelka's growth chart showing growth failure (as documented in the serious case review).

Emotional abuse

This is the persistent emotional maltreatment of a child such as to cause severe and persistent adverse effects on the child's emotional development. It may involve conveying to a child that they are worthless or unloved, inadequate, or valued only in so far as they meet the needs of another person. It may include not giving the child opportunities to express their views, deliberately silencing them or 'making fun' of what they say or how they communicate. It may feature age- or developmentally-inappropriate expectations being imposed. These may include interactions that are beyond a child's developmental capability, as well as overprotection and limitation of exploration and learning, or preventing the child participating in normal social interaction. It may involve seeing or hearing the ill treatment of another. It may involve serious bullying (including cyberbullying), causing children frequently to feel frightened or in danger, or the exploitation or corruption of children. Some level of emotional abuse is involved in all types of maltreatment of a child, though it may occur alone.

The key indicators of emotional abuse and neglect are found in the quality of the interaction between child and parent/carer and will vary with the age of the child.

In babies under 12 months:

- Parent/carer not being emotionally engaged with child's needs
- Parent/carer not speaking to the child, or speaking very little
- Parent/carer describing babies as irritating and demanding

In toddlers (aged 1–3 years):

- Parent/carer is unresponsive to the child and fails to respond to them appropriately
- Parent/carer is critical of child or verbally aggressive, often has developmentally unrealistic expectations
- Parent/carer not showing affection towards their child and not distressed by their child being in distress

In children (aged 3–6 years):

- Parent/carer not playing with their child
- No praise or positive reinforcement
- Negative beliefs about the child, 'scapegoating'
- Neglectful parent/carer is more likely to use physical chastisement

Independent from the parent/carer, there are signs that may be observed in the child as a result of emotional neglect and abuse. The child may show abnormal behaviour in terms of attachment to their parent/carer, for example being unnaturally passive, poor feeding, sleeping problems and developmental delay.

Toddlers start to have behavioural problems with aggression and hostility towards other children. Speech and language delay, the most sensitive milestone for maltreatment, starts to be more apparent. Children who are on the autism spectrum need to be included in the differential diagnosis of emotional abuse and neglect; such children may present to the child development centre, as both Daniel Pelka and Peter Connelly did before their deaths.

In school aged children (5–15 years), the features that were poorer compared with age-matched controls noted in the Welsh Systematic Review of emotional abuse and neglect in 2014 were:

- Educational – lower IQ, poorer at tasks requiring auditory attention, response set and visual motor integration but better at problem solving, abstraction and planning
- Emotional – lower understanding, recognition and regulation of emotions, lower self esteem, more depressive symptoms and suicidal ideation
- Behavioural – more difficulties with friendships, quick to anger, problems interacting with their peers, and being withdrawn.

Various labels, such as 'autism spectrum disorder (ASD)' or 'attention deficit hyperactivity disorder (ADHD)', may be used erroneously. As adolescents, there may be depression and self-harm, substance abuse and delinquent behaviours.

When assessing any child for poor school performance, conduct disorder, ASD or ADHD, the potential for emotional abuse should be considered.

Fabricated or induced illness (FII), including perplexing presentations

This is a spectrum from the normally anxious parent, keen to get the best help for their child, to the abusive parent intentionally fabricating symptoms in their child (previously known as Munchausen's by proxy), which is a form of physical abuse. In the latter and rarer case, one study found that the most common presentations at the severe end of the spectrum were: –

- Fits and apparently life-threatening events (ALTE) in about half the cases
- Drowsiness, coma
- Blood loss in vomit, faeces and urine
- Faltering growth.

It is often suspected and later confirmed when reported or observed symptoms do not have a medical explanation. They are 'perplexing', which is a useful term when talking to the parent. Management of these children and families can be challenging and multiple referrals need to be avoided and it is best to have one paediatrician working closely with the GP. Thorough history-taking is paramount; it may be appropriate to perform some baseline investigations to exclude common causes of reported symptoms. In general, the approach should be one of transparency, acknowledgement of anxiety and reassurance, while trying to avoid iatrogenic harm with unnecessary investigations. There will often be improvement following reassurance that a medical cause is not present, some will need referral to child and adolescent mental health services and only a minority will need consideration of child protection proceedings.

Recently recognized issues in maltreatment

Adolescence

A good understanding of the particular needs of the adolescent is integral to the practice of paediatrics. In a recent study, 13% of 11 to 17-year-olds said they felt neglected and 20% of serious case reviews of children who die from maltreatment are adolescents. So, although many adolescents are abused or at risk of abuse, it is far less likely to be recognized or managed than in a younger child. Reasons for lack of recognition of abuse include professionals thinking adolescents are resilient to abuse, that they will run away if it is very bad, or that they will tell someone. They may give too much credibility to parents' views rather than listening to the adolescent.

Teenagers may be at risk due their own risk-taking behaviours, involvement in gangs, self-harm, sexual exploitation, trafficking and even younger children who have access to the internet are at risk of cyberbullying and abuse. Long-term neglect may result in offending, drug and alcohol misuse, sexual exploitation, absconding and depression.

When taking a history from an adolescent you should speak to them alone as well as with a parent or carer present. The routine history covers:

- School, college or work
- Internet use and cyber bullying, mobile phones
- Relationships with peers, boyfriends and girlfriends
- Depression, self-harm and suicide risk
- Drugs and alcohol
- Home environment.

Question 8.4

Child protection management

This is a list (A–I) of management options:

A. Admit for observation

B. Ask to talk to the child alone

C. Check with social care to see if child is known

D. Contact child's mother

E. Contact police

F. Examine her vagina and anus and clearly document all findings

G. Get security to bring her back even though she has left the hospital

H. Send child to the local sexual abuse referral centre (SARC)

I. Take a detailed history of all events and document it clearly

Select the most appropriate initial management action for each of the case histories below:

1. A 13-year-old girl is brought to the emergency department by the police. She was picked up from a local park, the police having been contacted by other park goers, as she was seen to be giving a male oral sex in full view of small children who were playing on the swings. On arrival in the emergency department, she appears to be drunk, slurring her words but orientated. She says she had had an argument with her mother and had been sleeping in a shopping precinct for the last two nights. She had only just met the man in question, who had offered to buy her alcohol.

2. A 14-year-old boy is seen in the emergency department having cut his wrists with a razor blade. The bleeding has stopped but he is not orientated in time and place. His friends had brought him to the emergency department and then promptly left. He does not smell of alcohol, but has very dilated pupils.

3. A 14-year-old girl presents to the emergency department with her mother. She says she had a fight the day before and wants to 'get her checked out'. She reports that a boy tried to stab her when she broke up the fight. On examination she has multiple fine superficial cuts on her upper left thigh. When you ask her about it, she suddenly changes her mind about being 'checked out', becomes verbally abusive and leaves.

Answer 8.4

1. I. Take a detailed history of all events and document it clearly

   Despite the fact the girl is apparently drunk, it is really important to document the history, asking about sexual abuse and gang involvement specifically. She is obviously a vulnerable child and you need to contact her mother, but it is best to do that with her acquiescence. By establishing a rapport with her through history-taking, you are more likely to enable communication between her and her mother.

   You need to do C and F, but there is no allegation of rape so you cannot send her to a SARC. It would be good practice to examine her for bruising or signs of abuse. You need to admit her as she is under the influence of drugs/alcohol.

2. A. Admit for observation

   This boy appears to be under the influence of drugs. He has evidence of deliberate self-harm. You also need to do C, but this can be done later as he will be in a place of safety on the ward. You need to do I when he has woken up and also D.

3. E. Contact police.

   Security cannot touch her – either on or off the hospital premises. It would be better to get someone she has established a relationship with (maybe one of the nurses if she has already engaged with them or is known) to persuade her to come back.

   You do want her back – cutting the thighs is concerning and the fact she is involved in fights is also a worry.

Self-harm

A common presentation in teenagers will be self-harm. Although not maltreatment itself, this is often a symptom of maltreatment, for example undisclosed sexual assault, emotional abuse or bullying. In assessing and managing these children, it is important that you consider their wider needs. Most children who present with acute self-harm will need to be admitted to hospital, referred to social care and assessed by the mental health team.

Bullying

According to an NSPCC study, almost half of all children (46%) have been bullied at some point in their lives; as such, it represents a huge cause of child maltreatment with wide-ranging consequences for children's emotional and physical well-being. Bullying can take many forms, including verbal, non-verbal, exclusion, racial, sexual, cyberbullying or physical abuse by a peer or sibling. Bullying should be part of

your differential diagnosis in any school-aged child seen. It may be worth asking specifically about cyber-bullying and sexual bullying, including texting and use of social networking sites, which represent an increasing problem.

Sexual exploitation

> **Case history**
>
> **Sexual exploitation**
>
> A young woman has disclosed that she was sexually exploited from the age of 11–13 years by a local street gang. Although this is statutory rape, her former friends thought that she had given consent and labelled her a 'slag'.

Sexual exploitation in the UK remains a largely hidden problem. The report *If Only Someone had Listened* (Office of the Children's Commissioner's Inquiry into Child Sexual Exploitation in Gangs and Groups in 2013) highlighted this important and unrecognized issue for young people. It can involve a range of practices where a person or persons use a position of power over a child to coerce the child into sexual activities. Both boys and girls are at risk and many children are unaware that abuse is taking place, are tricked into thinking they are in a loving relationship and feel unable to speak out against their abusers. The Inquiry found that the following groups are at increased risk:

- History of running away or missing from home
- Special needs
- Those who are in or have been in residential and foster care
- Migrant children
- Unaccompanied asylum-seeking children
- Excluded from mainstream school
- Poor social relationships and associating with others who are exploited
- Drugs and alcohol misuse
- Mental health problems
- History of physical or sexual abuse
- Involvement in gangs.

Another recent report highlighted the confused attitudes to consent amongst young people and even among professionals. A child under 13 is not legally capable of consenting to sexual activity, and intercourse with a child under 13 is classified as rape. Sexual activity with a young person over 13 but under 16 is also an offence, but the imperative is to ascertain whether it is consensual or whether there is sexual exploitation.

Sexual exploitation of a child may start with a grooming period, where the abuser forms a relationship with the child, often supplying them with drugs and alcohol prior to the abuse starting. Suspicions that a child is being sexually exploited include relationships with older men, behavioural changes, going missing and self-harm. These young people may present to health professionals in emergency departments, sexual health clinics, school health centres and as paediatric outpatients, and the warning signs are:

- Recurring or multiple STIs
- Pregnancy and/or seeking an abortion
- Sexually risky behaviour
- Physical symptoms (e.g. bruising suggestive of either physical or sexual assault)
- Chronic fatigue
- Evidence of drug, alcohol or substance misuse
- Mental health problems, e.g. depression, self-harm, overdose and eating disorders
- Difficulties in forming relationships with others
- Extreme array of mood swings, hostility or physical aggression
- Leaving home/care setting in clothing unusual for the individual child (inappropriate for age, borrowing clothing from older young adults)
- Possession of large amounts of money, expensive clothes or mobile phones with no plausible explanation.

Female genital mutilation

Female genital mutilation (FGM) is a cultural practice involving cutting or removal of parts of the female genitals, practised on millions of women worldwide. With an increasingly multicultural patient population, FGM needs to be considered and understood by all UK health professionals, particularly those working with children.

It is essential to ask about FGM routinely in both primary and secondary care settings. It may be found during any anogenital examination or procedure such as catheterization. Since 2015 there has been mandatory reporting of FGM – this means that if a girl tells you she had FGM or you find signs of FGM, it is mandatory to report it to the police (call 101) and also to social care. Failure to do so could incur investigation by the GMC and prosecution. In all other situations, such as a suspicion of FGM, refer to social care.

As with any other child protection concern, FGM should involve social care and the multi-disciplinary team, in addition to considering whether a crime has been committed. Physical findings may vary from a small ceremonial cut or prick, which may leave no scar (WHO type 4) to total excision of the external genitalia and sewing up of the orifice (infibulation) (WHO type 3).

Unaccompanied asylum seekers

Immigrants to the UK on their own who are thought to be under the age of 18 are the responsibility of the State. Many of these children will have had traumatic experiences in their past and they may well have unmet health needs. A thorough paediatric assessment should be undertaken, considering failure of immunizations, possibility of post-traumatic stress disorder, behavioural problems or signs of chronic disease.

What to do when you suspect abuse

The role of social care

In the UK, when there is suspicion of abuse or neglect, social care are responsible for assessment of risk, deciding if the child is 'in need' or 'suffering significant harm', providing support for the child and family, and the ultimate decision on whether to keep a child with their family. In reaching this decision, social care work closely with other agencies and professionals.

If you are concerned that a child is at risk of abuse or has been abused, you should discuss with your paediatric consultant and, if you are still concerned, the named or designated doctor or nurse for safeguarding. If you decide to refer to social care, there is a multi-agency framework for doing so.

The flowchart shown in Figure 8.7 can be used by any professional working with children.

What happens next?

After receiving a referral, social care will make a decision within one working day on what response is required. This will include a decision about whether immediate action is required; for example, removing the child under an emergency protection order. If there are concerns that a child may be 'in need', social care can initiate an assessment. Further details of social care proceedings can be found in the multi-agency document 'Working Together 2015'.

The role of health professionals

Although the ultimate decision-making responsibility rests with social care, the health professionals have an important role, including:

- Recognizing and referring children at risk of significant harm
- Diagnosing non-accidental injury (NAI)
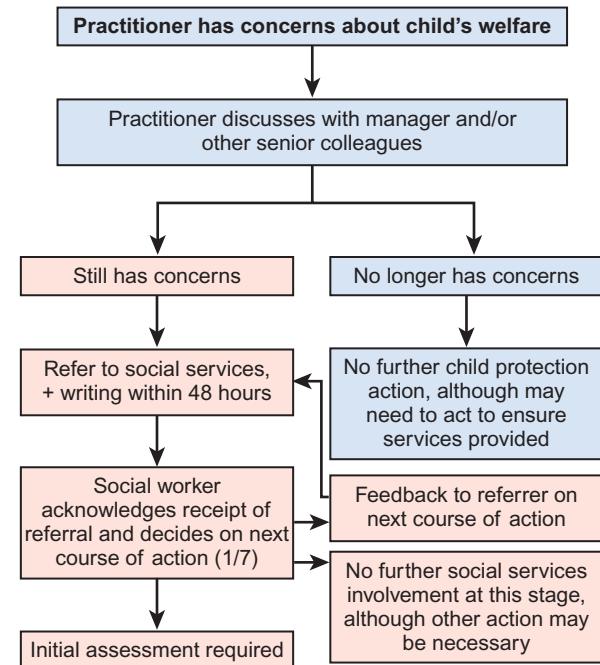
Fig. 8.7 Referral pathway when a practitioner has concerns about a child's welfare. *(From: What to do if you're worried a child is being abused. DFES publications; Crown © 2006. Contains public sector information licensed under the Open Government Licence v3.0.)*

- Diagnosing and treating coexisting medical developmental conditions
- Providing a chronology, with explanation of the medical findings that can be understood by a non-medical professional or parent/carer
- Contributing to enquiries about a child and family
- Participating in the child protection case conference
- Playing a part, through the Child Protection Plan, in safeguarding children from significant harm, for example by referral for early intervention
- Providing therapeutic help to abused children
- Writing reports for court and appearing as a witness when called.

Conclusion

Key take-home messages are:

- Keep the focus on the child – talk to the child, even if the parent is present, particularly during the examination. For the most part, parents do not want to abuse their children and this should be borne in mind.
- Remember to 'think the unthinkable' and have maltreatment in your differential diagnosis, as it often coexists with existing medical conditions.
- Your role is summarizing the health aspects of the child, from primary to secondary care, providing

vital (and otherwise unobtainable) evidence for the social worker.

- Understand the point of multi-agency work; what you contribute is a part of the jigsaw.

Child safeguarding is everyone's business. Given its high incidence in our society, all paediatricians will be involved in it and so thorough knowledge about it and an understanding of appropriate action when there is a suspicion is vital. Understanding of child maltreatment will prevent fear within the medical profession. One would hope that this will lead to earlier intervention and happier outcomes for individuals and society.

Further reading

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Richard H Scott, Shereen Tadros

Genetics

Chromosomal disorders

Chromosomes

The term 'chromosome' comes from the Greek for 'colour' and 'body', and was coined in the late 19th century in reference to their staining behaviour when dyes were applied. Chromosomes are string-like bodies present in the nucleus of every nucleated cell. Each chromosome consists of DNA that is tightly coiled around proteins known as histones that support its structure. Much of what we know about chromosomes comes from observations during cell division, when the DNA becomes more tightly coiled and is thus visible under a microscope. Humans normally have 22 pairs of numbered chromosomes – autosomes – and one pair of sex chromosomes – XX or XY. Each parent contributes one chromosome to each pair; therefore, children get half of their chromosomes from their mother and half from their father.

Each chromosome has a constricted region known as a centromere. The regions on either side of the centromere are the chromosome's arms. The shorter arm is the 'p arm' (for 'petit' or small) and the longer arm is the 'q arm' (as next letter in the alphabet!). The ends of the chromosomes are called telomeres.

Each chromosome arm is divided into regions or bands which can be seen microscopically with special stains. The bands are labelled counting out from the centromere, with p1 and q1 being closest to the centromere. Within the bands, there are sub-bands (only seen at very high resolutions), which are also numbered outwards from the centromere.

Types of chromosomal abnormalities

Chromosome abnormalities can be classified into two groups.

Numerical abnormalities involve a missing (monosomy) or extra (trisomy or tetrasomy) whole chromosome from a pair. Examples include Turner's syndrome (monosomy X) and Down's syndrome (trisomy 21) (Fig. 9.1).

Structural abnormalities can take several forms (Fig. 9.2):

- Translocation – a portion of one chromosome is transferred to another chromosome
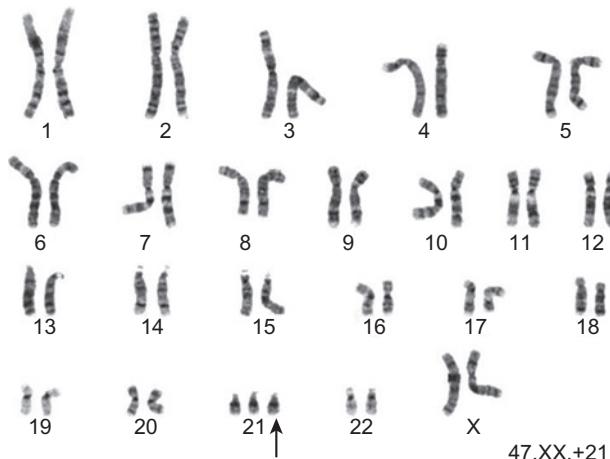
Fig. 9.1 Karyotype showing trisomy 21.

1 2 3 4 5
6 7 8 9 10 11 12
13 14 15 16 17 18
19 20 21 22 X

47,XX,+21

Fig. 9.2 Chromosome rearrangements. *(From: Levene M. MRCPCH Mastercourse 2007, Elsevier Churchill Livingstone.)*

- Insertion – a segment of a chromosome is inserted into another position on a chromosome
- Deletion – a portion of the chromosome is missing, e.g. 22q11 deletion
- Inversion – a portion of a chromosome has broken off, turned upside down and reattached, e.g. genetic information is inverted
- Duplication – a portion of the chromosome is duplicated, meaning there is extra genetic material
- Ring – a chromosome has formed a circle. This can happen with or without a loss of genetic material.

Chromosome testing
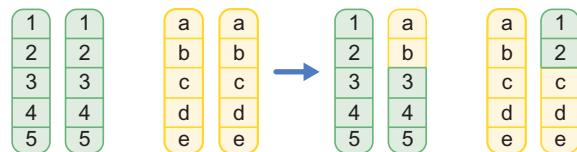
Karyotyping

As chromosomes are only visible microscopically in dividing cells, chromosome analysis involves taking some non-dividing cells (usually peripheral blood lymphocytes) and culturing them to encourage cell division. The cytogeneticist then stains and subsequently examines the cells for any extra or missing chromosomes, or large scale structural chromosomal abnormalities. This method will miss any changes smaller than 5–10 megabases (5–10 million bases) in size, so is unsuitable for the detection of most microdeletions or duplications. It may be helpful in identifying the structural basis for abnormalities detected by other methods, including array comparative genomic hybridization.
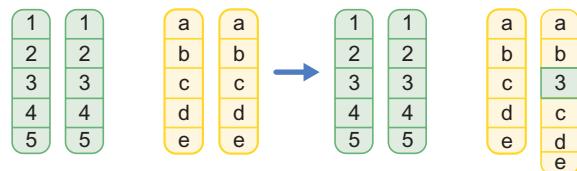
Array comparative genomic hybridization (aCGH)

Array CGH, or microarray (Fig. 9.3), is a relatively new technique which looks for chromosomal copy number variations (CNVs) by comparing a patient's DNA to normal control DNA. It has taken over from karyotype as the first line test for most chromosome abnormalities in paediatric practice.

In CGH, the patient DNA is labelled green and the normal control DNA is labelled red. Thousands of different probes (fragments of DNA) which bind specifically to regions spanning the whole genome are immobilized on a slide, the array. The array is immersed in a solution containing equal proportions of the fluorescently-labelled test and control DNA allowing green 'patient' DNA to compete with red 'control' DNA to hybridize with each of the probes. At probes where there is a deletion (i.e. lower patient

Patient DNA
(labelled green)

Control DNA
(labelled red)

Hybridised to array

Scanned

Data analysed
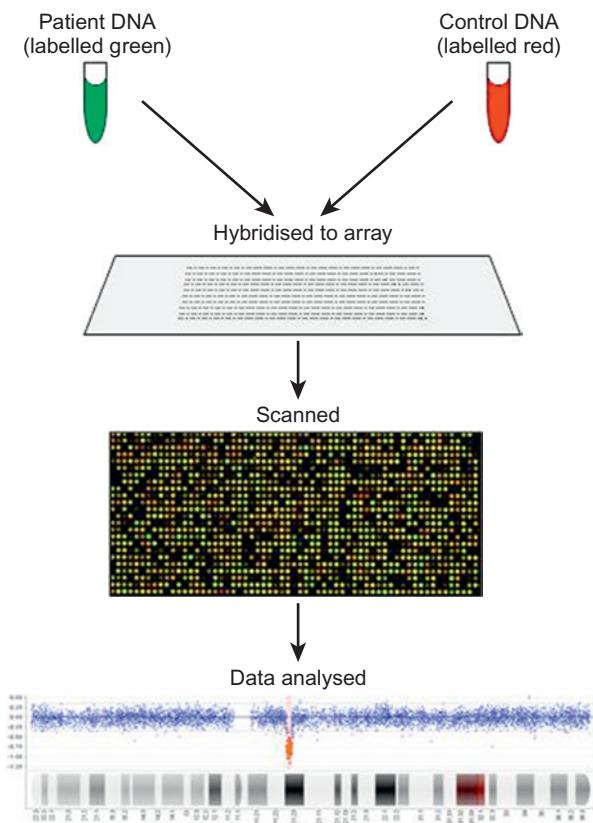
Fig. 9.3 Schematic diagram of array-CGH testing in a child with Williams syndrome. Patient and control DNA samples are labelled with different dyes and hybridized to an array with many thousand immobilized oligonucleotide probes for specific regions of the genome. The array is scanned and the data analysed to detect regions of deletion (which fluoresce red due to an excess of control DNA) or duplication (which fluoresce green due to an excess of patient DNA). Here, the array has detected a deletion at chromosome position 7q11.23, indicating Williams syndrome.

Fluorescence in situ hybridization

Fluorescence in situ hybridization (FISH) is a modification of conventional chromosome analysis using fluorescently labelled probes. It allows targeted testing for copy number variations and structural rearrangements that would otherwise be beyond the technique. Chromosomes are immobilized and denatured on a microscope slide and exposed to a solution containing a fluorescently labelled probe specific to a specific chromosomal region. After hybridization (the formation of a double strand of DNA from complementary single strands), the slide is washed and examined microscopically. Where the probe has hybridized, fluorescent spots are seen over the relevant chromosome. For example, if a child were suspected of having 22q11 deletion syndrome, FISH using a 22q11-specific probe would show only one pair of fluorescent spots, rather than two.

As FISH testing only detects abnormalities in the region targeted by the chosen probe, it requires clinical recognition of the likely causative mechanism. For this reason, it has largely been replaced by array-CGH testing when detecting microdeletions. It is now most commonly used for rapid testing for aneuploidy (chromosome number not a multiple of the haploid

copy number than control), the array appears red, and where there is duplication, the array appears green. The array is scanned with a high resolution camera and the data interpreted using computer software.

Array CGH is typically able to detect deletions and duplications larger than approximately 50,000 bases. This is a resolution more than 100 times higher than karyotyping and allows the detection of microdeletions or duplications as well as other larger chromosome copy number abnormalities, including aneuploidies.

However, array CGH cannot detect balanced chromosomal rearrangements and does not distinguish unbalanced chromosome rearrangements caused by different mechanisms; for example, it does not distinguish conventional trisomy 21 from trisomy 21 caused by Robertsonian translocation.

number, i.e. of 23 chromosomes in humans) and for the follow-up of array-detected abnormalities.

Quantitative fluorescent PCR (QF-PCR)

This is another technique commonly used for rapid aneuploidy testing and for follow-up of array-detected abnormalities.

How do chromosomal abnormalities happen?

Mitosis is the process by which most cells replicate and results in the production of two identical daughter cells, each with a diploid genome (46 chromosomes). Meiosis is the process by which gametes are formed. It involves two successive cell divisions and results in cells with a haploid genome (23 chromosomes). However, errors can and do arise in this process.

Non-disjunction

Numerical chromosome abnormalities generally happen because of non-disjunction during meiosis. This is when either the two paired chromosomes (in meiosis I) or the two sister chromatids (in meiosis II) fail to separate and segregate into separate cells. The resultant gametes therefore have either too many (24) or too few (22) chromosomes. Following fertilization, the zygote is either trisomic or monosomic for the relevant chromosome. Embryos can be trisomic for every chromosome and most will spontaneously abort. The only commonly survivable trisomies are discussed below. Rarely, there are mosaic aneuploidies affecting other chromosomes (see below).

Non-disjunction can happen in both men and women. However, most cases of trisomy seem to take place because of non-disjunction at meiosis I in the mother. It is presumed that this might be due to the fact that this stage is very long in women – starting before birth and ending at ovulation. The risk of Down's syndrome (trisomy 21) increases with maternal age; from 1 in 1500 for a 20-year-old woman, to 1 in 30 for a 45-year-old woman. There is a similar age-dependence with all other aneuploidies except for Turner's syndrome.

Anaphase lag

Turner's syndrome (45, X) occurs by a different mechanism – anaphase lag, whereby one of the sex chromosomes (X or Y) moves too slowly to the pole of a daughter cell during cell division. It therefore ends up outside the nucleus and is broken down. It can happen

during meiosis when gametes are being made, or during early mitotic divisions of the embryo.

Mosaicism

Chromosome mosaicism refers to the presence of two cell lines with differing numbers of chromosomes in each, usually one is abnormal and one normal. Examples include mosaic Down's syndrome (e.g. 46, XX/47, XX+21) and mosaic Turner's syndrome (45, X/46, XX). Mosaicism usually results in milder phenotypes. Mosaicism can occur when the abnormal cell line arises post-zygotically or when aneuploidy is present from conception but some cells revert to a normal karyotype, for example by losing one copy of a trisomic chromosome – so-called trisomy rescue.

Chromosome translocations

A translocation is described as 'balanced' if there is no net loss or gain of genetic material or 'unbalanced' if there is deletion or duplication of genetic material. Balanced translocations are important to recognize as they can result in the transmission of an unbalanced chromosome translocation to offspring. Occasionally, balanced chromosome translocations can cause disease themselves, for example if a translocation breakpoint disrupts a disease gene.

Reciprocal chromosome translocations

These arise when any two chromosomes swap non-homologous segments. A carrier of a reciprocal translocation may potentially have offspring with trisomy of one of the translocated segments and monosomy of the other.

Robertsonian translocations

These are translocations involving the 'acrocentric' chromosomes: 13, 14, 15, 21, 22 and Y. These chromosomes have their centromeres close to one end. In a Robertsonian translocation, inappropriate non-homologous recombination means that two acrocentric chromosomes join to form a single fusion chromosome with breakpoints on the short arm, just above the centromere. As with reciprocal translocations, balanced Robertsonian translocations are important to recognize because they can cause transmission of an unbalanced chromosome complement to offspring. In the case of Robertsonian translocations, this causes trisomy or monosomy for the affected chromosome. The most frequently encountered Robertsonian translocations involve chromosome 21 and can predispose to trisomy 21 in offspring, as discussed below.

Autosomal aneuploidies

Most autosomal aneuploidies are fatal *in utero*. Three are survivable to term: Trisomy 13, 18 and 21. Children with trisomy 21 (Down's syndrome) are believed to have the most favourable outcome, as chromosome 21 has fewer genes than the other autosomes (it is short and has a low gene density).

Trisomy 13 (Patau syndrome)

Some 50% of babies die in the first month and most of the rest in the first year. Polydactyly and cardiac abnormalities are common, along with midline abnormalities of the head and face:

- Closely-spaced eyes, single central eye (cyclopia)
- Midline cleft lip and palate
- Holoprosencephaly

Trisomy 18 (Edwards syndrome)

Most babies die in the first year of life. Those that survive make little developmental progress. Dysmorphic features can be subtle and include ear anomalies, clinodactyly, overlapping fingers, micrognathia and rocker-bottom feet. Growth is poor, both antenatally and postnatally, and the head is small. Cardiac and renal abnormalities are common.

Trisomy 21 (Down's syndrome)

Question 9.2

Down's syndrome

You see the parents of a child with Down's syndrome. They are keen to have another baby but are worried they might have a further affected child. What test would be most useful in advising them? Select ONE answer only:

A. Formal eye examination in the child for Brushfield's spots

B. Karyotype in the child with Down's syndrome

C. Maternal ovarian function testing

D. Parental microarray

E. Skin biopsy for chromosomal mosaicism

Answer 9.2

B. Karyotype in the child with Down's syndrome
    More than 95% of all Down's syndrome is caused by non-disjunction resulting in simple trisomy 21. This has a low risk of recurrence in future pregnancies (~1% or the mother's age-related risk, whichever is higher). Approximately

2% of Down's syndrome is mosaic. The phenotype in these cases is often milder. The recurrence risk is low. Approximately 2% of Down's syndrome is caused by unbalanced Robertsonian chromosome translocation. In these cases, one parent may carry a balanced translocation, in which case the risk of having a child with trisomy 21 is much higher. The risks seen with the common translocations involving chromosome 21 are shown in Table 9.1.

To determine the recurrence risk in a child with aneuploidy, it is important to differentiate conventional trisomy 21 (which has occurred as a result of non-disjunction) from Down's syndrome caused by an unbalanced Robertsonian translocation, which can result from the unbalanced transmission from a parent with a balanced translocation. This can be achieved by karyotyping or FISH analysis, which directly visualize the chromosomes.

Parental microarray will not detect a balanced translocation. While aneuploidies are associated with increased maternal age, ovarian function testing will not be helpful. Skin biopsy for chromosomal mosaicism is also unlikely to be useful. The clinical features will not assist in determining the future risk.

This is the only autosomal trisomy frequently associated with survival into adulthood. Children are often hypotonic at birth. Dysmorphic features that allow clinical recognition include: epicanthic folds, upslanted palpebral fissures, protruding tongue, sandal gap (between the great and second toes), Brushfield's spots in the iris, single palmar crease. Cardiac and gastrointestinal abnormalities are common, and include atrioventricular septal defect (AVSD), ventricular septal defect (VSD), duodenal atresia and Hirschsprung's disease. Affected children have mild to moderate learning difficulties. Behaviour is often problematic when older (see Chapter 24, Emotions and behaviour). Long-term problems include short stature, obesity, increased risk of leukaemia and solid tumours and Alzheimer's disease.

Table 9.1 The risk of having a child with Down's syndrome to parents carrying the most common balanced Robertsonian translocations involving chromosome 21

Type of translocation	Parent carrying translocation	Risk of affected offspring
14/21 or 21/22	Mother	10%
	Father	2.5%
21/21	Mother or father	100%

Sex chromosome aneuploidies

The Y chromosome determines maleness – a person is male if he has a Y chromosome, regardless of how many X chromosomes are present.

45, X (Turner's syndrome)

This is the only survivable monosomy. Nonetheless, most fetuses abort spontaneously and can be grossly hydropic. The clinical features are described in Chapter 12, Growth and puberty.

47, XXY (Klinefelter's syndrome)

XXY is the commonest sex aneuploidy in humans – the prevalence is around 1 in 500 males. Boys with this condition have a normal facial appearance and may not be diagnosed until later in life. Babies and young children may present with hypospadias, micropenis, cryptorchidism or developmental delay. School-aged children may have language delay, learning difficulties and behaviour problems. Older children may present with incomplete pubertal development, gynaecomastia or small testes. Adults present with infertility.

Testosterone replacement therapy starting at around 12 years of age can improve behaviour and learning, as well as the development of secondary sexual characteristics. Most men with Klinefelter's syndrome do not produce sperm. However, intra-cytoplasmic sperm injection (ICSI) can help with fertility in men who produce minimal sperm.

Partial chromosomal deletions and duplications

The phenotypic effect of a deletion or duplication depends on the genes it encompasses. In general, deletion is more likely to have a phenotypic effect than duplication and there are more chromosome deletion than duplication syndromes recognized. As described above, with conventional karyotype many of the common pathogenic deletions and duplications are too small to be visible on conventional karyotyping. Historically, they required the clinician to recognize the disorder and request the correct FISH test. As array CGH has a much higher resolution than karyotype and tests across the whole genome for microdeletions and duplications in a single test, it has replaced karyotype as the first line test for suspected chromosomal abnormalities in paediatrics.

With the advent of microarray testing, an increasing number of recurrent microdeletion and microduplication syndromes are being recognized. The best

delineated syndromes, however, remain those that are clinically recognizable and detectable using karyotype and FISH.

22q11 deletion syndrome (DiGeorge or velocardiofacial syndrome)

DiGeorge or velocardiofacial syndrome is caused by deletion at the 22q11 region of one copy of chromosome 22. The deletion follows autosomal dominant inheritance. It is helpful to test the parents as they may have a milder phenotype and not be aware of it. However, the majority of cases are *de novo*.

Patients may have a long face, narrow palpebral fissures and over-folded ear helices. However, the facial phenotype is often subtle. Affected individuals can have very variable medical complications affecting almost every system:

- Cardiac defects (particularly tetralogy of Fallot, interrupted aortic arch, ventricular septal defect, and truncus arteriosus)
- Palatal abnormalities including cleft palate
- Immune deficiency (impaired T-cell production and function, thymic hypoplasia)
- Hypocalcaemia, especially in neonates (due to parathyroid dysfunction)
- Renal tract abnormalities
- Mild to moderate learning difficulties/developmental delay

Williams syndrome

Williams syndrome results from a deletion of a region of chromosome 7q11.23, containing the elastin gene. The deletion usually occurs *de novo*. Affected individuals often present with poor feeding and hypercalcaemia as a neonate.

The elastin deletion causes arteriopathy, which can affect any artery, but the characteristic lesion is supravalvular aortic stenosis. There is a characteristic facial appearance with puffy eyes, a long philtrum and sometimes a stellate iris.

Affected children have moderate learning difficulties. There is a distinct, recognizable behavioural phenotype and children are described as having a chatty demeanour and overfriendliness.

Single gene disorders

Most heritable genetic (Mendelian) disorders are caused by mutations in a single gene from the 20,000 individual genes in the human genome. They can follow a number of different patterns of inheritance depending on the chromosomal location of the gene, the nature of the mutations and the degree of dysfunction of the gene required to cause disease.

Genes, their structure and function

Genes, the basic unit of inheritance, account for only approximately 1–2% of the >3 billion deoxyribonucleic acid (DNA) base pairs in the human genome. The functions of the remaining 98–99%, and any role in disease, remain largely unknown.

When active, genes are transcribed into ribonucleic acid (RNA) molecules. For most genes, this RNA is then translated into a protein that exerts the gene's functions. Transcription is facilitated by a gene's promoter region, usually located outside the coding region of the gene, upstream of the transcription start site. Once the transcribed RNA molecule is produced, a process known as splicing occurs to remove the non-coding segments of the gene (the introns), leaving only the segments that will be translated (the exons).

Translation of the spliced RNA sequence occurs in the ribosomes. The RNA sequence is 'read' in three base pair units known as codons. Each codon is bound in turn by a tRNA molecule with a complementary base sequence and carrying the amino acid specified by the three-base sequence. This allows the addition of the correct sequence of amino acids to the polypeptide chain that will form the mature protein. Specific codons tell the translational machinery when to start and stop.

Classes of genetic mutation

Mutations that cause Mendelian disorders can disrupt genes at many of the stages described above.

Loss-of-function mutations are the most common group of Mendelian mutation. In many cases, loss-of-function mutations act by causing the production of a truncated protein product. For example, a single nucleotide mutation that generates a premature 'stop' codon (nonsense mutation) or disrupts splicing (splice mutation); deletion or duplication of RNA sequence to disrupt the codon reading frame of the translational machinery (frameshift mutation); or deletion of single or multiple exons of a gene or the whole gene.

Single nucleotide variants that result in the substitution of one amino acid for another in the protein (missense mutation) can also cause loss of function. Because of the wide variety of ways that loss of function can occur, disorders caused by loss of function can be caused by a correspondingly wide variety of mutations, often spread across the whole gene.

Gain-of-function mutations cause disease by preventing inactivation of the protein's normal function or by giving the protein a novel function. They are often missense mutations. Because there are fewer ways that gain of function can happen, disorders caused by gain of function are less common and often occur in a relatively narrow location within the gene itself (a so-called 'hot spot').

Triplet repeat expansion mutations are a distinct class of mutation that result from the abnormal expansion of the size of a repetitive tract of sequence; for example, a region which normally has a run of up to 40 repeats of the sequence 'CTG'. When the number of repeats expands to be abnormally large, it can affect gene expression or protein function to cause disease. The size of the expansion can increase with successive generations to cause more severe, earlier onset disease. This phenomenon is known as 'anticipation'.

Genetic testing

Testing for single gene disorders is usually performed by DNA sequencing techniques, which detect single nucleotide and other small-scale sequence alterations. DNA sequencing is often complemented by the use of copy number analysis techniques, which detect deletions or duplications.

Conventional genetic testing techniques

Until recently, most DNA sequencing has been carried out using a technique called Sanger sequencing (Fig. 9.4). This is where the target gene is amplified in small fragments using polymerase chain reaction (PCR), which are each sequenced separately. For genes affected by loss-of-function mutations, mutation testing typically requires sequencing all of the exons of the gene.

Sanger sequencing does not reliably detect larger scale copy number alterations, so comprehensive testing of such genes also requires a targeted copy number analysis technique such as MLPA (multiplex
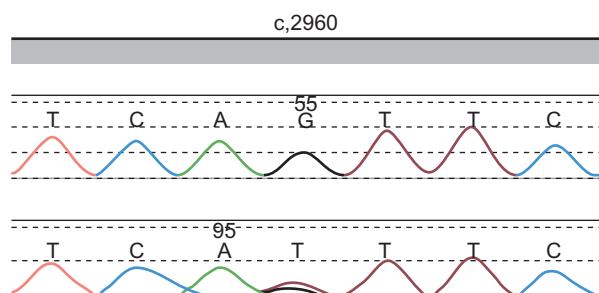
Fig. 9.4 A Sanger sequencing trace detecting a heterozygous mutation in the *SCN2A* gene. The upper trace shows the trace corresponding to the normal sequence. The lower trace shows the DNA sequence in the patient. The control has a single peak at position c.2960, indicating that the control is homozygous for the normal 'G' allele. The patient has two peaks at position c.2960, one normal 'G' allele and one mutant 'T' allele.

ligation-dependent probe amplification). Targeted copy number analysis is usually preferable to genome-wide copy number analysis by microarray, as it currently has greater sensitivity for small, single gene or intragenic copy number abnormalities.

As gain-of-function mutations often cluster in 'hot-spots', mutation testing to detect these can often be performed by targeted sequencing of selected exons or regions of the gene. Triplet repeat mutations are not usually detectable by DNA sequencing. They are detected by targeted PCR or Southern blotting-based tests that assess the size of a gene's triplet repeat tract.

Next generation sequencing

Since around 2010, a number of 'next generation' sequencing techniques (Fig. 9.5) have begun to enter clinical use. These techniques allow 'massively parallel' sequencing of millions of DNA fragments simultaneously, permitting larger scale genetic testing at lower cost per gene than conventional Sanger sequencing.
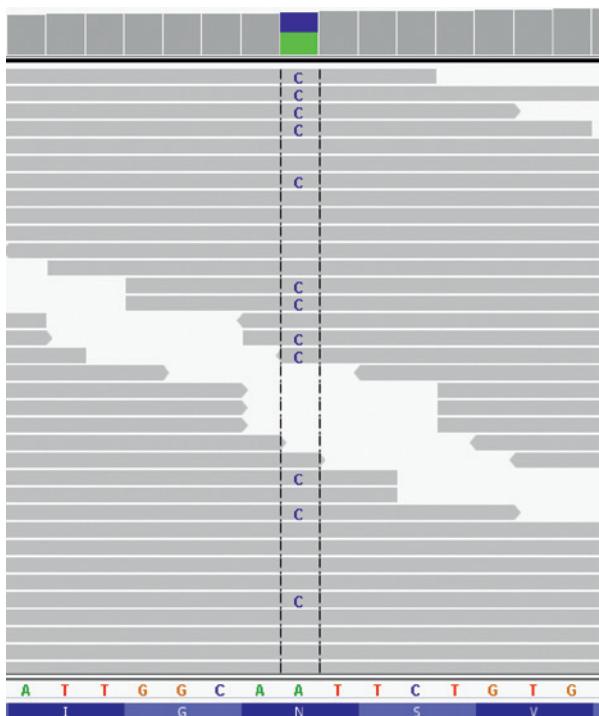
Fig. 9.5 Next generation sequencing data detecting a heterozygous mutation in the *SCN2A* gene c.2627A>C p.Asn876Thr. The normal sequence is given at the bottom of the figure. Each of the grey bands above corresponds to a single next generation sequencing 'read'. The dashed vertical lines indicate position c.2627. Where the read differs from the normal sequence, the base change is given. Approximately half of the reads show a 'C' at position c.22627, indicative of a heterozygous mutation.

Examples of current uses of next generation sequencing include:

- Sequencing of a single gene in large numbers of samples, e.g. cystic fibrosis (*CFTR*).
- Sequencing of panels of genes with overlapping phenotypes, e.g. sequencing of the 13 genes known to cause Fanconi's anaemia.
- Sequencing the coding sequence of all 20,000 known genes ('exome sequencing'). This is currently predominantly a research technique used when a single gene disorder is considered likely but where targeted gene testing fails to identify a cause.
- Whole genome sequencing. As with exome sequencing, this is predominantly a research technique used where more targeted approaches have failed.

Both exome sequencing and, to a greater extent, whole genome sequencing generate very large quantities of data. The challenge and cost of managing the data and searching for a single disease causing mutation amongst the many thousands of innocent genetic variants we all carry currently favour more targeted approaches when testing for single gene disorders where they are available. Allied to these challenges is the great caution required not to falsely ascribe pathogenicity to innocent, non-disease-causing variants (i.e. false positives). There are also ethical considerations, for example, the possibility of identifying an incidental gene mutation of medical consequence, such as a mutation causing an untreatable adult onset disorder.

Next generation sequencing is capable of detecting copy number alterations, but this remains technically difficult. Therefore, currently, conventional copy number testing techniques are used where a copy number abnormality is considered likely. As with Sanger sequencing, next generation sequencing is not currently suited to the detection of triplet repeat mutations. Conventional approaches remain necessary for triplet repeat disorders.
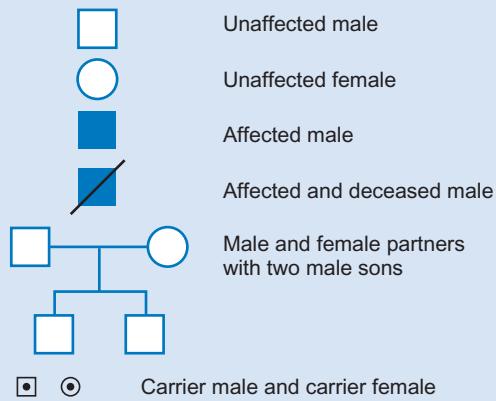
Autosomal dominant genetic disorders

Autosomal dominant disorders are caused by 'mono-allelic' mutations affecting one copy (allele) of a gene on an autosomal chromosome, i.e. not the X or Y chromosome. They can affect males or females (Box 9.1, Fig. 9.6). Autosomal dominant mutations can be inherited from an affected parent or occur *de novo* as a result of a new mutation. *De novo* mutations are more common in severe disorders which prevent affected individuals from having offspring. The risk

Drawing and interpreting family trees (pedigrees) is an important skill. A pedigree is usually started from the individual you are seeing (the consultand) and should encompass three generations, usually the consultand's generation, their parents' generation and their grandparents. If there is relevant history in the wider family, you may need to extend the pedigree more widely. The person through whom the family was first brought to medical attention is referred to as the proband and is usually marked with an arrow.

When constructing a pedigree, you should specifically but tactfully ask about consanguinity, miscarriages and stillbirths.

Unaffected male

Unaffected female

Affected male

Affected and deceased male

Male and female partners with two male sons

Carrier male and carrier female

Symbols used in pedigrees. *(From: Levene M. MRCPCH Mastercourse 2007, Elsevier Churchill Livingstone.)*
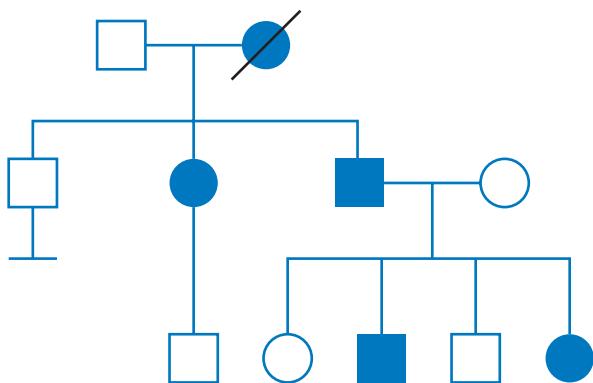
Fig. 9.6 A pedigree with a condition showing autosomal dominant inheritance. Both males and females are affected. The condition is present in successive generations.

of someone with an autosomal dominant disorder passing on the causative mutation to a child is 50%.

When a mutation has occurred *de novo*, the risk of the parents of the child having a further affected child is low. For most conditions, this risk is ~1%, reflecting the small risk of the presence of the mutation in mosaic form in one or other parent's gonads ('gonadal mosaicism'). Mosaicism is the presence of two or more genetically different cell lines that derive from the same zygote. Some autosomal dominant disorders show incomplete 'penetrance', i.e. not all individuals who inherit a pathogenic mutation manifest with clinical features of the disorder. Many disorders show variable 'expressivity', i.e. individuals who manifest with the condition show different severity of disease.

Some common examples of important autosomal dominant disorders are considered below.

Marfan's syndrome

Marfan's syndrome is an autosomal dominant disorder with an incidence of approximately 1 in 5000. It is caused by monoallelic loss-of-function mutations in the *FBN1* (fibrillin) gene, often inherited from an affected parent. *FBN1* sequencing is used increasingly to aid diagnosis, particularly to guide advice to other family members who may be at risk of disease. The clinical features of this condition are described in Chapter 27, Musculoskeletal disorders and Chapter 12, Growth and puberty.

Neurofibromatosis type 1 (NF1)

NF1 is an autosomal dominant disorder with an incidence of approximately 1 in 5000. It is caused by monoallelic loss-of-function mutations in the *NF1* gene, often inherited from an affected parent. *NF1* sequencing and copy number analysis is used increasingly to aid diagnosis, particularly to guide advice to other family members who may be at risk of disease.

Clinical diagnostic criteria require the presence of two or more of the following: (a) six or more café-au-lait patches sized >15 mm (or >5 mm before puberty); (b) a plexiform neurofibroma or two or more cutaneous neurofibromas; (c) axillary or inguinal freckling; (d) sphenoid wing dysplasia or long bone pseudarthrosis; (e) optic nerve glioma; (f) two or more Lisch nodules (iris hamartomas); (g) a first-degree relative with NF1.

Other features are:

- Renal artery stenosis and scoliosis
- Malignant peripheral nerve sheath tumours, which occur in ~10% of individuals
- Most individuals have normal learning but mild learning difficulties can be a feature

Annual review by a paediatrician is recommended, including assessment of any unusual neurological symptoms, growth, development, blood pressure and scoliosis.

Annual review by an ophthalmologist is also recommended in childhood for optic glioma.

Tuberous sclerosis

Tuberous sclerosis (TS) is an autosomal dominant disorder with an incidence of approximately 1 in 10,000. It is caused by monoallelic loss-of-function mutations in the *TSC1* (~25% of cases) or *TSC2* (~60% of cases) gene. The cause is unknown in ~15% of cases. Two thirds of mutations occur *de novo*, i.e. are not found in either parent. Sequencing and copy number analysis of the *TSC1* and *TSC2* genes is useful to assist diagnosis in atypical cases and to allow accurate advice to families regarding risks of recurrence in future children and/or allow prenatal or pre-implantation genetic diagnosis.

Tuberous sclerosis shows highly variable expressivity, with some individuals showing only very subtle features. Others manifest early with severe neurological complications, for example infantile spasms, and go on to have severe developmental delay and intractable seizures due to central nervous system tubers.

Clinical features are:

- Cutaneous manifestations are almost always present and include: Shagreen patches, hypopigmented 'ash leaf' macules, adenoma sebaceum and periungal fibromas. Hypopigmented patches can be hard to see without an ultraviolet Wood's lamp.
- Prenatal presentation with multiple cardiac rhabdomyomas is strongly suggestive of tuberous sclerosis. These usually resolve post-partum.
- Pulmonary complications (lymphangiomatosis) and renal complications (angiomyolipomas) are other causes of morbidity and mortality.

Achondroplasia

Achondroplasia is an autosomal dominant disorder with an incidence of ~1 in 27,000. It is caused by monoallelic gain-of-function mutations in the *FGFR3* gene. Two mutations account for ~99% of cases. Mutations can be inherited or *de novo*. Diagnosis can be made on the basis of clinical features and skeletal survey and confirmed by targeted sequencing for the common causative mutations. The condition is described in Chapter 27, Musculoskeletal disorders.

Myotonic dystrophy

Myotonic dystrophy is an autosomal dominant disorder with an incidence of approximately 1 in 8000. It is caused by monoallelic triplet repeat expansion mutation in the *DMPK* gene. The condition shows anticipation, i.e. disease is often more severe and younger onset with successive generations. In myotonic dystrophy, the greatest risk of expansion is when the condition is passed from mother to child. Diagnosis is clinical, with EMG providing supportive evidence. Targeted genetic testing for an expansion of the *DMPK* gene provides confirmation of the diagnosis. The clinical features are described in Chapter 27, Musculoskeletal disorders.

Autosomal recessive genetic disorders

Autosomal recessive disorders are caused by 'biallelic' mutations affecting both copies (alleles) of a gene on an autosomal chromosome, i.e. not the X or Y chromosome. The mutations can be homozygous (both alleles have the same mutation) or compound heterozygous (the two alleles have different mutations). Autosomal recessive disorders can affect males or females (Fig. 9.7). Some of the more common autosomal recessive disorders are listed in Table 9.2.

Autosomal recessive mutations are almost always inherited with one mutated allele inherited from each parent and both parents being unaffected 'carriers' of the disease, i.e. carrying one mutated copy of the gene and one normal copy of the gene. Autosomal recessive disorders are more common where parents are related.
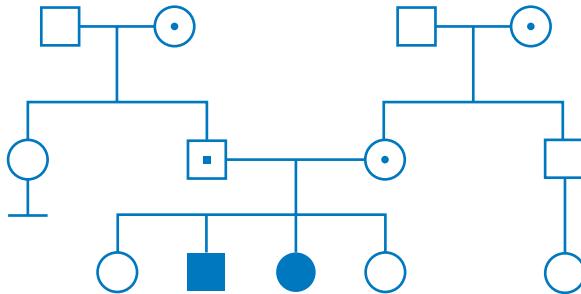
Fig. 9.7 A pedigree with a condition showing autosomal recessive inheritance. Both males and females are affected. Parents of affected individuals are carriers of the condition.

Table 9.2 Examples of some of the commoner autosomal recessive conditions

Sickle cell disease
Thalassaemias
Spinal muscular atrophy
Phenylketonuria
MCAD deficiency
Many inborn errors or metabolism

Concerning autosomal recessive inheritance

You see a family with one boy affected with Bardet–Biedl syndrome, an autosomal recessive condition with full penetrance. The diagnosis has been confirmed with genetic testing. Both parents are carriers. His older sister has been clinically assessed and is not affected. What is the chance that she is a carrier of the condition?

A. 1 in 2

B. 1 in 3

C. 1 in 4

D. 1 in 5

E. 2 in 3

Answer 9.3

E. 2 in 3.

The risk of a couple who are both carriers of the same autosomal recessive disorder having an affected child is 25%. The chance of them having a healthy child who is a carrier is 50% and the chance of them having a healthy child who is not a carrier is 25%. Therefore it follows that when such a couple have had an *unaffected* child (in this case the unaffected sister), the chance that the child is a carrier is 2 in 3 (67%).

The carrier frequency of rare autosomal recessive disorders in the general population is usually low. Therefore, carriers, for example, a sibling of an affected child, who have children with an unrelated partner are at very low risk of having an affected child. For the same reason, the risk of an affected individual having an affected child is low if their partner is unrelated. Commoner autosomal recessive disorders have high carrier frequencies, which has led to the suggestion that heterozygote status may have been beneficial at some point in history.

Cystic fibrosis

Cystic fibrosis is an autosomal recessive condition with an incidence of approximately 1 in 2500 in Western Europeans. It is caused by biallelic loss-of-function mutations in the *CFTR* gene. The carrier frequency of *CFTR* mutations in Western Europeans is relatively high, occurring in 1 in 25 individuals. A number of 'founder' mutations account for the large majority of mutations in Western Europeans. Targeted

testing for the most common nine mutations detects ~95% of mutations. Targeted mutation testing is less effective in other populations and in some cases extended mutation testing and/or sequencing of the whole gene is required.

Families in which a case or carrier of cystic fibrosis is identified are offered 'cascade' carrier testing. The partners of carriers are offered carrier testing to identify couples at risk of having an affected child. The clinical phenotype is described in detail in Chapter 17, Respiratory medicine.

X-linked recessive inheritance

X-linked recessive disorders are caused by mutations in genes on the X chromosome that cause disease in males and leave females carrying mutations unaffected or affected only mildly (Fig. 9.8). A boy affected with an X-linked recessive disorder can inherit the mutation from his carrier mother or the mutation can occur *de novo*.

A mother who is a carrier of an X-linked recessive disorder has a 25% chance of having an affected child. This is because half of her offspring will be male and half of her sons will inherit the X chromosome carrying the mutated gene. She also has a 25% chance of having a carrier daughter.

When a mutation has occurred *de novo*, the risk of a further affected child is lower than for carrier mothers. For some X-linked recessive conditions, including Duchenne muscular dystrophy, the risk of recurrence due to gonadal mosaicism is higher than the usual empiric ~1% risk. As a man passes on his Y chromosome and not his X chromosome to his sons, males affected with X-linked recessive disorders cannot have affected sons. Pedigrees of X-linked recessive disorders therefore do not show male-to-male transmission.
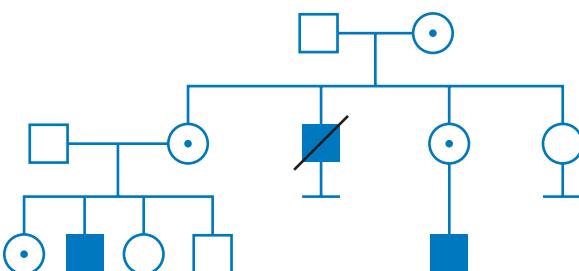
Fig. 9.8 A pedigree with a condition showing X-linked recessive inheritance. Males are affected. Mothers of affected boys are often carriers. The condition is not transmitted from a father to his son.

Duchenne muscular dystrophy

You see an 18-month-old boy in the paediatric clinic because he has not yet started to walk.

Which of the following features would be most likely to reinforce your suspicion of Duchenne muscular dystrophy? Select ONE answer only.

A. His creatine kinase is twice the normal range
B. His father had early-onset frontal balding
C. His mother's sister's 3-year-old son has an unusual gait
D. His paternal uncle died in adolescence, having been in a wheelchair
E. His sister has a cleft palate

Answer 9.4

C. His mother's sister's 3-year-old son has an unusual gait.

Duchenne muscular dystrophy (DMD) is an X-linked recessive condition. This means that male-to-male transmission is not possible. If the mutation has not occurred *de novo*, the maternal family history is relevant, but not the paternal history.

Whilst creatine kinase is elevated in DMD, it is usually 10 times the normal range in affected boys and frontal balding is associated with myotonic dystrophy. There is no reported association with cleft palate.

Fragile X syndrome

This is an X-linked recessive mutation with a frequency of ~1 in 2000 males. It is caused by a triplet repeat expansion in the *FMR1* gene. In common with all trinucleotide repeat disorders, the condition shows anticipation, with each generation showing progressively more severe features. A repeat length of >200 is a 'full mutation' and causes disease. Repeats of 55–200 are 'premutations' and can expand when transmitted to a child to become a full mutation.

Males typically have moderate learning difficulties. The physical phenotype is difficult to recognize but includes relative macrocephaly. Mitral valve prolapse is sometimes present. Females can show features of the condition but they are milder than in males. Targeted genetic testing for an expansion of the *FMR1* gene provides confirmation of the diagnosis.

X-linked dominant disorders

X-linked dominant disorders are caused by mutations in genes on the X chromosome that cause disease in females and are frequently lethal in males (often soon after conception). X-linked dominant mutations can be inherited by a girl from her affected mother or can occur *de novo*. As with autosomal dominant disorders, *de novo* mutations are more common in severe disorders.

A woman with an X-linked dominant disorder has a 50% chance of passing on the disorder each time she has a daughter. For most X-linked dominant disorders, the risk that a surviving male is affected is very low. When a mutation has occurred *de novo*, the risk of a further affected child is low. For most conditions, this risk is ~1%, reflecting the small risk of gonadal mosaicism.

Rett syndrome

Rett syndrome is an X-linked dominant disorder with an incidence of between 1 in 10,000 to 1 in 20,000 females. It is caused by heterozygous loss-of-function mutations in the *MECP2* gene. Mutations are *de novo* and the risk of recurrence of the condition for the parents of an affected child is low (~1%).

Rett syndrome results in severe learning disability. There is apparent normal early development followed by a period of regression and loss of language and motor skills accompanied by deceleration of head growth at 6–18 months. Stereotypic midline hand movements are often seen and seizures are common (see Chapter 5, Developmental problems and the child with special needs, for further details).

Molecular genetic testing is by sequencing and copy number analysis of the *MECP2* gene.

Mitochondrial disorders

Each mitochondrion carries a copy of its own genome, containing genes encoding proteins essential to mitochondrial function. Each cell in the body contains multiple mitochondria, meaning that there are multiple copies of the mitochondrial genome in each cell.

A number of disorders are caused by mutations in the mitochondrial genome. Mutations are usually present only in a proportion of the mitochondria in any given cell, with the remainder having a normal sequence. This is called 'heteroplasmy'. In part, the severity of the disorder depends on the level of heteroplasmy in different tissues.

Mitochondria are inherited by a child exclusively from the mother, since there are mitochondria in the
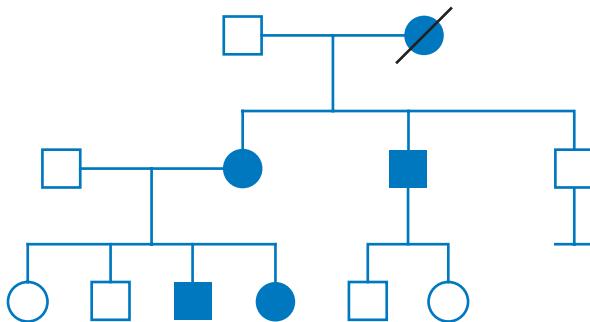
Fig. 9.9 A pedigree with a condition showing mitochondrial inheritance. Both males and females are affected. The condition is only passed on by females.

egg but not in the part of the sperm that forms the zygote. Mitochondrial mutations therefore cannot be passed on by a male (Fig. 9.9). It is hard to predict the level of heteroplasmy of the eggs of a woman, making it difficult to predict the level or risk of mitochondrial disease in her offspring.

Clinical features of mitochondrial disorders

Mitochondrial disorders overlap clinically. Mitochondrial dysfunction has a tendency to affect tissues that use large amounts of energy. These include muscle (myopathy), the retina (retinitis pigmentosa), the kidney (proximal tubulopathy and renal failure), nerves (neuropathy) and the brain (epilepsy, encephalopathy or stroke-like episodes), particularly the basal ganglia (dystonia) and the pons and cerebellum (pontocerebellar atrophy or hypoplasia and ataxia). They often show a progressive, degenerative course with episodes of decompensation during acute illness (see Chapter 29, Metabolic medicine, for further details). Lactic acidosis and/or elevated CSF lactate are often present, particularly during episodes of decompensation.

There are a number of classical mitochondrial phenotypes, although it is not unusual for patients to present with clinical features that do not precisely fit these groupings:

- Myoclonic epilepsy with ragged red fibres (MERRF)
- Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)
- Leigh's syndrome (subacute necrotizing encephalomyelopathy) and the overlapping disorder, neurogenic muscle weakness, ataxia and retinitis pigmentosa (NARP). These are caused by a variety of mitochondrial DNA mutations. Leigh's syndrome, like a number of other 'mitochondrial' phenotypes, can also be caused

by autosomal recessive mutations in conventional nuclear genes.

Clinical diagnosis of mitochondrial disorders

Due to their variability and wide variety of clinical manifestations, a high index of clinical suspicion is required to diagnose mitochondrial disorders. The mainstays of clinical diagnosis include neuroimaging, biochemical testing including blood and CSF lactate, muscle biopsy for histology and electron microscopy, skin or muscle respiratory chain enzyme analysis. Nerve conduction studies, urine biochemistry and electroretinography can also be useful.

Genetic testing for mitochondrial disorders

DNA sequencing for specific mitochondrial mutations can be targeted according to the presenting phenotype. It is also possible to sequence for a panel of common mitochondrial mutations, deletions and duplications. Using higher throughput techniques (for example, next generation sequencing) some labs now offer sequencing of the entire mitochondrial genome.

DNA sequencing is best performed with a method able to detect mutations at relatively low levels of heteroplasmy. Analysis of DNA extracted from muscle, where mutation load is often higher, maximizes sensitivity.

Where the phenotype is also consistent with mutation in a conventional nuclear gene, targeted sequencing and/or copy number analysis of these genes is also performed.

Imprinting disorders

We inherit two copies of the autosomal genes, one from our mother and one from our father. For most genes, both copies are active. The imprinted genes are different. Often arranged in clusters, imprinted genes are expressed only from the copy inherited from one parent. Within one cluster of imprinted genes, some genes are expressed only from the maternally-inherited copy and are silent on the paternally-inherited copy, while others are expressed only from the paternal copy and are silent from the maternal copy. The process is controlled by 'epigenetic' factors such as DNA methylation, which occurs in imprinted regions in a parent-of-origin-specific manner.

The causes of imprinting disorders

A number of diseases are caused by disruption of normal imprinting (Fig. 9.10). Mechanisms that can cause imprinting disorders include:
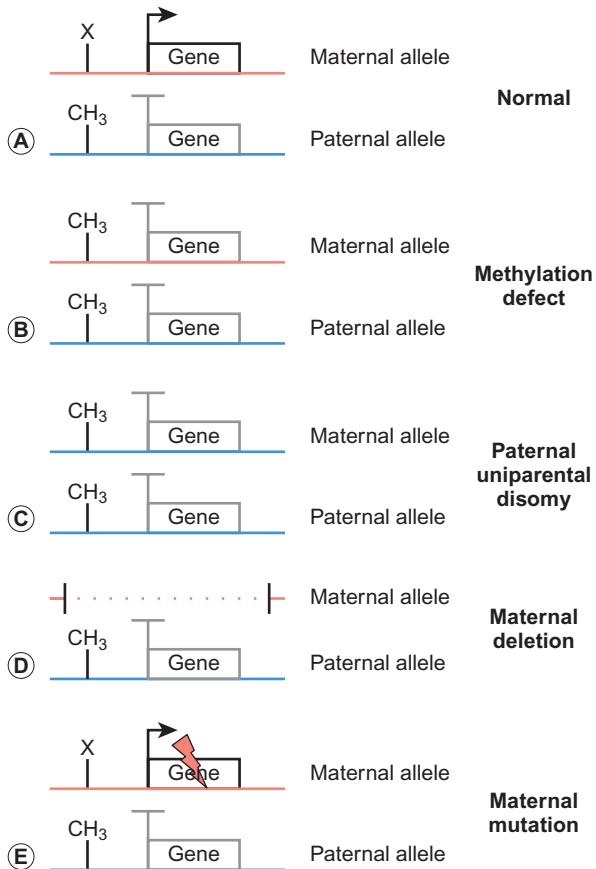
Fig. 9.10 Mechanisms of disruption of an imprinted locus. A. The normal region shows expression of an imprinted gene only from the maternal allele. There is DNA methylation that switches off gene expression on the paternal allele. The region is unmethylated on the maternal allele. **B.** A methylation defect resulting in silencing of the maternal allele of the gene. **C.** Paternal uniparental disomy for the region. **D.** A deletion of the region on the maternal allele. **E.** A mutation of the imprinted gene on the maternal allele.

- *Methylation defect*: abnormalities of the normal methylation pattern in an imprinted region can disrupt the normal parent-of-origin-specific expression pattern, either by switching off genes which are normally active, or switching on genes which are normally silenced.
- *Uniparental disomy (UPD)*: inheritance of both copies of a chromosome or chromosome region from the same parent. The genes retain the imprinted expression pattern of the parent of origin.
- *Deletion*: deletion of an imprinted region. The effect of deletion depends on the parent of origin of the chromosome carrying the deletion.
- *Single gene mutation*: loss-of-function mutations in imprinted disease genes. These mutations only cause disease when present on the copy of the gene that is normally active.

Uniparental disomy and methylation defects are 'epigenetic' alterations, i.e. they do not involve alterations in DNA sequence. As such, they are non-heritable and occur *de novo* in the affected child. They are generally associated with low risks of recurrence.

Deletions and single gene mutations can be inherited or occur *de novo*. They show autosomal dominant inheritance but only cause disease when inherited from the parent whose copy of the gene is normally active.

Testing for imprinting disorders

The method of testing for imprinted disorders depends on the mechanisms relevant to the disorder in question.

- *Methylation testing* using techniques such as methylation-specific PCR or MLPA (a multiplex PCR) is often a first line test for imprinting disorders. It is capable of detecting methylation defects, uniparental disomy and deletions (since the latter two result in altered DNA methylation patterns by removing one of the parental copies of the region).
- *Uniparental disomy testing* can be performed by microsatellite analysis (DNA fingerprinting) using samples from the child and both parents.
- *Deletion testing* can be performed by genome-wide microarray when looking for large deletions or by more targeted techniques such as MLPA when looking for smaller deletions.
- *DNA sequencing* of imprinted genes is used to detect point mutations and other small scale sequence changes in imprinted genes.

Some of the commoner examples of imprinting are listed below.

Prader–Willi syndrome

Prader–Willi syndrome (PWS) is an imprinting disorder with an incidence of between 1 in 10,000 to 1 in 20,000. It is caused by abnormalities at the imprinted 15q11 Prader–Willi/Angelman syndrome region, which can be:

- Maternal *uniparental disomy* at chromosome 15q11 (25% of cases)
- Large deletions of the paternal copy of 15q11 (70%)
- Methylation defects (<1%)

These changes are reciprocal to those seen in Angelman syndrome and abnormalities usually occur *de novo*. Hypotonia and poor feeding in the neonatal period is common. Later, there are mild to moderate learning difficulties. Hyperphagia and obesity develop from 12–18 months. Hypogonadotrophic hypogonadism is present in >80% of males.

Molecular genetic testing is by methylation testing followed by microarray (for deletions) and uniparental disomy testing as appropriate.

Angelman syndrome

Angelman syndrome is an imprinting disorder with an incidence of ~1 in 10,000. It is also caused by abnormalities at the imprinted 15q11 Prader–Willi/Angelman syndrome region that inactivate the *UBE3A* gene, which is normally only active on the maternal allele. It occurs as a result of three main mechanisms:

- Paternal *uniparental disomy* at chromosome 15q11 (10% of cases)
- Large deletions of the maternal copy of 15q11 (70%)
- Loss-of-function mutations on the maternal allele of *UBE3A* (10%)

These abnormalities are reciprocal to those seen in Prader–Willi syndrome. *UBE3A* mutations are usually inherited from the proband's mother, in which case the risk of recurrence is 50%. Most other causes occur *de novo* and have a low recurrence risk.

Angelman syndrome causes severe developmental delay and ataxia. There is a definite behavioural phenotype and children are described as having a happy disposition with a wide mouth and microcephaly. Seizures occur in >80%. Some children with deletions have fair skin and hair colour due to the presence of a pigment gene near the Angelman syndrome region.

Molecular genetic testing is by methylation testing followed by microarray (for deletions) and uniparental disomy testing as appropriate. *UBE3A* sequencing is carried out in cases where methylation is normal and the diagnosis is still considered likely.

Beckwith–Wiedemann syndrome

Beckwith–Wiedemann syndrome (BWS) is an imprinting disorder with an incidence of approximately 1 in 10,000. It is caused by abnormalities at the imprinted 11p15 growth regulatory region. The exact mechanism varies and it may be as a result of:

- Decreased methylation (at the KvDMR region) (50% of cases)
- Increased methylation (at the H19 region) (5%)
- Paternal *uniparental disomy* at chromosome 11p15 (20%)
- Loss-of-function mutations on the maternal allele (of *CDKN1C*) (5%)

These abnormalities are reciprocal to those seen in Silver–Russell syndrome (a cause of short stature). Uniparental disomy and methylation defects usually occur *de novo*. *CDKN1C* mutations are usually inherited from the proband's mother and are inherited in an autosomal dominant manner. Beckwith–Wiedemann syndrome results in pre- and postnatal overgrowth, neonatal hypoglycaemia, coarse facial features, macroglossia, exomphalos or umbilical hernia, hemihypertrophy, earlobe creases and posterior helical pits.

Providing neonatal hypoglycaemia is prevented, intelligence is normal. However, there is an increased risk of embryonal tumours, mainly Wilms' tumour. Wilms' tumour risk is only increased in some molecular subgroups. It is not increased in the largest group, KvDMR methylation defects. Those with other causes (or no detectable cause) should have renal ultrasound scans every 3–4 months until 7 years.

Molecular genetic testing allows confirmation of diagnosis and assessment of tumour risk.

Other imprinting disorders

Other imprinting disorders include:

- Albright's hereditary osteodystrophy
- Transient neonatal diabetes mellitus

Prenatal screening and prenatal diagnosis

This is considered in Chapter 10, Perinatal medicine.

Predictive testing and ethical issues

Case history

Predictive testing for an adult onset disorder

You see Sally, aged eight, about her asthma. Her mother has recently had breast cancer and has been found to carry a mutation in *BRCA1*, an autosomal dominant breast and ovarian cancer susceptibility gene. She asks you to arrange *BRCA1* testing for Sally. How do you deal with her request?

Predictive genetic testing

In children who are already symptomatic for a genetic disease, carrying out a genetic test is straightforward and compatible with their best interests. This is known as *diagnostic genetic testing*. An example would be a baby with an omphalocele and macroglossia in whom Beckwith–Wiedemann testing is carried out. Such testing would help plan long-term follow-up and inform recurrence risks for the parents.

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Difficulties arise when considering testing a child in whom there is a family history of a particular condition but the child herself is asymptomatic. This is known as *predictive genetic testing*. Predictive testing in children should only be performed if it is in their best interests.

The important ethical principles to bear in mind in such cases are autonomy, beneficence (doing good) and non-maleficence (avoiding harm).

In some genetic conditions, there are important interventions or screening tests that can be carried out at an early age, thereby avoiding a harm that could otherwise take place. An example of this is familial adenomatous polyposis (FAP), an autosomal-dominant, hereditary colon cancer syndrome caused by mutations in the adenomatous polyposis coli (*APC*) gene. Affected individuals generally begin to develop precancerous polyps as teenagers, although some have developed polyps as early as age 7. Colon cancer is inevitable, and the average age of colon cancer diagnosis in untreated individuals is 39 years. Routine colonoscopy is recommended, beginning between the ages of 10 and 12 years. In this condition, there is a clear medical benefit to childhood testing in the form of a useful screening programme for those with the condition or release from this invasive screening for those who test negative. In a non-competent child, this overrides any potential loss of autonomy that arises from childhood testing.

In the *BRCA1* example above, however, there is no early screening or intervention that can be offered. Screening for breast cancer in BRCA mutation carriers starts in adulthood and testing a child would confer no benefits and the potential for certain 'harms'. These include:

- Loss of autonomy – many adults who are at risk of genetic disease decide not to have a predictive test. Testing a child before they can have a say in the matter thus takes away their choice not to know.
- Discrimination – this may be financial, perhaps in the form of difficulties in obtaining insurance at a later date.

- Psychological 'harms', such as anxiety, which may be increased in the event of a positive predictive test.

BRCA1 testing would therefore not be offered to Sally, aged eight, at her mother's request.

However, if Sally approached her paediatrician aged fifteen, and it was felt she was competent to consent, the issues would be different.

If, after a thorough genetics consultation, it was clear she understood the possible risks and benefits as applicable to her situation, it might be appropriate to offer her a test. In such situations, if a competent young person is able to make the decision to test by herself and without coercion, her autonomy has been preserved. There are no medical benefits to testing at such a young age, but non-medical benefits might be framed in terms of self-knowledge and life-planning.

Prenatal predictive genetic testing

Prenatal test for an adult-onset condition is only indicated when the woman wishes to undergo termination of an affected fetus. Prenatal testing for information only should not be performed as it amounts to predictive testing of a child.

Further reading

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Mithilesh Kumar Lal, Nazakat Merchant, Sunil K Sinha
With contributions by
Helen Yates, Lawrence Miall, Steve Byrne

Perinatal medicine

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Know the definitions used in perinatal medicine and their uses and limitations
- Know about pre-pregnancy and prenatal conditions which may affect the fetus
- Understand the difference and importance of small for gestational age and intrauterine growth restriction
- Understand how multiple births may affect the fetus
- Be aware of the embryology of the human fetus and how congenital anomalies may occur
- Know about teratogens and how maternal drugs, alcohol and substance misuse may affect the infant
- Know about maternal medical conditions that may affect the fetus
- Know about congenital infections
- Understand the fetal circulation and circulatory changes after birth
- Know about the effect of perinatal hypoxia on the fetus and infant

Perinatal definitions and epidemiology

Even simple definitions in perinatology can be contentious. It is traditional to calculate the baby's due date by asking the mother about the first day of her last menstrual period and relying on this, unless there is a discrepancy with ultrasound dates of more than 10 days. However, expert opinion is divided and some would advise that when results of an ultrasound dating scan are available, the due date should be derived from ultrasound biometry alone (Perinatal Institute of Maternal and Child Health recommendations).

It follows that obtaining accurate data relating to stillbirths and mortality/survival rates in extremely preterm infants is difficult. Comparing data from different countries is even more difficult. This is due to variation in legislation, regulation, and practices of registration of stillbirth, live birth and death. There

is wide variation between different countries in gestational age at which fetal deaths are registered as stillbirths, which influences the decision whether extremely preterm births are registered as live birth or miscarriage. Some definitions used in perinatal medicine are listed in Box 10.1. The main causes of perinatal deaths in the UK are listed in Table 10.1.

Maternal risk factors for poor fetal outcomes in the UK include coexisting medical conditions, parity, socio-economic status, age, nutrition, antenatal service provision and their utilization. The perinatal mortality rate has decreased from 13.3 in 1980 to 6.0 in 2013 in England and Wales. Improved maternal health and nutrition, socio-economic conditions, better antenatal and perinatal care, high antenatal steroid uptake and improved survival of preterm infants have contributed. Changes in neonatal, postneonatal and infant mortality rates are shown in Figure 10.1.

Globally, almost 99% of neonatal deaths occur in low- and middle-income countries and the main

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- Gestational age in completed weeks is calculated from the first day of the last menstrual period (LMP) to the date of birth.
- Neonate – infant ≤28 days old.
- Preterm – gestation <37 weeks of pregnancy. Often subclassified into extreme preterm (<28 weeks' gestation), very preterm (28–31 weeks' gestation), moderate preterm (32–33 weeks' gestation) or late preterm (34–36 weeks' gestation).
- Term – 37–41 weeks of pregnancy.
- Post-term – gestation ≥42 weeks of pregnancy.
- Stillbirth – fetus delivered at or after 24^{+0} weeks gestational age showing no signs of life.
- Neonatal death – a live born baby (born at 20^{+0} weeks gestational age or later, or with a birth weight of 400 g or more where an accurate estimate of gestation is not available) who died before 28 completed days after birth.
- Perinatal mortality rate – stillbirths + deaths within the first week per 1000 live births and stillbirths.
- Neonatal mortality rate – deaths of live-born infants within the first 4 weeks after birth per 1000 live births.
- Postneonatal mortality rate is the number of deaths aged 28 days and over, but under one year per 1000 live births.
- Infant mortality rate is the number of deaths under 1 year of age per 1000 live births. This includes neonatal deaths.
- Low birth weight (LBW) – <2500 g
- Very low birth weight (VLBW) – <1500 g
- Extremely low birth weight (ELBW) – <1000 g
- Small for gestational age – birth weight <10th centile for gestational age.
- Large for gestational age – birthweight >90th centile for gestational age.

causes are preterm birth (34%), infection (23%), and perinatal asphyxia (25%).

The epidemiology of mortality statistics and their collection is considered in more detail in Chapter 2, Epidemiology and public health, and a global overview is considered in Chapter 33, Global child health.

Placental physiology and early embryology

Placental function

The placenta has three major functions: transport, immunity and metabolism. The placenta starts to develop as soon as the blastocyst implants in the uterine endometrium, forming the trophoblast (Fig. 10.2). A network of umbilical blood vessels then develop and branch through the chorionic plate to form villi. On the maternal side of the placenta, the blood supply is complete by 11–12 weeks. The uterine spiral arteries dilate and straighten and bathe the intervillous space with blood.

Transport

The placenta transports nutrients from the mother to the fetus, and waste products in the other direction. This occurs in a number of ways, including simple

Table 10.1 Stillbirths and neonatal deaths in the UK, 2013

Stillbirths (4.2 per 1000 total births)	Neonatal deaths (1.8 per 1000 live births)
Unexplained antepartum fetal death 52%	Immaturity 44%
Intrapartum 9%	Congenital malformation 22%
Congenital malformation 6%	Intrapartum causes 6%
Infection 3%	Infection 6%
Placenta 19%	Fetal 5%
Other 11%	Other 17%

(Source: MBRACE report, June 2015)
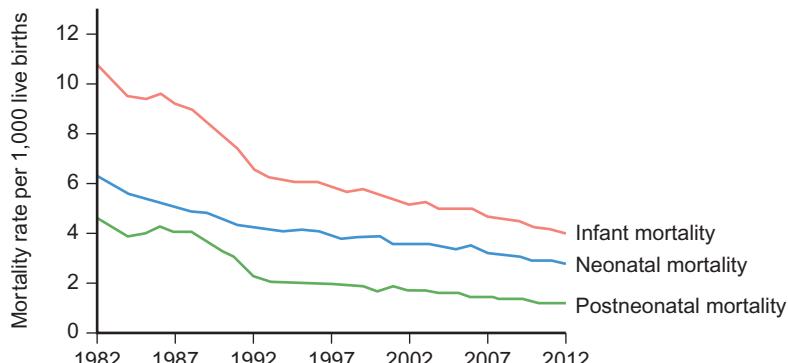
Fig. 10.1 Infant, neonatal and postneonatal mortality rates in England and Wales 1982–2012. *(Data from Office of National Statistics).*
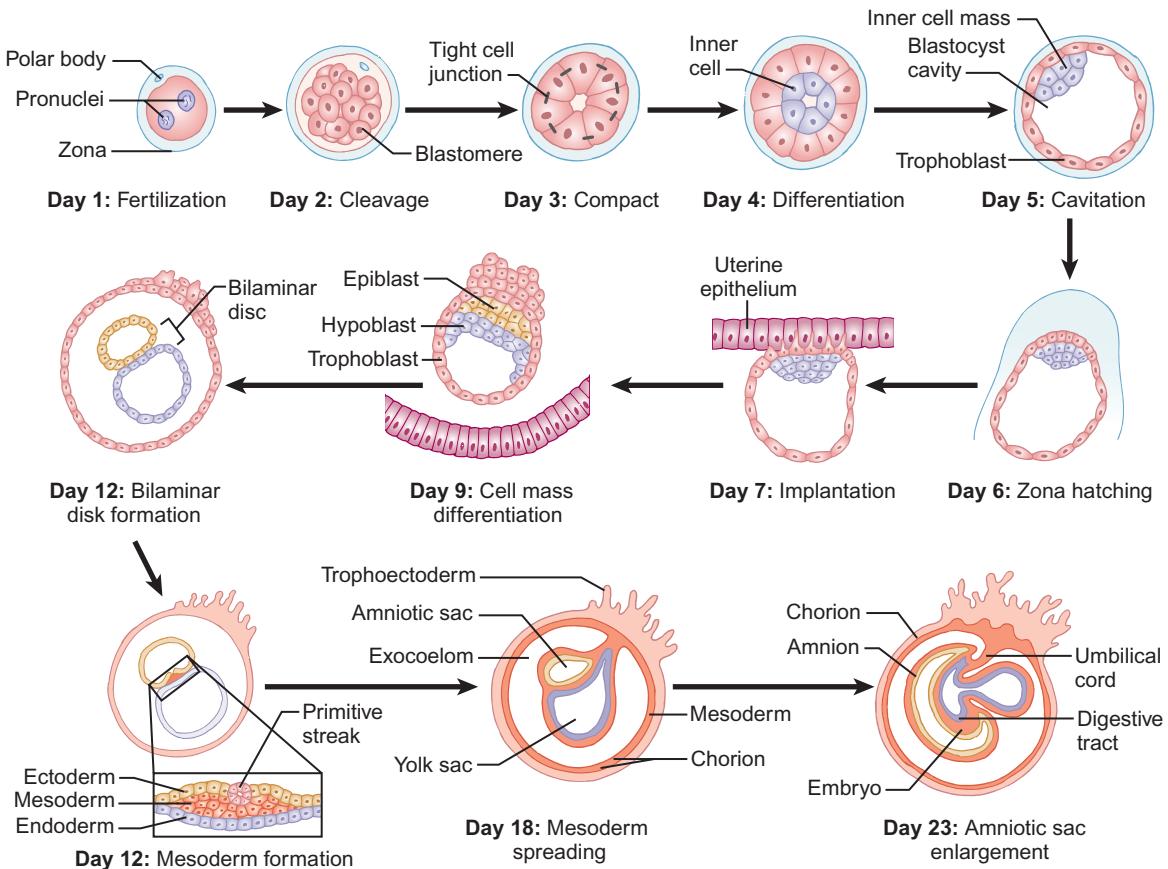
Fig. 10.2 Early embryology of the fetus.

Day 1: Fertilization — Polar body, Pronuclei, Zona, (egg)
Day 2: Cleavage — Blastomere
Day 3: Compact — Tight cell junction
Day 4: Differentiation — Inner cell
Day 5: Cavitation — Inner cell mass, Blastocyst cavity, Trophoblast

Day 6: Zona hatching
Day 7: Implantation — Uterine epithelium
Day 9: Cell mass differentiation — Epiblast, Hypoblast, Trophoblast
Day 12: Bilaminar disk formation — Bilaminar disc

Day 12: Mesoderm formation — Primitive streak, Ectoderm, Mesoderm, Endoderm
Day 18: Mesoderm spreading — Trophoectoderm, Amniotic sac, Exocoelom, Yolk sac, Mesoderm, Chorion
Day 23: Amniotic sac enlargement — Chorion, Amnion, Umbilical cord, Digestive tract, Embryo

diffusion (for small molecules) and active transport of larger molecules. The placenta is crucially also responsible for gaseous exchange of O_2 and CO_2. Oxygen diffuses from the mother (pO_2 = 10–14 KPa) to the fetus (pO_2 = 2–4 KPa), where it binds to fetal haemoglobin (Hb), which has a higher affinity for oxygen than maternal Hb for a given pO_2. This off-loading of oxygen from maternal Hb is also facilitated by a change in maternal blood pH.

Immunity

The placental trophoblast prevents the maternal immune system from reacting against 'foreign' fetal antigens. Rejection does not occur because the trophoblastic cells appear non-antigenic, although it is known that some fetal cells do cross into the maternal circulation where they can trigger an immune reaction (e.g. Rhesus haemolytic disease). Maternal IgG antibody, the smallest of the immunoglobulins, can cross the placenta, where it provides the newborn with innate immunity to infectious diseases. IgM immunoglobulins do not cross the placental barrier. This is of particular relevance in the diagnosis of congenital infection.

Metabolism and homeostasis

The placenta is metabolically active and produces hormones, including human chorionic gonadotrophin (HCG) and human chorionic thyrotrophin (HCT). It also detoxifies drugs and metabolites. Because of its metabolic activity, the placenta has very high energy demands and consumes over 50% of the total oxygen and glucose transported across it. The placenta is not solely responsible for fetal homeostasis – the fetal liver produces albumin, red cells and clotting factors and the fetal endocrine glands produce thyroid hormone, corticosteroids and insulin from about 12 weeks. The kidney excretes large volumes of dilute fetal urine from 10–11 weeks, which contributes to amniotic fluid volume.

Advising a mother planning a pregnancy

A 32-year-old mother attends your clinic for a review of her 18-month-old child, who has gross motor delay. She tells you that she is planning another child. Current UK advice suggests she should avoid eating significant quantities of the following foods, true (T) or false (F):

A. Folate-supplemented foods

B. Honey

C. Liver

D. Tuna

E. Unpasteurized cheese

Answer 10.1

A. False; B. False; C. True; D. True; E. True.

Honey should be avoided in early childhood because of the theoretical risk of infant botulism, but avoidance in pregnancy is not currently advised. The other dietary considerations are discussed below.

Pre-pregnancy care

Advice for mothers includes:

Avoidance of smoking in pregnancy: This is because smoking reduces birth weight which becomes particularly important if there is intrauterine growth restriction. It also increases pregnancy-related risks of miscarriage and stillbirth and preterm delivery. In the infant, it increases the risk of sudden infant death syndrome and wheezing, asthma, bronchitis, pneumonia and otitis media. It has been associated with psychological problems in childhood, such as attention and hyperactivity problems.

Folic acid supplementation: This is advised for all mothers before conception and throughout the first 12 weeks of pregnancy, as it reduces the risk of neural tube defects (NTD) such as anencephaly and spina bifida. Although eating folate-rich foods may help, it is often insufficient. Higher-dose supplements are recommended for those at increased risk (previous NTD pregnancy, family history including partner and maternal diabetes). In the UK, Healthy Start provides free vitamin supplements (folic acid with vitamins C and D) for low-income pregnant women and those who have an infant less than 1 year. In the US and some other countries, folic acid is required to be added to cereals and grains.

Vitamin D supplementation: Vitamin D is required for fetal bone mineralization and accumulation of infant vitamin D stores. A newborn baby's vitamin D status is largely determined by the mother's level of vitamin D during pregnancy. Breast milk is not a significant source of vitamin D. The main source of vitamin D is sunlight. For a significant number of months in the UK, there is little ambient ultra-violet sunlight of appropriate wavelength. Vitamin D supplements are advised for all women who are planning to breastfeed their infants and is included in the Healthy Start vitamins, available to all low-income women who are pregnant or have a child under 1 year old.

Avoid medications with teratogenic effects: In addition, all medications should be avoided unless essential.

Avoid alcohol ingestion and drug abuse (opiates, cocaine): These may damage the fetus.

Congenital rubella: Prevent by maternal immunization before pregnancy.

Toxoplasmosis: Minimize exposure by avoiding eating undercooked meat and wearing gloves when handling cat litter.

Listeria infection: Avoid eating unpasteurized dairy products, soft ripened cheeses, e.g. brie, camembert and blue-veined varieties, patés and ready-to-eat poultry.

Eating liver: Best avoided as it contains a high concentration of vitamin A.

Fish: Avoid eating swordfish, shark, marlin and limit tuna intake as they may contain high levels of mercury. Also limit oily fish as they may contain pollutants such as dioxins.

If pre-existing maternal medical conditions, e.g. diabetes and epilepsy: Optimize control.

If at increased risk of fetal abnormality: Genetic counselling should be obtained. This includes previous congenital anomaly, positive family history, parents being known carriers of genetic disorder, ethnic group with increased risk, e.g. Tay–Sachs, a neurodegenerative disorder, in Ashkenazi Jews.

Prenatal care

Routine prenatal screening includes maternal blood sampling, ultrasound scanning and attendance at an antenatal clinic.

Maternal blood

Maternal blood should be tested for blood group, antibodies for rhesus (D) and other red cell incompatibilities, hepatitis B (surface and e-antigen), syphilis serology, rubella, HIV serology, haemoglobin electrophoresis to identify thalassaemia and sickle cell traits.

Ultrasound

It is usual for mothers to have late first and mid-trimester scans. The initial scan allows gestational age estimation and can identify multiple pregnancy, the later scan structural abnormalities and amniotic fluid volume abnormalities. If fetal growth or other problems are identified, monitoring with serial scans may be performed.

Antenatal clinic attendance

Antenatal clinical attendance allows identification of pre-existing maternal medical condition (e.g. hypertension, HIV) or obstetric risk factors for complications of pregnancy or delivery (e.g. recurrent miscarriage or previous preterm delivery). It also facilitates monitoring for pregnancy complications.

Screening

Prenatal screening for disorders affecting the mother or fetus allows:

- Reassurance where disorders are not detected (though many abnormalities which are detected on ultrasound screening are not confirmed on repeat or more expert scanning, or are transient or minor but may cause considerable anxiety)
- Optimal obstetric and neonatal management to be planned and parental counselling provided when problems are detected
- Interventions for a limited number of conditions with fetal medicine or surgery (see below)
- The option of termination of pregnancy to be offered for severe disorders affecting the fetus or compromising maternal health. Parents require accurate, rapid medical advice and counselling to help them with this difficult decision.

Genetic disorders

Pregnancies at increased risk of genetic disorders may be identified on prenatal or antenatal screening. Trisomy 21 (Down's syndrome) may be suspected on first trimester ultrasound screening of nuchal translucency measurement, which may be combined with maternal serum biochemical screening.

Non-invasive prenatal testing

Non-invasive prenatal testing (NIPT) is where cell-free fetal DNA is obtained from maternal blood. This can now be performed for identification of fetal gender (for X-linked disorders), fetal genotyping (Rhesus) and exclusion of common aneuploidy (especially trisomy 21). It is likely to become increasingly refined and available in clinical settings. It is debated if this should be offered alone or with nuchal translucency

ultrasound screening to identify trisomy 21. The advantage is that it avoids the risk of miscarriage with invasive testing procedures, however there are technical, ethical and financial issues.

Invasive prenatal testing

Invasive prenatal testing (see Fig. 10.3) requires an invasive test in pregnancy with the aim of collecting fetal cells. These can be used for:

- Cytogenetic analysis to look for chromosomal abnormalities.
- Molecular analysis in the case of a known genetic mutation.
- Biochemical analysis in the case of a defined disorder with a suitable prenatal biochemical test.

In families already affected by a genetic condition, a prenatal test is only possible where the genetic mutation in the family is known. In a small number of disorders, mainly metabolic, prenatal biochemical or enzyme testing may be possible if the diagnosis has been confirmed in an affected family member.

Fetal medicine

The techniques involved in fetal medicine and their indications are shown in Figure 10.3. Examples of fetal therapy include:

- Glucocorticoid therapy before preterm delivery to accelerate lung maturity and surfactant production
- Digoxin or flecainide given to the mother to treat fetal supraventricular tachycardia
- Rhesus or other isoimmunization causing severe anaemia and hydrops fetalis (oedema and ascites) can be monitored with fetal middle cerebral artery Doppler ultrasound and managed with fetal blood transfusion via the umbilical vein
- Perinatal isoimmune thrombocytopenia, due to antiplatelet antibodies crossing the placenta. Severe thrombocytopenia can be treated with intrauterine intravenous immunoglobulin or platelet transfusion. This is to prevent intracranial haemorrhage, which occurs in up to 25%.

Fetal surgery

This is performed in a few specialist perinatal centres, although outcomes have been highly variable. Some examples include:

- Catheter shunts inserted under ultrasound guidance to drain fetal pleural effusions (pleuro–amniotic shunts), often from a chylothorax (lymphatic fluid) or congenital cystic

Imaging
High definition ultrasound
Fetal MRI
For identification and deliniation of fetal abnormalities

Fetoscopy
Fetoscopic laser ablation for feto-fetal transfusion syndrome

Amniocentesis
Chromosome/micro-array and DNA analysis
Fetal infection - PCR (polymerase chain reaction) for CMV, toxoplasmosis, rubella, parvovirus

Fetal blood sampling
Fetal hemoglobin for anemia
Fetal infection serology
Fetal blood transfusion

Chorionic villous sampling
Chromosome/micro-array and DNA analysis
Enzyme analysis of inborn error of metabolism

Non-invasive prenatal testing (NIPT)
Free fetal DNA obtained from maternal blood for identification of fetal gender (for x-linked disorders), fetal genotyping (Rhesus) and identification of common aneuploidy (especially Trisomy 21).

Pre-implantation genetic diagnosis (PGD)
In-vitro fertilisation (IVF) allows genetic analysis of cells from a developing embryo before transfer to the uterus

Fig. 10.3 Techniques in fetal medicine and their indications. *(Adapted from Neonatology at a Glance. Tom Lissauer, Av Fanaroff, Lawrence Miall, Jonathan Fanaroff (eds). Wiley-Blackwell. 3rd Edn. 2015.)*

adenomatous malformation of the lung. One end of a looped catheter lies in the chest, the other end in the amniotic cavity. The aim is to reduce the risk of fetal death from hydrops and pulmonary hypoplasia.

- Fetoscopic laser therapy to ablate placental anastomoses which lead to the twin–twin transfusion syndrome (TTTS).
- Intrauterine shunting for urinary outflow obstruction as with posterior urethral valves. Results have been disappointing in reducing morbidity or death because of pre-existing renal damage.
- Fetal endoscopic tracheal occlusion (FETO) for congenital diaphragmatic hernia. As fetal tracheal obstruction promotes lung growth, this is replicated *in utero* by inflating a balloon in the fetal trachea. This is not recommended outside research trials.
- Spina bifida surgical correction by hysterotomy at 22–24 weeks' gestation has been performed in a few specialist centres but may precipitate preterm delivery and its benefit remains uncertain. Hydrocephalus requiring shunting may be reduced. Such interventions still remain experimental and without proven long-term benefit.

- Surgery for sacrococcygeal teratoma to remove a growing tumour has been done with mixed results.

Intrauterine growth restriction

An infant's gestation and birth weight influence the nature of the medical problems likely to be encountered in the neonatal period. In the UK, 7% of babies are of low birth weight (<2.5 kg). However, they account for about 70% of neonatal deaths.

Babies with a birth weight below the 10th centile for their gestational age are called small for gestational age (SGA) or small-for-dates (SFD). The majority of these infants are normal, but constitutionally small. An infant's birth weight may also be low because of preterm birth, or because the infant is both preterm and small for gestational age. SGA infants may have grown normally but are small, or they may have experienced intrauterine growth restriction (IUGR), i.e. they have failed to reach their full genetically determined growth potential and appear thin and malnourished. Babies with a birth weight above the 10th centile may also be growth restricted, e.g. a fetus growing along the 80th centile who develops growth failure and whose weight falls to the 20th centile.

As the incidence of congenital abnormalities and neonatal problems is higher in those whose birth weight falls below the second centile (two standard deviations (SD) below the mean), some restrict the term SGA to this group of babies.

In obstetric care, fetal centiles may be customized for maternal characteristics (weight, height, parity, and ethnicity) as well as gestation and gender; this is more predictive of morbidity and mortality.

Patterns of growth restriction

Intrauterine growth restriction implies a pathological restriction of genetic growth potential; this may be identified or monitored by evidence of fetal compromise, such as reduced liquor volume and abnormal Doppler waveforms. It has traditionally been classified as symmetrical or asymmetrical. In the more common asymmetrical growth restriction, the weight or abdominal circumference lies on a lower centile than that of the head. This occurs when the placenta fails to provide adequate nutrition late in pregnancy but brain growth is relatively spared at the expense of liver glycogen and skin fat. This form of growth restriction is associated with uteroplacental dysfunction secondary to maternal pre-eclampsia, multiple pregnancy, maternal smoking or may be idiopathic. These infants rapidly put on weight after birth.

In symmetrical growth restriction, the head circumference is equally reduced. It suggests a prolonged period of poor intrauterine growth starting in early pregnancy. It is usually due to a small but normal fetus, but may be due to a fetal chromosomal disorder or syndrome, a congenital infection, maternal drug and alcohol abuse or a chronic medical condition or malnutrition. These infants are more likely to remain small permanently. In practice, distinction between symmetrical and symmetrical growth restriction often cannot be made.

Monitoring the growth-restricted fetus

The fetus with IUGR is at risk from intrauterine hypoxia/intrauterine death and asphyxia during labour and delivery. The growth-restricted fetus should be monitored closely to determine the optimal time for delivery. Progressive uteroplacental failure results in:
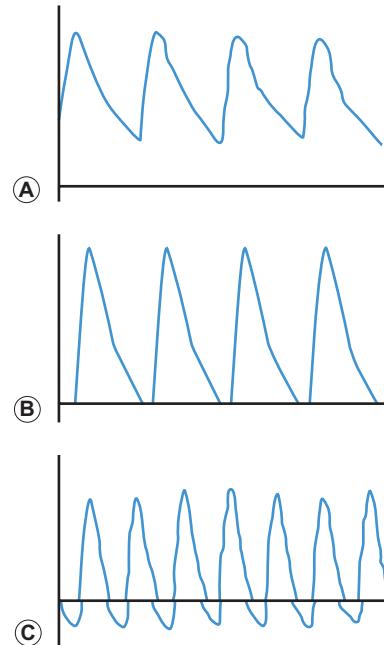
- Reduced growth in femur length and abdominal circumference (<10th centile)
- Reduced amniotic fluid volume
- Abnormal umbilical artery Doppler waveforms due to increased placental impedance – absent and then reversed end-diastolic flow velocity

- Redistribution of blood flow in the fetus – increased to the brain, reduced to the gastrointestinal tract, liver, skin and kidneys
- Abnormal ductus venosus Doppler waveform denoting diastolic cardiac dysfunction
- Reduced fetal movements
- Abnormal CTG (cardiotocography)
- Intrauterine death or hypoxic damage to the fetus.

Risks and complications after birth include:

- Hypothermia because of their relatively large surface area
- Hypoglycaemia from poor fat and glycogen stores
- Hypocalcaemia
- Polycythaemia (venous haematocrit >0.65).

Umbilical artery Doppler

In the healthy fetus, there is forward flow in the umbilical artery throughout systole and diastole. In IUGR due to placental disease, the resistance in the placenta increases (e.g. due to loss of placental villi or pre-eclampsia) resulting in reduced, then absent or even reversed flow during diastole (Fig. 10.4). If end-diastolic flow is absent, detailed Doppler studies of the middle cerebral artery (MCA) and ductus venosus are indicated.

EXAMPLES OF UMBILICAL ARTERY DOPPLER FLOW WAVEFORMS

A: Normal
B: Absent end-diastolic flow waveform
C: Reversed end-diastolic flow waveform

Fig. 10.4 Umbilical artery Doppler waveforms showing (A) normal, (B) absent end-diastolic velocity and (C) reversed end-diastolic velocity.

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Middle cerebral artery Doppler

As IUGR becomes increasingly severe, there is redistribution of fetal blood flow, with an increase in flow to the brain, and *increased* end-diastolic velocity. Evidence of cerebral redistribution should trigger intensive regular monitoring.

Ductus venosus Doppler

This reflects the physiological state of the right heart. In the second trimester growth-restricted fetus, reversed flow during atrial contraction represents cardiac decompensation. It is a better predictor of stillbirth than umbilical artery Doppler alone. Timing of delivery will be based on Doppler findings, gestation and estimated fetal weight.

Large-for-gestational-age infants (LGA)

Large-for-gestational-age infants are those above the 90th weight centile for their gestation. Macrosomia is a feature of infants of mothers with either permanent or gestational diabetes mellitus, or a baby with a congenital syndrome (e.g. Beckwith–Wiedemann syndrome). The problems associated with being large for gestational age are:

- Birth trauma, especially from shoulder dystocia at delivery (difficulty delivering the shoulders from impaction behind maternal symphysis pubis)
- Birth asphyxia from a difficult delivery
- Breathing difficulty from an enlarged tongue in Beckwith–Wiedemann syndrome
- Hypoglycaemia due to hyperinsulinism
- Polycythaemia

Question 10.2

Multiple births

Which of the following statements about multiple births are true (T) and which are false (F)?

A. Dichorionic twins are dizygotic

B. In twin–twin transfusion syndrome, the donor twin is growth restricted

C. Monochorionic twins can have one placenta, one chorion but two amnions

D. Triplet pregnancies which occur naturally in the UK occur at a rate that is roughly the square of the rate of twin pregnancy

E. Twin–twin transfusion syndrome occurs in both dichorionic and monochorionic twins

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Answer 10.2

A. False; B. True; C. True; D. True; E. False.
See below for discussion.

Multiple births

The natural incidence of multiple births is:

- 1 in 89 for twins
- 1 in 89^2 (1 in 8,000) for triplets
- 1 in 89^3 (1 in 700,000) for quadruplets

However, the incidence of twins is now 1 in 67 and of triplets 1 in 4000. This is mainly because of increased maternal age of childbearing and fertility-enhancing therapies.

Twins may be:

- Dizygotic – have 2 chorions and 2 amnions (dichorionic-diamniotic) (Fig. 10.5)
- Monozygotic – have 1 chorion but 2 amniotic sacs (monochorionic–diamniotic) or have 2 chorions and amniotic sacs (dichorionic–diamniotic) (Fig. 10.6)

The main complications of multiple pregnancies are:

- Preterm delivery – median gestation of 37 weeks, 34 weeks for triplets. Monochorionic twins are likely to need to be delivered preterm.
- Intrauterine growth restriction – common, especially for monochorionic twins
- Congenital abnormalities – risk twice normal in dichorionic twins, as there are two infants, but four times normal in monochorionic twins
- Twin–twin transfusion syndrome – occur across placental arteriovenous anastomoses in monochorionic twins. The donor is hypovolaemic and has growth restriction, oliguria and oligohydramnios. The recipient is hypervolaemic and may have high output cardiac failure, polyuria and polyhydramnios. Fetoscopic laser therapy may be required to divide placental blood vessels.
- Death of a fetus – death of one twin may result in preterm labour. In monochorionic twins, there may be blood loss from the live to the dead twin resulting in hypovolaemia, severe anaemia and neurological impairment or death of the surviving twin.

Congenital anomalies

Congenital anomalies affect approximately 3–6% of all live births and account for 20–25% of all neonatal deaths in the UK. They may result in cosmetic
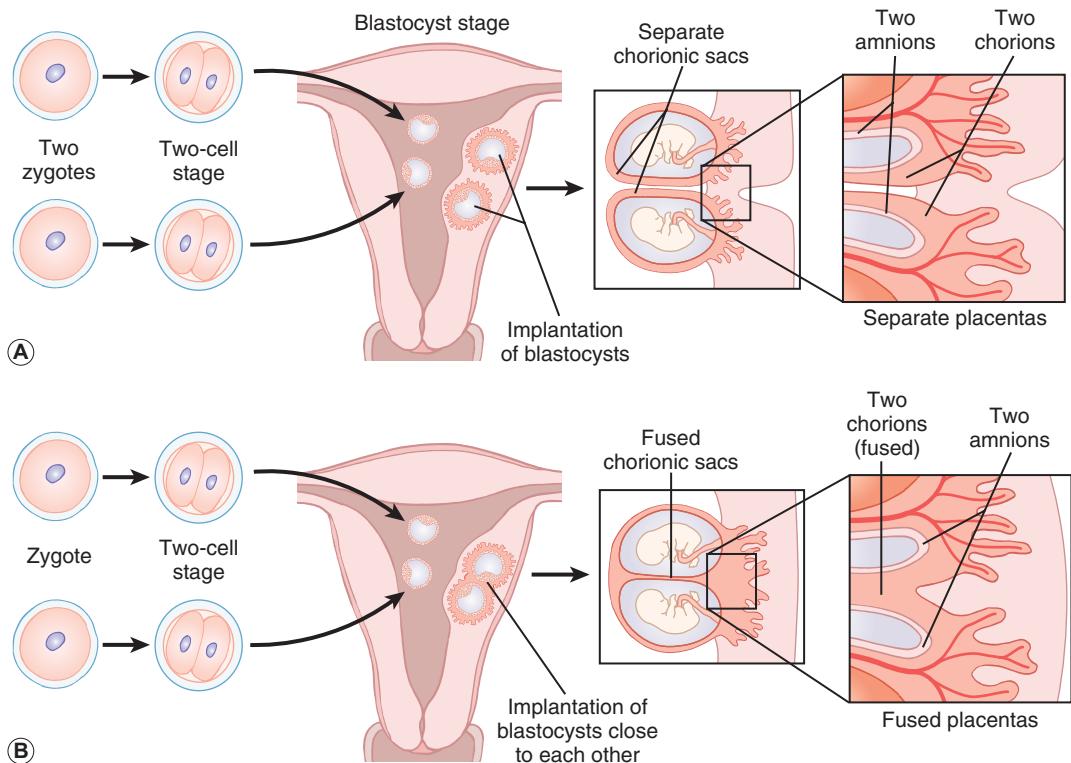
Fig. 10.5 Dizygotic twins. They have two amnions and two chorions (A) but the chorions and placentas may be fused (B).
(From Moore KL, Persaud TVN, Torchia MG. The developing human, 9th edition, Saunders 2012, with permission.)

disfigurement and long-term disability, impacting on individuals, families and societies.

Some definitions

Congenital malformation: A defect in the structure of an organ or part of an organ due to abnormal development. Around a quarter are from genetic causes. However, most have multifactorial or unknown causes, e.g. congenital heart defects, developmental dysplasia of the hip (DDH), cleft lip and palate. About 5–10% may be caused by teratogens, i.e. any chemical, maternal physical condition or deficiency that can alter fetal development or function. Examples include maternal alcohol, drug misuse or anticonvulsant therapy, congenital infections or maternal disorders, e.g. type 1 diabetes mellitus.

Disruption: An anomaly which occurs when a fetal structure starts off growing normally but growth is arrested by something which disrupts the process. Two examples of disruptions that cause terminal limb defects as a result of disrupted blood supply are:

- Amniotic bands – thought to be formed when the amnion ruptures early and a fetal limb is forced into the chorionic cavity, resulting in vascular compression followed by necrosis. It results in absent digits or limbs.

- Chorionic villus sampling (CVS) – if carried out too early in pregnancy (around 8–10 weeks) may result in a similar clinical abnormality. The mechanism is again thought to be vascular disruption, perhaps due to haemorrhage from injured chorionic villi.

Deformation: An external force results in an alteration of shape of a previously normally formed structure. Usually develop in the second half of the pregnancy when the size of fetus is large in comparison to the uterine size.

Dysplasia: Abnormal organization of cells into tissues and usually develops during embryogenesis, e.g haemangiomas, osteogenesis imperfecta, achondroplasia.

Sequence: Groups of related anomalies that stem from a single initial major anomaly that alters the development of other surrounding or related tissues or structures. Examples are:

- Pierre Robin sequence – a small jaw (micrognathia) leads to the tongue being displaced posteriorly which results in a cleft palate

- Potter's sequence – a single anomaly (renal abnormality) causes decreased fetal urine output and associated oligohydramnios. This leads to pulmonary hypoplasia and typically
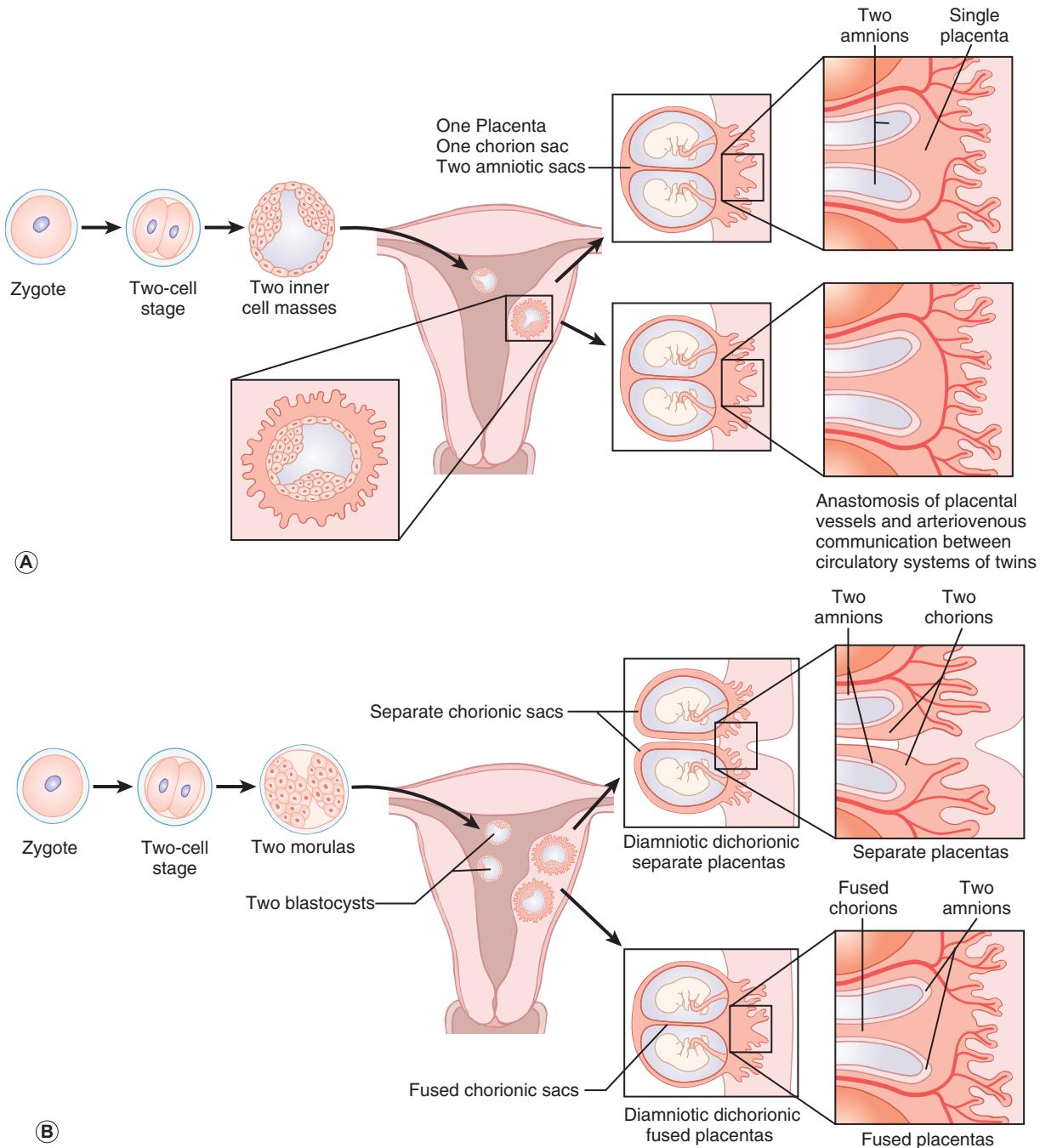
Fig. 10.6 Monozygotic twins. A. 65% of monozygotic twins develop from one zygote and have separate amnions, a single chorionic sac and a common placenta. There may be anastomosis of the placental vessels, in which case one twin may receive most of the nutrition from the placenta. B. 35% of monozygotic twins develop from one zygote but produce two identical blastocysts, each of which develops its own amniotic or chorionic sacs. In most there is a single placenta, but in some there are two placentas. *(From Moore KL, Persaud TVN, Torchia MG. The developing human, 9th edition, Saunders 2012, with permission.)*

flattened facial features. Potter's sequence is also an example of a deformation, as an external force (in this case oligohydramnios), results in a flattened face from being compressed against the uterine wall.

Syndromes: Group of anomalies that can be traced to a common origin, e.g. Down's syndrome, fetal alcohol syndrome

Associations: Patterns of anomalies that occur together more frequently than expected by chance but are

not identified as syndromes, e.g. VACTERL, (*Verte-bral* anomalies, *A*nal atresia, *C*ardiac anomalies, *T*racheo-*e*sophageal fistula, *R*enal anomalies, *L*imb anomalies).

Embryogenesis

The embryology can help in understanding the evolution and configuration of many congenital anomalies. During the first 14 days post conception the development and implantation of the bilaminar germ disc occurs. This begins the process of gastrulation and invagination, transforming it, by the end of the third week, into a trilaminar disc consisting of ectoderm, mesoderm and endoderm. It is from these three layers that all the body structures develop (Table 10.2). At this stage, any dysmorphogenetic events may disrupt more than one of the essential events of blastogenesis, such as fusion, lateralization, decussation or segmentation. For example, the VACTERL association is from a field defect of embryonic mesoderm.

The major organ systems develop during the 4th to 8th weeks from secondary developmental fields as the trilaminar disc folds both cephalocaudally (as a result of the rapid growth of the neural tube) and laterally (as a result of the developing somites).

Primary defects of organogenesis

CNS development

The neural plate develops from the ectoderm in the 3rd week. It folds laterally, forming the neural tube (see Fig. 28.1). Neural tube fusion begins in the cervical region and is complete by the end of the 4th week. The cranial end develops three distinct dilations, which go on to become the forebrain, midbrain and hindbrain. Failure of the neural tube to close cranially results in anencephaly, failure to close in the caudal region is known as spina bifida. The length and position of the defect determines its severity. Failure of skull ossification results in meningoencephalocele. The occipital region is most frequently affected.

Development of the rudimentary brain structures continues until the 8th week. They undergo further growth and elaboration throughout the fetal period. This long developmental duration increases the time frame during which the developing CNS is at risk of teratogenicity.

Neuronal proliferation begins on day 42 and is complete by 20 weeks. Neuronal migration and the establishment of the major fibre pathways is complete by term (Fig. 10.7). Primary sulci appear in an ordered manner from the 8th week through to the 26th week, secondary sulci develop in weeks 30–35. Defects of neuronal migration result in significant neurodevelopmental sequelae. Lissencephaly, a disorder of neuronal migration, disrupts the normal pattern of sulci and gyri and results in severe developmental delay.

These conditions are considered in detail in Chapter 28, Neurology.

Gastrointesinal tract

Rapid growth of the ectoderm and mesoderm folds the endodermal layer. As it folds, part of the yolk sac is incorporated into the body cavity forming the basis of the gastrointestinal tract. The ends of the tract are covered by membranes, which rupture forming the mouth and anus.

In the 4th week, the foregut develops respiratory, hepatic and pancreatic buds. Failure of the respiratory bud to separate from the foregut by development of the oesophagotracheal septum results in tracheo-esophageal fistulae.

Table 10.2 The embryonic layers and their derivatives

Embryonic layer			Organ
Ectoderm			Central nervous system Peripheral nervous system Sensory epithelium (ear/eye) Skin/hair/nails Pituitary, mammary, sweat glands
Mesoderm	Somites	Sclerotome Dermatome Myotome	Skeleton Dermis Muscle
	Intermediate Visceral Parietal Blood vessels		Urogenital system Gastrointestinal/cardiac muscle Body wall
Endoderm			Gastrointestinal tract Respiratory Endocardium
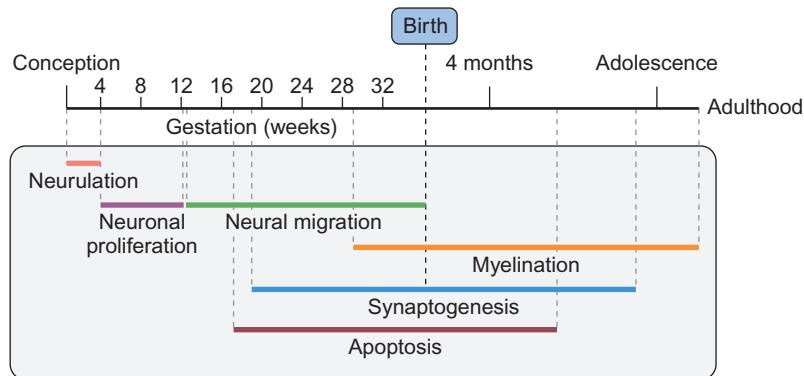
Fig. 10.7 Timeline of major events in brain development. *(From Tau GZ, Peterson BS. Normal development of brain circuits. Neuropsychopharmacology 2010;35(1):147–68, with permission.)*

As the mid-gut undergoes rapid growth it herniates into the extraembryonic coelom (6th week). The loops rotate as they retract and the normal embryonic return of the intestine to the abdominal cavity occurs at 10 weeks of gestation. Failure to retract produces exomphalos. Failure of the mid-gut to rotate adequately on return to the body cavity leads to malrotation with a shortened mesenteric pedicle with a risk of later volvulus. Gastroschisis occurs later, after 10 weeks gestation, when bowel herniates through an anterior abdominal wall defect. This is described in detail in Chapter 14, Gastroenterology.

The hindgut combines with the surface ectoderm at its distal end forming the urogenital sinus. This separates into the urogenital system and rectum in the 7th week. Failure of this separation results in rectal fistula. The anal membrane ruptures in the 9th week. Failure results in rectal atresia or imperforate anus (Fig. 10.8).

Head and neck

The head and neck develop from the frontonasal prominence and six pharyngeal arches, separated by five pharyngeal clefts. The first arch divides into the maxillary and mandibular prominences bilaterally and fuses with the frontonasal prominence to form the mandible, upper lip, palate and nose (Fig. 10.9). Failure of the pharyngeal arches to develop correctly gives rise to lateral cysts and fissures, thyroglossal cysts and sinuses. Failure of the facial prominences to fuse correctly results in a variety of clefts of the lip and palate. Cleft lip is due to the failure of fusion of the maxillary and medial nasal processes (formation of the primary palate). Cleft palate occurs when the two plates of the skull that form the hard palate are not completely joined. The uvula in a cleft palate is usually split.

Teratogens

Question 10.3

Maternal drugs

The following is a list (A–J) of drugs that could be taken during pregnancy:

A. Alcohol
B. Diethylstilbestro
C. Lithium
D. Phenytoin
E. Progesterone
F. Sodium valproate
G. Streptomycin
H. Tetracycline
I. Thalidomide
J. Warfarin

Select the most likely maternal medication responsible for each of the adverse effects described below. Each answer may be used once, more than once or not at all:

1. A child with enamel hypoplasia and discolouring of the teeth
2. Babies with short or missing limbs
3. An infant with Ebstein anomaly

Answer 10.3

1. H. Tetracycline
2. I. Thalidomide
3. C. Lithium
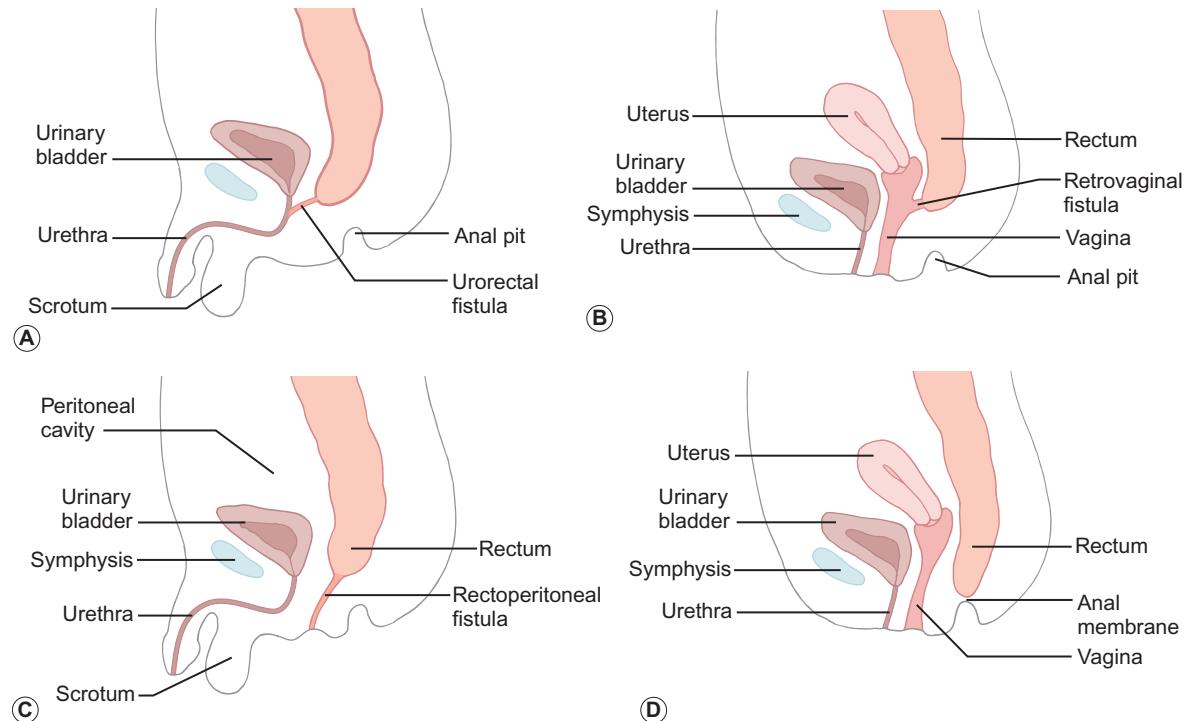
Fig. 10.8 A. Urorectal fistula with rectal atresia. B. Rectovaginal fistula with anal atresia. C. Rectal atresia. D. Imperforate anus.
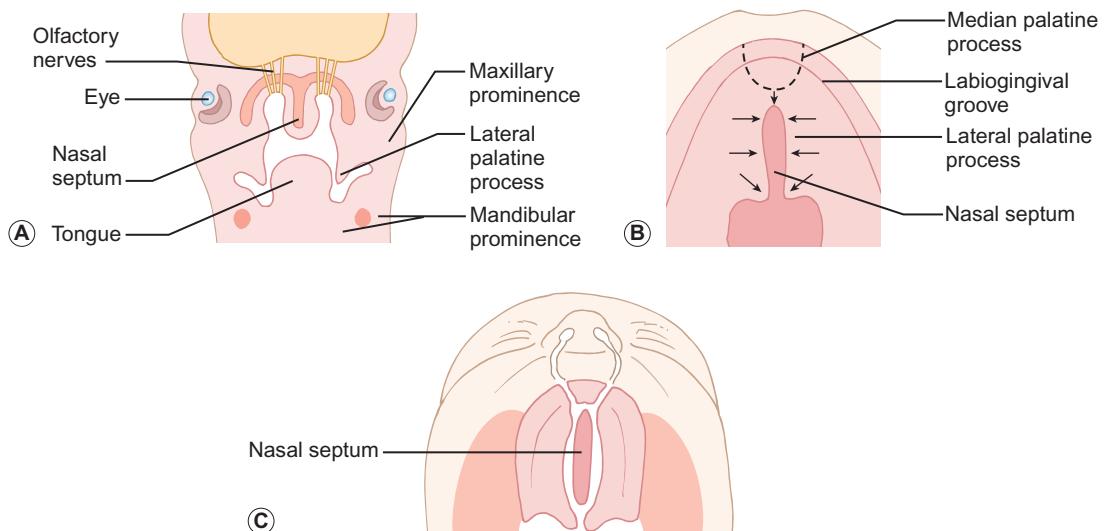
Fig. 10.9 Cleft lip and palate. A. Frontal section of the head showing fusion of the lateral palatine processes with each other and the nasal septum. B. The roof of the mouth at 8 weeks showing palatal development. The dotted line shows the fusion of the palatine processes. The arrows indicate direction of growth. C. Complete bilateral cleft of the lip and the alveolar processes of the maxilla and complete bilateral cleft of the anterior and posterior palate.

Teratogens produce disruption of embryogenesis by either deformity or malformation. They include chemical, physical and infectious agents. The pattern of the ensuing anomaly depends on the timing and magnitude of the exposure, maternal metabolism, placental transfer and the genetic susceptibility of the embryo (Fig. 10.10).

Teratogenic *chemical agents* include drugs, hormones, alcohol and environmental chemicals such as organic mercury, which can cause neurological damage resembling cerebral palsy. *Physical agents* include exposure to high levels of ionizing radiation in pregnancy, which produces major teratogenic effects, such as microcephaly, spina bifida, cleft palate and limb

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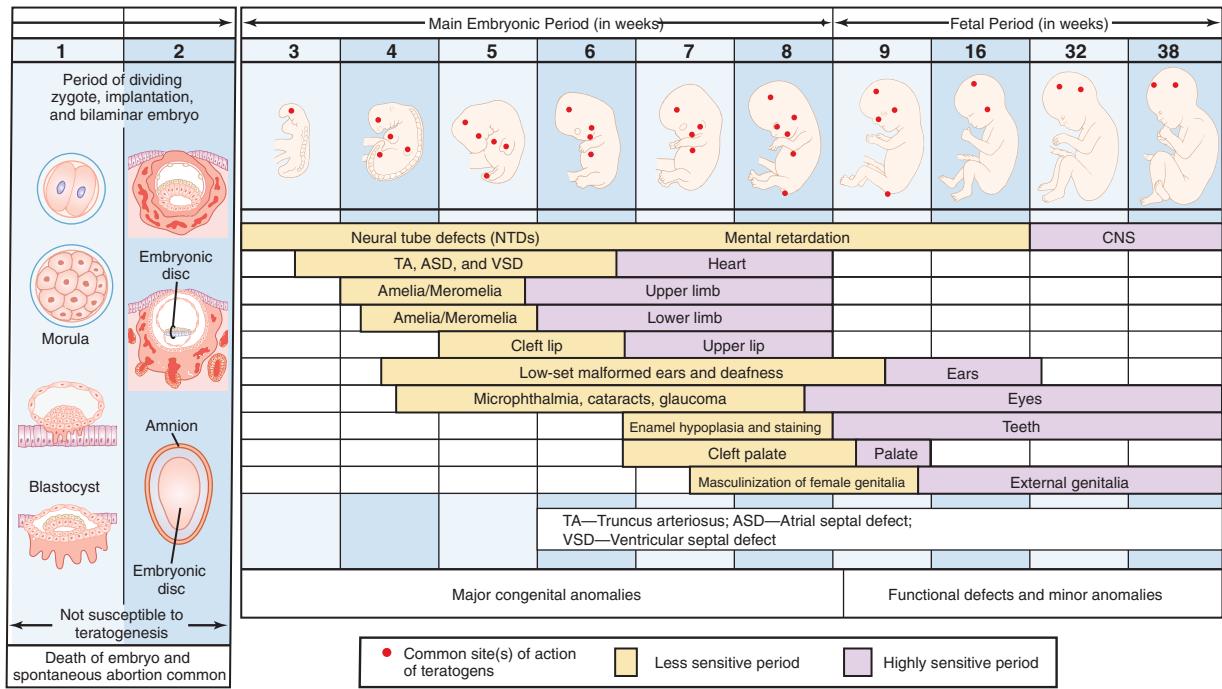
Fig. 10.10 Periods of sensitivity to teratogenic exposure. *(From Moore KL, Persaud TVN, Torchia MG. Before we are born, 8th edition, Saunders 2013, with permission.)*

Table 10.3 Maternal drugs which may affect the fetus

Type of pharmacological agent	Drug	Effect
Hormones	Progesterone Diethylstilbestrol	VACTERL Vaginal or clear cell carcinoma
Anti-psychotic	Lithium Thalidomide	Ebstein anomaly Short limbs (phocomelia), absent auricles, deafness
Anticonvulsants	Sodium valproate/ phenytoin/carbamazepine	Fetal valproate/hydantoin/carbamazepine syndrome: craniofacial, cardiac and limb defects, developmental delay
Antimicrobial	Tetracycline Streptomycin	Tooth enamel hypoplasia, yellow staining of teeth Sensorineural deafness
Anticoagulant	Warfarin	Fetal warfarin syndrome: nasal hypoplasia, microcephaly, optic atrophy, hydrocephalus, congenital heart defects, stippled epiphyses, purpuric rash
Antithyroid	Iodine, propylthiouracil	Goitre, hypothyroidism
Vitamin A analogues	Isotretinoin	Craniofacial anomalies, conotruncal cardiac defects
Folic acid inhibitors	Methotrexate	Microcephaly, neural tube defects, short limbs

defects. Carcinogenic effects and mutagenic effects (changes to DNA which can be passed to future generations) are also described.

Infectious agents include congenital infections.

Maternal drugs affecting the fetus

Drugs act by either interfering directly with embryogenesis or by exerting their pharmacological actions on developing fetal organs. Table 10.3 lists some of the more common teratogenic drugs. Adverse effects of medicines are difficult to recognize unless they produce recognizable patterns of malformation. Even when malformations are marked, as occurred with thalidomide, there may be considerable delay before it is recognized and the drug is withdrawn. Presentation may also be delayed, e.g. diethylstilbestrol was prescribed for over 30 years for threatened miscarriage before the association with clear cell adenocarcinoma of the vagina and cervix in female adolescent and adult offspring was recognized. Mothers should avoid taking medication, whether prescribed or over-the-counter, whenever possible.

Alcohol

Alcoholism affects 1–2% of women of child-bearing age. Alcohol and its acetaldehyde metabolite impair embryogenesis by disrupting cellular differentiation and growth, inhibiting cell migration and disrupting DNA synthesis. This produces a constellation of features known as fetal alcohol spectrum disorder (FASD) (Table 10.4, Fig. 10.11). It is detected in 1 to 2 per 1000 live births and is a cause of learning difficulties. The effect of low or moderate alcohol ingestion or occasional binge drinking is unknown, so it is recommended that pregnant women avoid alcohol completely (Department of Health in the UK).

Maternal substance misuse

The neonatal abstinence syndrome (NAS) is most commonly associated with chronic narcotic misuse,

Table 10.4 Features of fetal alcohol syndrome

Neurological	Microcephaly
	Abnormalities of corpus callosum, cerebellar vermis, dentate gyrus
	Cognitive impairment and developmental delay
Craniofacial	Short palpebral fissures
	Smooth philtrum
	Maxilla hypoplasia
	Cleft palate
	Micrognathia
Cardiac	VSD
Limb	Joint abnormalities

Fig. 10.11 Baby with fetal alcohol syndrome. *(From Leifer G. Introduction to maternity and pediatric nursing, Saunders 2011, with permission.)*

but it may also be seen with many other classes of drugs including non-narcotic sedatives, stimulants, anti-depressants, anti-epileptics and neuroleptics.

Narcotic misuse

Chronic narcotic misuse stimulates the opiate receptors in the locus ceruleus of the fetal brainstem. Acclimatization occurs and when this is suddenly removed after birth, increased adrenergic activity of the locus ceruleus causes 'withdrawal' symptoms. The situation is more complicated with multiple drug use. Opiate replacement therapy (ORT) with methadone is recommended, as it provides clinical improvement, better control of drug use and less crime. There is an increased risk of hepatitis B and C and HIV in intravenous drug users. Onset of withdrawal is usually within 48 hours of birth, but can be delayed for up to two weeks. The features of withdrawal are listed in Table 10.5. They are best monitored by recording them regularly using a standardized scoring system. Irritable or restless behaviour may continue for a number of months after birth.

Management

Mild withdrawal symptoms can be managed conservatively by swaddling, frequent feeds and decreased sensory stimulation. First-line treatment is usually oral morphine, which is titrated against clinical features. Seizures are treated with intravenous morphine or anti-convulsants. Hepatitis B immunization is usually recommended. Follow-up by the multidisciplinary team is often indicated. Breastfeeding is usually encouraged for mothers on opiate replacement therapy as the concentration of methadone in breast milk is low.

Cocaine
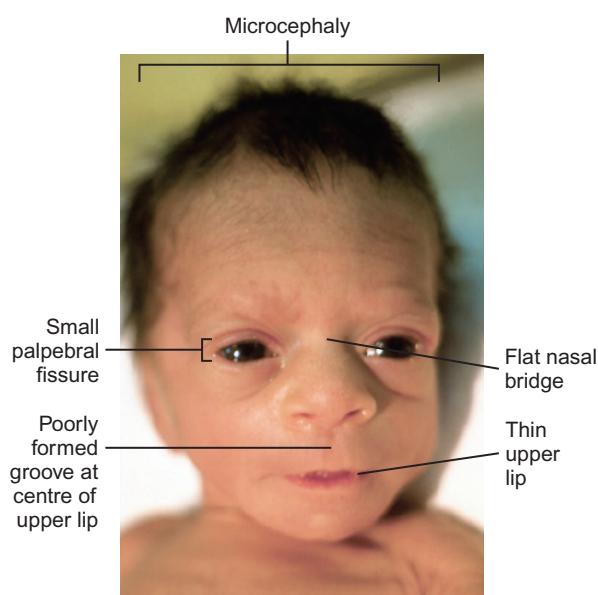
Cocaine is a potent vasoconstrictor affecting both the uteroplacental bed and fetal vasculature. It is associated with increased risk of miscarriage, abruption and premature birth. Cerebral artery infarction is described, most likely in the second and third trimesters.

Neonatal symptoms occur early. Breastfeeding should be avoided if the mother continues to use cocaine, as it may be transferred in breast milk.

Table 10.5 Features of opiate withdrawal

Central nervous system	Gastrointestinal	Autonomic symptoms
Irritability and high-pitched cry	Poor feeding	Sweating
Hyperactivity with reduced periods of sleep	Vomiting	Fever
Tremors	Diarrhoea	Yawning
Increased tone		Sneezing
Seizures (rare)		

Maternal diseases

Maternal diabetes mellitus

Maternal insulin-dependent diabetes (type 1) is associated with increased perinatal morbidity and mortality, which can be markedly reduced by good blood glucose control from preconception.

The fetal problems are:

- Congenital malformations – risk increased to four times normal, particularly cardiac malformations and caudal regression syndrome (sacral agenesis)
- Sudden intrauterine death – in third trimester
- Macrosomia (LGA >90th centile) – secondary to maternal hyperglycaemia. Glucose crosses the placenta and results in fetal hyperinsulinaemia, which promotes growth. Up to 25% of infants of diabetic mothers have a birthweight >4 kg, compared with 8% of infants of non-diabetic mothers. Predisposes to cephalo-pelvic disproportion causing obstructed labour, shoulder dystocia and birth trauma.
- Intrauterine growth restriction – threefold increased risk; associated with maternal microvascular disease
- Preterm labour – in 10%, either spontaneous or induced; induction of labour is usually planned for 38 weeks' gestation

Neonatal problems are:

- Hypoglycaemia – common in the first 48 hours after birth due to residual hyperinsulinism. Often accompanied by hypocalcaemia and hypomagnesaemia.
- Hyperbilirubinaemia – exacerbated by polycythaemia
- Respiratory distress syndrome – from delayed maturation of surfactant
- Hypertrophic cardiomyopathy – uncommon, from fetal hyperinsulinism, may cause transient outflow tract obstruction
- Polycythaemia – from chronic fetal hypoxia. Increases the risk of stroke, seizures, necrotizing enterocolitis and renal vein thrombosis.

Maternal red blood cell alloimmunization

Maternal antibody is formed to fetal red blood cell antigens such as rhesus D, anti-Kell and anti-c.

Rhesus haemolytic disease

This was a major cause of fetal and neonatal morbidity and mortality (see Chapter 23, Haematology, for further details). It is now uncommon, since the introduction of anti-D prophylaxis. Haemolytic disease is now mostly due to anti-Kell and anti-c.

Case history

A 29-year-old mother is having her 3rd child. She is found to have anti-Kell antibodies on her initial routine blood screening.

How has she developed her isoimmunization?
The mother is Kell negative but the fetus is Kell positive. A few Kell positive fetal red cells enter the maternal circulation and antibodies are formed. Although this usually occurs at delivery, it may be during a miscarriage or placental abruption or sometimes during normal pregnancies. At a subsequent pregnancy, maternal anti-Kell antibodies cross the placenta and cause haemolysis of fetal red cells.

Maternal immune mediated disease

IgG antibodies are small molecules and can cross the placenta. This transfer of maternal IgG confers passive immunity to the infant but where the maternal IgG is part of a disease state then transplacental passage may result in damage to the fetal tissues or cause transient disease in the infant.

Maternal hyperthyroidism (Graves' disease)

If mother is on treatment, fetus and infants are usually unaffected. Transient neonatal thyrotoxicosis may occur from transplacental transfer of TSH receptor antibodies (TRAbs), causing tachycardia in the fetus and features of neonatal hyperthyroidism requiring treatment for several months. Transient hypothyroidism may result from maternal anti-thyroid drug therapy.

Maternal hypothyroidism

Neonatal problems are rare in mothers treated with thyroxine. Globally, this is an important cause of congenital hypothyroidism secondary to maternal iodine deficiency.

Maternal autoimmune thrombocytopenia (AITP)

Antiplatelet IgG autoantibodies in maternal thrombocytopenia can cross the placenta causing fetal thrombocytopenia. This rarely requires treatment, but if severe may cause cerebral haemorrhage before birth or from birth trauma. Intrauterine intravenous platelet transfusions may be required. In the neonate with

severe thrombocytopenia or petechiae at birth, intravenous immunoglobulin should be given. Because of antiplatelet antibodies, platelet transfusions are only given for extremely low platelet counts or active bleeding.

Maternal systemic lupus erythematosus

Vasculopathy associated with maternal systemic lupus erythematosus (SLE) increases the risk of recurrent miscarriage. Mothers with SLE have a 0.5–2% chance of having a baby affected by congenital heart block due to the presence of anti-Ro and anti-La autoantibodies. These may permanently damage the conduction system in the fetal heart necessitating pacemaker insertion.

Transient neonatal myaesthenia

Maternal acetylcholine receptor (AChR) IgG antibodies can cross the placenta causing transient hypotonia after delivery. This manifests as problems with feeding and occasionally respiration. Administration of anticholinesterase (neostigmine) leads to rapid improvement and is diagnostic. Recovery usually occurs within two months as the circulating antibodies wane.

Perinatal alloimmune thrombocytopenia

Fetal platelets contain an antigen (usually HPA-1a or 5b) which the mother lacks. The mother develops antibodies which cross the placenta and bind to fetal platelets. It is analogous to Rhesus D alloimmunization, but

often affects the first pregnancy and maternal antiplatelet antibody titres are not predictive of the severity of the fetal thrombocytopenia. If it is identified from a previously affected infant, it can be treated with repeated intrauterine infusions of IVIG (intravenous immunoglobulin) and platelets if necessary. Severe thrombocytopenia after birth is treated with platelet transfusions negative for the platelet antigen (HPA-1a, 5b).

Congenital infections

Congenital infection refers to infection acquired by the fetus transplacentally. Its consequences depend on the nature of the infection and the gestation when it is acquired. For example, the risk of serious congenital defects following rubella infection is greatest in the first trimester and as it interferes with early embryogenesis it causes heart defects, cataracts and deafness. The fetus may also become infected from ascending infection or direct contact with infected secretions during delivery (see Chapter 11, Neonatal medicine).

Congenital cytomegalovirus (CMV) infection

This is the commonest congenital infection (0.5–1 per 1000 live births), with 1–2% of mothers seroconverting during pregnancy and a mother-to-infant transmission rate of about 40%. The risk to the infant is much lower with reactivation than primary disease. About 5–10% are severely affected (Table 10.6),

Table 10.6 The features of congenital infection with Toxoplasma, CMV and Rubella

	Rubella	CMV	Toxoplasma
Eyes	Glaucoma Cataracts Chorioretinitis Microphthalmia	Chorioretinitis	Chorioretinitis Microphthalmia Cataracts
CNS	Microcephaly	Calcification, periventricular Microcephaly	Learning difficulties Microcephaly Calcification, peripheral Hydrocephalus Hypotonia Seizures
Congenital cardiac defects	Patent ductus arteriosus Pulmonary artery stenosis	–	–
Sensorineural deafness	++	++	–
Hepatosplenomegaly	+	+	+
Pneumonitis	+	++	+
Bones	Viral osteodystrophy	Viral osteodystrophy	Epiphyseal plate anomaly
Rash	+	+	+
IUGR	++	+	+

but 80–90% are asymptomatic. However, 10–15% of the asymptomatic infants develop sensorineural deafness, which is important to diagnose, as treatment with oral valganciclovir has been shown to reduce the severity of hearing loss. Diagnosis is with viral DNA (by PCR amplification) from amniotic fluid, fetal blood, or infant's blood, urine, cerebrospinal fluid (CSF) or saliva collected at less than three weeks of age.

The infant will continue to excrete CMV in the urine for several months.

Congenital toxoplasmosis

This is uncommon in the UK. It is usually from primary maternal infection. The earlier in pregnancy infection occurs, the more severe the fetal abnormalities (see Table 10.6). However, the transmission rate is higher during the second trimester, but is usually subclinical, presenting later in childhood with chorioretinitis or with seizures or learning problems.

Rubella

This is very rare as it is prevented by maternal vaccination. Clinical features are shown in Table 10.6.

Congenital syphilis

This is rare, as mothers are routinely screened. Antibiotic treatment given more than four weeks before delivery prevents congenital infection. Primary infection in pregnancy has a very high transmission rate and high risk of miscarriage or stillbirth. Clinical features are similar to those in Table 10.6, but those specific to congenital syphilis are a rash and desquamation of the soles of the feet and hands and metaphyseal bone lesions in infancy.

Varicella zoster virus (VZV) infection

It is uncommon for mothers to develop chickenpox as most are immune. Intrauterine infection is rare, but may cause congenital varicella fetopathy, including marked scarring of the skin. The main risk is from maternal viraemia shortly before birth, as the infant will not have received protection from transfer of maternal antibodies.

Parvovirus B19

Usually the fetus is unaffected, but it may cause severe fetal anaemia causing fetal hydrops (oedema and ascites). Anaemia in the fetus is monitored by middle cerebral artery velocity waveform on Doppler ultrasound and treating with intrauterine transfusion, if necessary.

Fetal circulation

Question 10.4

Fetal circulation

Below is a list (A–J) of the components of the fetal circulation:

A. Ductus arteriosus
B. Ductus venosus
C. Iliac artery
D. Inferior vena cava
E. Placenta
F. Pulmonary bed
G. Systemic bed
H. Superior vena cava
I. Umbilical arteries
J. Umbilical vein

Select ONE item from the list that is most accurately described by each of the terms below. Each answer can be used once, more than once or not at all:

1. The part of the fetal circulation with the lowest vascular resistance.
2. The part of the fetal circulation with the highest oxygenation.
3. The part of the fetal circulation with the highest vascular resistance.

Answer 10.4

1. E. Placenta
2. J. Umbilical vein
3. I. Umbilical arteries

In the fetal circulation, oxygenated fetal blood is carried in the single umbilical vein, which bypasses the liver via the ductus venosus to reach the inferior vena cava. This oxygenated blood then enters the right atrium as a 'jet', which is shunted to the left atrium via the foramen ovale (Fig. 10.12). From here it passes into the left ventricle and aorta, thus feeding the coronary arteries and cerebral vessels. In this way, the fetal heart and brain receive the most oxygenated blood. Some of the deoxygenated blood is pumped by the right ventricle into the pulmonary artery, but the majority bypasses the lungs via the ductus arteriosus to flow into the aorta where it is carried back to the placenta via the two umbilical arteries. Only 7% of the combined ventricular output of blood passes into the lungs. The right ventricle is the dominant ventricle, ejecting 66% of the combined ventricular output.

Schematic diagram of fetal circulation

Head and forelimbs

Superior vena cava

Aorta

Lungs

PA

Ductus arteriosus

RA   FO   LA   Lungs

Caudal vena cava

Abdominal aorta

RV   LV

Ductus venosus

Liver

Rest of body

Umbilical vein

Umbilical artery

Placenta

■ Highly oxygenated blood   ■ Mixed blood   ■ Poorly oxygenated blood

FO - Foramen ovale	RV - Right ventricle
LV - Left ventricle	RA - Right atrium
LA - Left atrium	PA - Pulmonary artery

Fig. 10.12 Schematic diagram of fetal circulation, with red indicating the highest level of oxygen saturation, blue the lowest, and purple an intermediate level. *(From Dorland's Medical Dictionary for Health Consumers. © 2007 by Saunders, an imprint of Elsevier, Inc.)*

Although fetal pO_2 is usually in the range of 2–4 kPa, the fetus is able to metabolize aerobically (is not hypoxic) due to adequate delivery of oxygen to the peripheral tissues. This is due to a combination of the layout of the circulatory system, the high levels of fetal haemoglobin, high perfusion rates of the organs (higher than in the adult) and decreased oxygen requirement.

Role of fetal haemoglobin

The fetus has a higher percentage of haemoglobin F (75%) and high haemoglobin concentration (18 g/dl). HbF has a lower affinity for 2,3 diphosphoglycerate (2,3 DPG). This allows increased binding of oxygen with greater affinity and better oxygen extraction in the placenta, which compensates for the relatively lower oxygen tension of the maternal blood supplying the chorion. Notably, the P50 value for fetal haemoglobin (i.e. the partial pressure of oxygen at which the protein is 50% saturated; lower values indicate greater affinity) is roughly 2.4 kPa, whereas adult haemoglobin has a value of approximately 3.5 kPa. As a

Question 10.5

Clamping of the umbilical cord

A term infant is born after spontaneous vaginal delivery. The baby cries as soon as he is delivered. His breathing and tone are normal. What is the best practice for clamping of the umbilical cord? From the following list of options, select the ONE best answer.

The cord should be clamped:

A. After at least one minute and baby transferred to the resuscitation table for observation

B. After at least one minute, baby dried and skin-to-skin with mother initiated

C. After more than 5 minutes, baby dried and skin-to-skin with mother initiated

D. Immediately and baby transferred to the resuscitation table for observation and drying

E. Within a minute and baby dried and skin-to-skin with mother initiated

result, the 'oxygen saturation curve', which plots percent saturation *vs* pO_2, is left-shifted for fetal haemoglobin in comparison to the same curve in adult haemoglobin (see also Fig. 17.5).

Clamping of the umbilical cord

For uncompromised babies, a delay in cord clamping of 1–3 minutes from the complete delivery of the infant, or until the cord stops pulsating, is now recommended as part of active management of the third stage of labour (NLS, UK Resuscitation Council; NICE guideline CG190, Dec 2014). As yet, there is insufficient evidence to recommend an appropriate time for clamping the cord in babies who require resuscitation, which is the priority. There is no additional benefit of delaying cord clamping beyond 5 minutes.

One of the main advantages of delayed cord clamping is that the neonate continues to receive oxygen via the placenta for as long as the cord is pulsating. This may be particularly advantageous if there was fetal hypoxia during labour. Haemoglobin is increased immediately after delivery from the transfusion of placental blood. However, there is no significant difference in the haemoglobin at 2–6 months of age, although iron stores are increased. There is an increased risk of neonatal jaundice but not in polycythaemia requiring treatment. Timing of the cord clamping does not affect maternal outcomes in terms of postpartum haemorrhage or maternal mortality, nor does it improve neonatal mortality. Only one trial has looked at long-term neurodevelopmental outcomes and no difference was found.

In preterm infants, delayed cord clamping is associated with a reduction in blood transfusions, lower incidence of intraventricular haemorrhage (IVH) and of necrotizing enterocolitis. However, the peak bilirubin concentration is increased. There is no significant difference in severe intraventricular haemorrhage (grade 3, 4), periventricular leukomalacia, mortality or neurodevelopmental outcomes (Cochrane reviews 2012).

Transitional changes after birth

At birth, the circulation through the placenta ceases and the infant's lungs inflate. The three shunts that permitted blood to bypass the liver and lungs are no longer necessary and cease to function. Some of these changes occur with the first breath, whereas others may take place over hours and days. Initially, there are functional changes, which are followed by definitive anatomical changes.

Features of the changes from fetal to extrauterine life are:

- Removal of the placenta increases systemic vascular resistance, and cessation of blood flow in the umbilical vein results in closure of the ductus venosus. All blood entering the liver now passes through the hepatic sinusoids. The ductus venosus becomes the ligamentum venosum, which passes through the liver from the left branch of the portal vein to the IVC to which it is attached.
- Lung expansion and aeration causes an increase in alveolar oxygen tension, which causes a rapid fall in the pulmonary vascular resistance due to the vasodilatory effect of oxygen on the pulmonary vasculature. Because of the increased pulmonary blood flow, together with removal of the placenta decreasing right atrial return and increasing systemic vascular resistance, the pressure in the left atrium is now higher than that in the right and the foramen ovale functionally closes. Anatomical closure occurs by 3 months of age, when the valve fuses with the septum primum and the interatrial septum becomes a complete partition between the atria. An oval depression remains in the lower part of the interatrial septum of the right atrium, the fossa ovale.
- Between 6 and 8 weeks after birth there is a second, slower fall in the pulmonary vascular resistance and pulmonary artery pressure, associated with the thinning of the pulmonary arterioles.
- The ductus arteriosus closes due to increase in prostaglandin E_2 (PGE_2) metabolism, arterial oxygen concentration (PaO_2), bradykinin and other vasoactive substances secondary to increased oxygen content of aortic blood. Functional closure in term newborns occurs in 50% by 24 hours, 75% by 48 hours and close to 100% by 96 hours. Anatomical closure normally occurs by 3 months of age.
- Delay in closure of the arterial duct can occur in preterm infants (persistent ductus arteriosus, PDA; see Chapter 11, Neonatal medicine) or can be induced in duct-dependent congenital heart disease by infusing prostaglandin E_2.
- If there is either perinatal asphyxia or neonatal hypothermia, sepsis or meconium aspiration, the

pulmonary vascular resistance may not fall as usual with the infant's first breaths. This 'persistent pulmonary hypertension of the newborn' (PPHN) means that the fetal pattern of right to left shunting across the foramen ovale and ductus arteriosus persists, which in turn leads to intrapulmonary shunting and further hypoxia and acidosis.

Effect of perinatal hypoxia on the infant

During labour, as uterine contractions strengthen, there are periods of decreased placental perfusion, which temporarily impairs gas exchange. Subsequent uterine relaxation allows the fetus to recover, at least partly. During normal labour, there is a gradual decrease in fetal pO_2 and increase in pCO_2 (and a gradual increase in base deficit).

Respiratory adaptation to extrauterine life is influenced by an infant's mode of delivery. Caesarean delivery is associated with retained fetal lung fluid and relatively impaired lung function during the first hours of life. One explanation for this is the absence of mechanical pressure on the thorax to squeeze lung fluid from the respiratory tract experienced by infants delivered vaginally. However, animal studies and improved understanding of the pathophysiology of respiratory disorders in neonates has shown that clearance of fetal lung fluid is largely dependent on reabsorption of alveolar fluid via sodium channels in the lung epithelium. This mechanism is thought to be influenced by the level of circulating catecholamines in the newborn. Newborns delivered by caesarean section have lower concentrations of circulating catecholamines, particularly following delivery without prior labour, and this is thought to explain the delay in early fetal lung fluid clearance.

At birth, the neonate must undergo a remarkable panoply of changes in a short period to survive independently of the placenta. The baby must breathe and rapidly establish a functional residual capacity (FRC) to act as a gas reservoir and allow gas exchange to continue between breaths. The circulation must adapt so that the lungs, which were preferentially not perfused, must now be perfused sufficiently to allow adequate gas exchange and tissue oxygen delivery. Also the baby must clear lung fluid (about 100 mL in a term baby) quickly to allow the establishment of functional residual capacity. For the few days before onset of spontaneous labour, alveolar fluid production (and hence lung fluid volume) decrease markedly.

The majority of the lung fluid is absorbed within the first few breaths, it is believed by generating positive end expiratory pressure (PEEP) by exhaling against a partially closed glottis (usually crying). This leads to the development of FRC, distribution of gas throughout the lungs and then to the release of surfactant, due to lung stretching, which lowers alveolar surface tension.

The physiology of neonatal hypoxia

Babies have been 'resuscitated' at birth by a variety of means, many of which we would now find either bizarre and/or downright dangerous. Due to pioneering research on laboratory mammals by physiologists Geoffrey Dawes and Kenneth Cross in the UK, we now have a much better understanding of what happens during acute asphyxia around the time of birth and this knowledge has guided change in the way resuscitation is performed.

Figure 10.13 shows data derived from experiments showing the response of fetal mammals to total acute hypoxia. The gravid uterus was opened and a bag of normal saline placed over the fetus's head to prevent lung aeration. The umbilical cord was then totally obstructed.

Following acute, severe asphyxia, the breathing movements become more rapid and deeper, and there is a corresponding rise in the heart rate. The pO_2 falls rapidly from its already low levels to virtually zero. After a few minutes breathing ceases, the period of 'primary apnoea'. The heart rate falls markedly, but is maintained, at a lower rate, probably due to a combination of vagal nerve stimulation and the onset of less efficient myocardial anaerobic respiration enabled by glycogen stores within the heart. Cardiac output and systemic blood pressure are partially maintained by increased stroke volume and a rise in systemic vascular resistance from peripheral vasoconstriction, with a degree of protection of blood supply to essential organs such as the brain and heart. After several minutes, the primitive spinal centres, released from the inhibition of the respiratory centres, start to produce whole body gasps at a rate of 10–12/minute. Cardiac output is maintained, but eventually the gasping stops due to increasing acidosis. The acidosis is due to a combination of increasing pCO_2 and metabolic acids from anaerobic respiration in the tissues. Whilst the fetus has some buffering capacity (which can overcome the mildly asphyxial process of normal labour), this is soon overwhelmed. Eventually, the acidosis leads to changes in synaptic function and the gasping stops. The baby enters a further, final period of apnoea, known as secondary apnoea (also called 'terminal apnoea'). In humans, the whole process is thought to take up to 20 minutes. Recovery at this stage requires resuscitation with lung expansion.
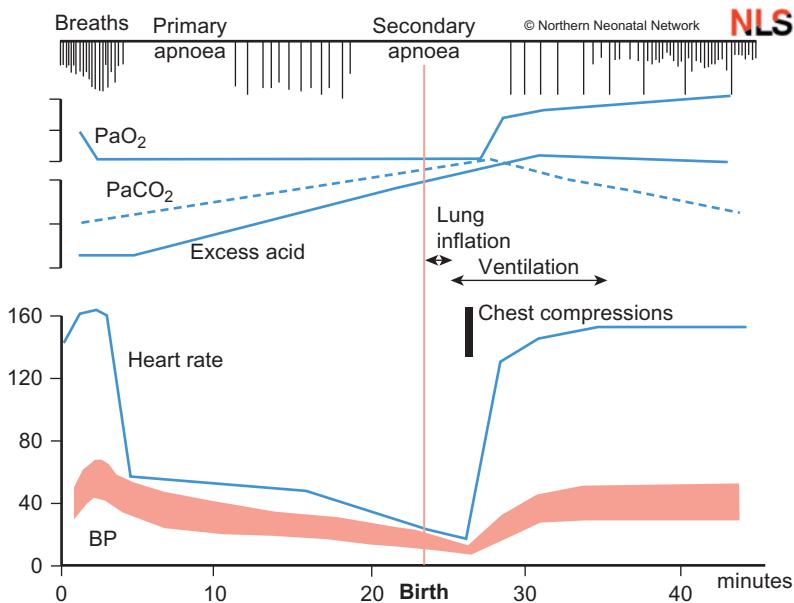
Fig. 10.13 Diagrammatic representation of changes in breathing, heart rate, blood pressure and blood gases following acute, severe asphyxia in mammals before birth and following resuscitation. *(From Northern Neonatal Network, Neonatal life support manual, with permission. <http://www.nornet.org.uk>)*

Chronic in-utero partial asphyxia

In clinical practice, episodes of acute total asphyxia are rare, occurring only after emergency events such as placental abruption, ruptured uterus, cord compression from shoulder dystocia or cord prolapse. Much more common is the gradual development of fetal hypoxia and acidaemia *in utero*. Some fetuses will survive and make a full recovery. Others have limited energy stores before labour commences, as in intra-uterine growth restriction, and will not only be less able to tolerate the mild asphyxia of normal labour, but will certainly not tolerate a more severe acute hypoxic event. Some babies will survive, but will have already sustained significant neurological damage before the onset of labour. Such babies can appear to be fine at birth, as they may have made a full biochemical recovery. A major aim of modern obstetric practice is the prevention of hypoxic–ischaemic encephalopathy, where the infant has depressed breathing at birth and subsequently develops encephalopathy and multi-organ failure and may subsequently die or develop neurodevelopmental impairment. Fetal scalp pH monitoring is widely used during labour to identify significant acidaemia and expedite delivery before damage has occurred.

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Mithilesh Kumar Lal, Nazakat Merchant, Sunil K Sinha
With contributions by
Shalabh Garg

CHAPTER

Neonatal medicine

11

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Understand the scientific basis of diseases and conditions affecting the newborn, including the consequences of prematurity
- Know about the acquired infections in newborn infants
- Know about the physiology and principles of treatment of jaundice in the neonatal period
- Understand the causes and mechanism and sequelae of brain injury in term infants
- Know about the pathophysiology of respiratory disorders in term newborns and the principles of respiratory support
- Know about the principles of nutrition and fluid and electrolyte management in the neonate

Most newborn infants are healthy or have minor, transient problems which should whenever possible be managed on the postnatal or transitional care wards to avoid separation from their mothers. However, 6–10% of infants are admitted to special care baby units and 1–2% need intensive care. There are 775,000 births per year in the UK, so 7750–15,500 babies require intensive care, with extremely preterm infants needing intensive, high dependency or special care for many weeks.

Perinatal and neonatal care in the UK are now organized in regional networks, with mothers or infants with significant medical problems referred to specialist tertiary centres. The advantages and disadvantages of this arrangement are listed in Box 11.1. There are convincing data that good outcomes require sufficient throughput for staff to establish and maintain expertise in complex conditions. However, large, specialist units do not in themselves guarantee good outcomes; national and international comparisons of outcomes, for example of very-low-birth-weight infants, show marked variations between intensive care units. This highlights the importance of all units collecting and monitoring standardized outcome data and undertaking quality improvement programmes.

The main causes of morbidity and mortality of newborn infants are prematurity, infection, jaundice, respiratory and neurological problems, which will be described in this chapter. Whilst some congenital abnormalities will also be described, most are covered in the system chapters.

The preterm infant

In the UK, 7% of births are preterm. The initial requirements for stabilizing the extremely preterm are listed in Table 11.1. Preterm delivery may be:

- Spontaneous onset of labour with intact membranes (40–45%)
- Following preterm premature rupture of the membranes (PPROM) (25–30%)
- For medical or fetal indications (30–35%).

  Most are idiopathic but causes include:

- Intrauterine stretch – multiple gestation, polyhydramnios, uterine abnormality
- Intrauterine bleeding – abruption, antepartum haemorrhage
- Intrauterine infection – chorioamnionitis, bacterial vaginosis
- PPROM

Advantages

Brings together many specialists working as a team
Allows experience of rare conditions to be
    developed and maintained
Potentially provides better outcomes
Facilitates staff training and research
Minimizes cost by avoiding duplication

Disadvantages

Parents and family have to travel further from
    home
Staff at other centres become de-skilled
Establishes a hierarchy of care
Good communication between all staff is more
    difficult because of geographical separation
Increased transfer of mothers and infants –
    specialist transport needs to be available
Parents may encounter more healthcare
    professionals, with teams at both local and
    tertiary centres

- Fetal causes – IUGR, congenital malformations
- Maternal medical conditions – pre-eclampsia, hypertension, chronic medical conditions
- Cervical weakness

The epidemiological risk factors for preterm birth are poorly understood but include:

- Previous preterm delivery
- Maternal age – risk increased if <20 or >35 years old
- Maternal nutrition – low BMI associated with spontaneous preterm birth, obesity because of increased risk of pre-eclampsia and diabetes mellitus
- Ethnicity – increased in Black mothers (mothers from south-east Asia have increased incidence of low birth weight rather than preterm infants)
- Multiple births – responsible for 15–20% of preterm births
- Maternal infection – localized or generalized
- Maternal stress, socio-economic deprivation
- Maternal smoking, substance misuse.

Management of threatened preterm delivery

Whenever possible, the aim is to deliver the infant at full term whilst ensuring the well-being of both mother and infant. The decision to deliver infants less than 28 weeks' gestation is especially difficult, and should involve the obstetrician, neonatologist and parents after detailed assessment of the risks to mother and infant.

Table 11.1 Initial requirements for stabilizing the extremely preterm

Airway, breathing	Respiratory support with clearing airway, oxygen, CPAP, high flow nasal therapy, mechanical ventilation as required Surfactant for preterm infants with respiratory distress
Circulation	Intravenous fluids to treat shock if required
Monitoring	Oxygen saturation – if preterm, keep at 91–95% (see Box 37.14) Heart rate, blood pressure, respiratory rate and temperature monitoring – peripheral and central Weight Urine output
Temperature control	Plastic bag and hat if extremely preterm at birth, radiant warmer or incubator, humidification
Venous and arterial lines	Peripheral intravenous line: • Required for intravenous fluids, antibiotics, other drugs Umbilical venous catheter: • Sometimes used for immediate intravenous access or giving fluid or medications. Arterial line: • If frequent blood gas analysis, blood tests and continuous blood pressure monitoring required; usually umbilical artery catheter (UAC) Central venous line: • For parenteral nutrition
Investigations	Full blood count, CRP, urea and electrolytes, blood glucose, blood gases Chest X-ray +/– abdominal X-ray if respiratory distress and for position of tracheal tube and central lines
Medication	Antibiotics – usually indicated Analgesia and sedation – as required Vitamin K – routine prophylaxis against haemorrhagic disease of the newborn
Parents	Time needs to be found to explain to parents and immediate relatives what is happening. If the mother cannot be with the baby, e.g. following caesarean section, photos or videos are reassuring.

Management known to improve neonatal outcome includes:

- Antenatal steroids – reduces rate of respiratory distress syndrome, intraventricular haemorrhage and neonatal death (see Box 1.4 for details)
- Magnesium sulphate – shown to reduce the risk of cerebral palsy in infants <32 weeks' gestation. Its mechanism of action is poorly understood.

Following PPROM, there is increased risk of neonatal morbidity and infection. It is associated with ascending maternal infection from the lower genital tract, with one third having positive amniotic cultures. Antibiotics are given to the mother to treat chorioamnionitis and reduce the risk of neonatal infection.

Tocolytics are often used to suppress contractions to allow time for antenatal corticosteroids or maternal transfer to a perinatal centre, but there is no clear evidence that they improve outcome.

Overview of the preterm infant

The preterm infant at 23–25 weeks' gestation differs markedly in size, appearance and development from babies born at later gestations. Typical birth weight at 24 weeks is only 620 g for females, 700 g for males (50th centile). Their skin is red, thin and gelatinous, making them prone to high evaporative heat loss and is easily damaged, making it a potential portal for infection. They adopt an extended posture with unco-ordinated movements, reflecting their early stage of neural development (see Chapter 28, Neurology). Their eyelids may be fused or partially open, with infrequent eye movements, in contrast to the term infant who looks and follows faces. They are unlikely to breathe without respiratory support because of sur-factant deficiency and lung immaturity. They are unable to coordinate sucking and will require nasogas-tric feeding, often augmented by parenteral nutrition; the ability to suck and coordinate swallowing usually only develops at 34–35 weeks. Babies born weighing less than 1.5 kg are at increased risk for a range of complications (Table 11.2).

Table 11.2 Significant short-term complications and supportive therapy of very-low-birth-weight infants (birth weight <1.5 kg)

Condition	Complications and supportive therapy
Respiratory distress syndrome/lung immaturity – 70%	Surfactant therapy – 65% Conventional ventilation – 59% High-frequency ventilation – 26% Nasal CPAP – 73% Inhaled nitric oxide – 5% Air leaks/pneumothorax – 3% Bronchopulmonary dysplasia – 25% (O_2 therapy at 36 weeks)
Infection – 21%	Early-onset – 2% Late-onset – 13%
PDA (patent ductus arteriosus) – 29%	Medical treatment – 21% Surgical ligation – 5%
NEC (necrotizing enterocolitis) – 5%	Surgical treatment – 3%
Intraventricular haemorrhage – 19% PVL (cystic periventricular leukomalacia) – 3%	Severe (Grade III/IV) – 8%
ROP (retinopathy of prematurity)	Severe – 6% Laser treatment – 3%

(Data from Vermont-Oxford Network, 2012.)

Answer 11.1

A. A decrease in pulmonary surfactant, a compliant chest wall and a higher surface tension at the alveolar surface. See below for discussion.

Question 11.1

Respiratory distress syndrome

A baby is born at 25 weeks' gestation following a pregnancy complicated by preterm prolonged rupture of membranes. The child develops signs of respiratory distress syndrome (RDS). Regarding the pathophysiology of respiratory distress syndrome, which one of the following statements best describes the underlying problem. Select ONE answer only?

There is:

A. A decrease in pulmonary surfactant, a compliant chest wall and a higher surface tension at the alveolar surface

B. An absence of functional alveoli accompanied by an increase in the relative proportion of cartilage in the airways, which critically limits pulmonary oxygen exchange

C. An absence of pulmonary surfactant, a stiff chest wall and increased airways resistance

D. An increase in the relative protein content of surfactant which impairs surfactant recycling

E. Homogenous airways collapse with reduced airway resistance

Respiratory distress syndrome

Respiratory distress syndrome (RDS) is the most common lung problem that accompanies prematurity. It may lead to severe respiratory failure and death. It is caused by deficiency of surfactant, which leads to higher surface tension at the alveolar surface, difficulty in achieving adequate functional residual capacity and interferes with the normal exchange of respiratory gases. The incidence and severity of RDS is inversely proportional to gestational age because of the smaller number of functional alveoli with decreasing gesta-tional age. The airways of the preterm infant are also incompletely formed and lack sufficient cartilage to remain patent. This contributes to collapse of lungs and increased airway resistance. The higher surface tension requires greater distending pressure to inflate the alveoli, according to Laplace's law: $P = 2T/r$, where P is the pressure, T is the surface tension and r is radius (Figs 11.1–11.2). The chest wall of the preterm newborn is also more compliant than the lungs, thus tending to collapse when the infant attempts to increase nega-tive intrathoracic pressure.
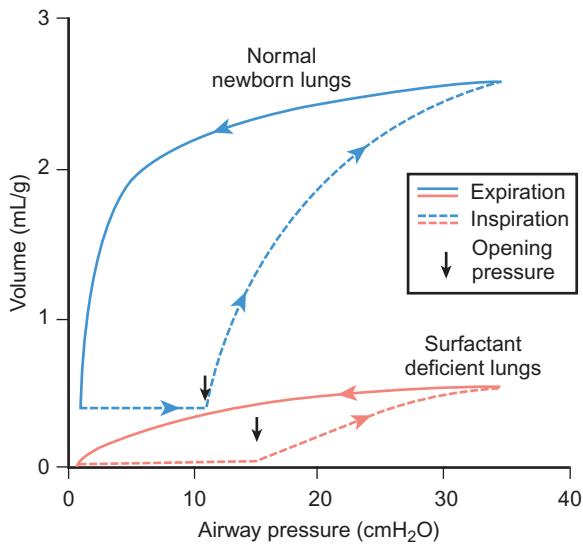
Fig. 11.1 The difference in lung volume for a given airway pressure. If surfactant is present, there is a lower opening pressure, a larger change in volume for a given change in pressure and the lungs do not collapse on expiration.
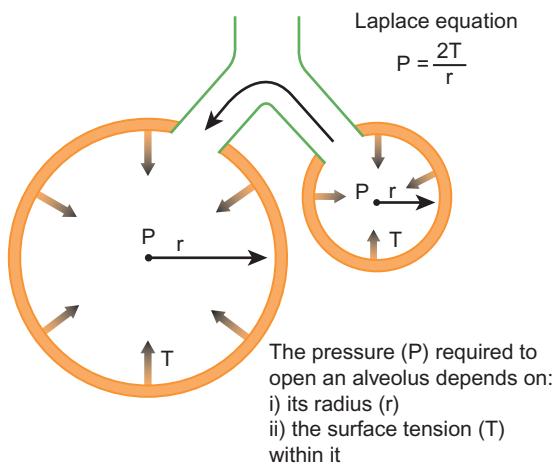
Fig. 11.2 Heterogeneous alveolar collapse in respiratory distress syndrome. In the absence of surfactant, the pressure at the surface of the alveolus is greater in the smaller than in the larger alveolus, so the small alveoli collapse and the large ones expand. *(Reproduced with permission from Neonatology at a glance, 3rd ed, Tom Lissauer, Avroy Fanaroff, Lawrence Miall, Jon Fanaroff. Oxford: Wiley-Blackwell, 2015.)*

In summary, functional abnormalities which contribute to respiratory failure in preterm newborns include:

- Decreased compliance
- Increased resistance
- Ventilation–perfusion imbalance
- Impaired gas exchange
- Increased work of breathing.

Pulmonary surfactant

Pulmonary surfactant is synthesized and secreted into the alveolar spaces by type 2 epithelial cells. It is a complex suspension of several phospholipids (85%) and proteins (10%). Most of the phospholipids consist of phosphatidylcholine (PC), and one particular PC molecule, DPPC (dipalmitoyl phosphatidylcholine). The structure of DPPC is suited to form a stable monolayer generating the lower surface tension required to prevent alveolar collapse at end-expiration. Phospholipids alone do not exhibit all the biophysical properties of pulmonary surfactant. The contribution of low molecular weight SP-B and SP-C to both structural organization and functional durability is essential. The surfactant specific proteins SP-B and SP-C promote the rapid absorption of phospholipids at the air–liquid interface and account for the sustained low surface tension activity after dynamic compression. SP-B deficiency, inherited as an autosomal recessive condition, is lethal and results in fulminant respiratory failure. SP-C dramatically enhances the spread of phospholipids. Unlike SP-B deficiency, mutation in the SP-C gene presents later as chronic interstitial lung disease. The other specific proteins, such as SP-A and SP-D, are only marginally involved in the surface tension lowering ability of pulmonary surfactant but play an important role in the defence barrier against pathogenic organisms and in the recycling of surfactant.

The total surfactant lipid pool in preterm babies is less than 10 mg/kg compared to the surfactant lipid pool size in term infants of around 100 mg/kg. Furthermore, preterm infants with RDS have a lower per cent of saturated phosphatidylcholine species, phosphatidylglycerol, and surfactant-associated proteins in their pulmonary surfactant.

Exogenous surfactant preparations are either derived from animal sources (bovine and porcine) or can be prepared synthetically. Animal-derived surfactants consist of more than 80% phospholipids and specific proteins SP-B and SP-C, but not SP-D. The synthetic surfactants are composed mainly of DPPC. Unlike the older generation of synthetic surfactants that did not contain specific proteins, newer synthetic surfactants, such as lucinactant, do contain synthetic peptides whose spatial structure resembles one of the domains of SP-B and is clinically as effective as animal-derived surfactants, but is much less widely used than natural surfactants. Another newer synthetic surfactant is being developed which contains recombinant SP-C.

Administration of exogenous surfactant in a surfactant-deficient preterm newborn decreases the minimum pressure required to open the lungs, increases the functional residual capacity (FRC) and

maximal lung volume, thus preventing lung collapse at low pressure and end-inspiration. It diminishes the work of breathing, stabilizes the respiratory tract, improves mucociliary transport, prevents oedema and contributes to lung defence against pathogens.

Diagnosis

RDS is diagnosed using a composite of clinical features including gestational age, the presence of respiratory distress with impaired gas exchange and characteristic radiographic abnormalities.

Management

This includes:

- Prevention, using antenatal glucocorticoid (betamethasone) to induce endogenous surfactant formation
- Exogenous surfactant replacement therapy (see below)
- Artificial respiratory support either in the form of continuous distending pressure, such as CPAP, or intermittent positive airway pressure ventilation through a mechanical ventilator
- Adjunctive measures include maintenance of adequate blood pressure, adequate oxygen-carrying capacity and physiological pH
- Avoidance of complications such as air leaks and bronchopulmonary dysplasia (BPD).

The benefits of exogenous surfactant replacement therapy are well established, either given 'prophylactically' or as a 'rescue treatment'. The clinical response to exogenous surfactant administration can be divided into three stages:

1. Acute treatment response (occurring within 10 minutes). This initial response results from the biophysical properties of surfactant and depends on rapid distribution of surfactant to distal lung areas. An improvement in oxygenation is usually the first clinical response to surfactant instillation.
2. The second stage involves sustained response to the initial surfactant dose (hours post administration). It results from improving lung mechanics and recycling of surfactant components from the air spaces into type 2 cells, where the lipids are, in part, diverted into lamellar bodies for re-secretion. In general, this cycling is more efficient in the preterm lungs, where recycling rates may be as high as 80–90%. This, however, does not guarantee that only one dose of surfactant will be effective. About 20–30% of infants receiving surfactant may still be receiving mechanical ventilation with FiO_2 of more than 30–40% several hours after the first dose and require re-treatment.
3. This comprises continued response to the initial surfactant dose and is attributed to the long

half-life of surfactant components. The net balance of slow synthesis, secretion, metabolism and clearance of surfactant and its components allow the infant with RDS to accumulate a large amount of surfactant over many days.

Surfactant therapy in preterm infants with RDS reduces neonatal mortality and complications such as pneumothorax. However, none of the trials or meta-analysis have shown any benefit in terms of reducing the incidence of BPD (bronchopulmonary dysplasia).

Nutrition

Human breast milk is the optimal form of nutrition even for extremely preterm infants. Its gastrointestinal tolerance is better and the incidence of necrotizing enterocolitis and the risk of systemic infection are lower than in infants fed with infant formula. Even minimal volumes may help prime bacterial colonization of the gut.

Lack of success in producing sufficient breast milk is often a problem, which may be aggravated by physical separation of mother and baby, difficulty in maintaining milk supply over a long period, lack of motivation and inadequate support. Frequent expression, kangaroo care or skin-to-skin contact and relaxation tapes improve the volume and duration of breastfeeding. Breast pumping, massage prior to pumping and dopamine antagonists may improve production. Expressed donor milk (DBM), which has been pooled and pasteurized, is increasingly used when mother's milk is not available. If these options are not available then preterm infant formula can be given. It has been modified to meet the increased nutrient requirements of extremely preterm infants and results in faster weight, length and head circumference growth, reduced incidence of hyponatraemia, bone disease of prematurity, hypophosphataemia and hyperbilirubinaemia than breast milk. However, tolerance of feeds is poorer and risk of NEC (necrotizing enterocolitis) is increased.

Human milk fortifiers containing protein, energy, macrominerals, trace minerals and a range of vitamins are widely used to supplement expressed breast milk to meet the additional nutritional requirements. They provide short-term improvements in weight gain, linear and head growth, but evidence is lacking for long-term benefits. As they are based on cows' milk, their precise biological properties differ from that of human milk. More recently, 'humanized' milk fortifier and infant formula, produced from pooled donor breast milk, have been developed and appear to have a lower risk of necrotizing enterocolitis compared to preparations based on cows' milk.

Parenteral nutrition is required if adequate enteral feeding is not possible, as extremely preterm infants have very limited ability to withstand starvation due to their low protein, fat and carbohydrate stores. Further details about nutrition in preterm infants are covered in Chapter 13, Nutrition.

Patent ductus arteriosus (PDA)

The role of the ductus arteriosus in the fetus and its functional and anatomical closure after delivery are described in Chapter 10, Perinatal medicine. Its patency is maintained by high blood flow, hypoxia and locally derived prostaglandin E2. In preterm infants, the ductal wall is thinner, the lumen is larger and post-natal constriction does not wholly obliterate the lumen. The incidence of functional PDA varies inversely with gestational age. Predisposing risk factors are respiratory distress syndrome, sepsis and fluid overload.

Haemodynamics

The left-to-right shunting of blood through the PDA results in increased pulmonary blood flow and higher venous return to the left atrium and left ventricle (high preload). This increased pulmonary blood flow can lead to pulmonary oedema, congestive cardiac failure or, less commonly, pulmonary haemorrhage and may increase the risk of bronchopulmonary dysplasia. A haemodynamically significant PDA decreases systemic blood flow and leads to hypotension (especially diastolic, resulting in wide pulse pressure), reduced gut and renal perfusion and metabolic acidosis. This in turn may lead to increased risk of complications such as necrotizing enterocolitis and intraventricular haemorrhage.

The clinical effects of PDA include tachypnoea, increased oxygen requirement, increased ventilatory requirement, extubation failure, apnoea, hepatomegaly from congestive heart failure and impaired weight gain. These are often accompanied by a systolic or pansystolic murmur at the left sternal edge (though this may be absent if the shunt is large), loud second heart sound, gallop rhythm, bounding pulses from wide pulse pressure and hepatomegaly from right heart failure.

Management

Recent studies suggest that conservative management is often appropriate as in infants >1 kg birth weight, two thirds of PDA close spontaneously, and even if <1 kg, PDA closes in just over a third. Conservative treatment of restricted fluid early on in the first week has been shown to significantly decrease the risks of PDA. However, prolonged fluid restriction may worsen systemic hypoperfusion.

Pharmacological closure with indomethacin or ibuprofen works by decreasing the production of PGE_2. However, indomethacin use is associated with more nephrotoxicity, NEC, gastrointestinal haemorrhage, platelet dysfunction and impaired cerebral blood flow. Ibuprofen, a non-selective cyclo-oxygenase inhibitor, is therefore currently recommended as first line medical treatment. Diuretics may worsen systemic hypoperfusion and increase the renal production of prostaglandins, which may promote ductal patency. Therefore, these should only be used in babies with heart failure. Surgical ligation may be indicated if medical intervention fails.

Question 11.2

The immune system of the newborn

Which of the following statements are true (T) and which are false (F)?

A. A newborn term infant typically has IgG levels higher than its mother

B. At 24 weeks' gestation, a preterm infant has no maternal IgG

C. Breast milk is a significant additional source of IgG

D. Maternal antibodies attenuate infant responses to vaccination at birth

E. Vaccination accelerates the induction of the infant immune response

Answers 11.2

A. True; B. False; C. False; D. True; E. True.
See below for discussion.

Infection

Preterm infants are particularly vulnerable to early-onset and nosocomial (hospital-acquired) infection. This is partly due to lack of maternal IgG antibody transfer across the placenta (fetal IgG rises from approximately 10% of the maternal concentration at 17–22 weeks' gestation to 50% at 28–32 weeks' gestation; Fig. 11.3) and breach of natural defence barriers from invasive central and peripheral lines, catheters and tubes, including artificial ventilation. Transplacental transfer of antibodies is an active process that results in fetal IgG levels in excess of maternal levels by full term. Breast milk is another important source of passive immune protection for infants and is rich in IgA but contains little or no IgG.

Following birth, a preterm infant should receive their immunizations at the same postnatal age as a term baby. Whilst immune response in very preterm infants may be suboptimal, these infants are also at increased risk of infection, so vaccination should not be delayed. Primary protection against infectious diseases at birth is provided mainly by maternal antibodies. However, these antibodies can hamper the humoral antibody response of the infant to vaccination, so the timing of vaccination should take their presence into consideration. The timing for childhood immunizations is based upon a complex risk–benefit analysis that takes account of this effect, which is why, for example, primary MMR vaccination is delayed until 12 months of age.
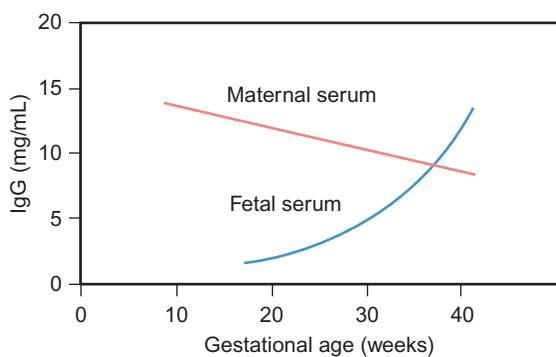
Fig. 11.3 Changes in maternal and fetal IgG levels with gestational age, showing that fetal IgG levels exceed those of the mother at term. *(Adapted from Malek A, et al. Evolution of maternofetal transport of immunoglobulins during human pregnancy. Am J Reprod Immunol 1996;38:248–255. © Wiley.)*

Necrotizing enterocolitis

About 5% of all very-low-birthweight (VLBW) infants will develop necrotizing enterocolitis (NEC), with mortality ranging from 15–25%. It is a clinical diagnosis of abdominal distension and tenderness, bilious aspirates, bloody stools and intramural air (pneumatosis intestinalis) on abdominal X-ray. It may progress to peritonitis and bowel perforation.

The exact cause is unknown but is probably multifactorial, including loss of bowel mucosal integrity leading to macromolecular absorption and bacterial translocation. There is significant deficiency of secretory IgA, with increased permeability to small and large molecules. Antenatal glucocorticoid therapy improves intestinal maturation and reduces permeability and hence offers a degree of protection. Infection may initiate mucosal injury leading to invasion of gas-producing bacteria, which can result in pneumatosis intestinalis. This gas in the bowel wall is mainly nitrogen and hydrogen. There may also be gas in the portal venous system. Histologically, there is necrosis of the mucosa with microthrombus formation, patchy mucosal ulceration, oedema and haemorrhage. Cytokines and inflammatory markers such as interleukins, tumour necrosis factor alpha (TNFα) and platelet activating factors (PAF) have an important role and enterocyte death may be induced due to imbalance in the pro- and anti-inflammatory mediators and increased pro-apoptotic protease activity. Any part of the small or large bowel may be affected, but the terminal ileum or sigmoid colon is usually involved. Risk factors for the development of NEC are shown in Figure 11.4.
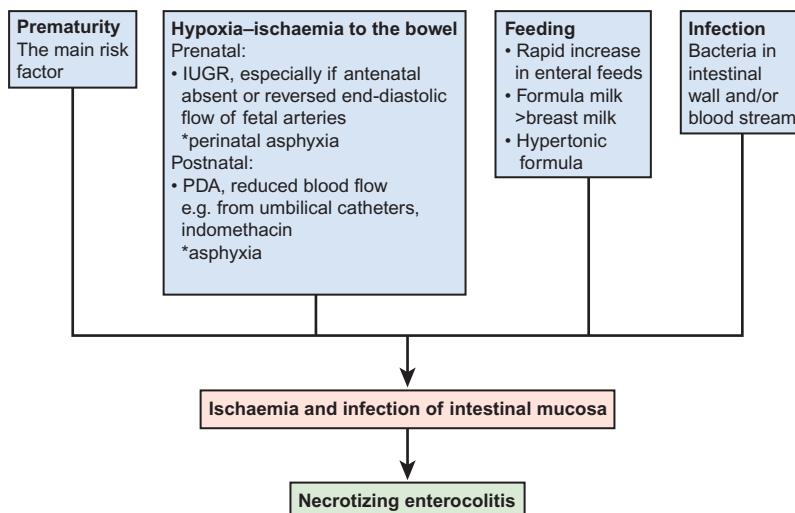
Fig. 11.4 Risk factors for the development of necrotizing enterocolitis. *(Adapted from Neonatology at a glance, 3rd ed, Tom Lissauer, Avroy Fanaroff, Lawrence Miall, Jonathan Fanaroff. Oxford: Wiley-Blackwell, 2015.)*

A recent proposal is that anaemia leads to compromise of the mesenteric blood flow causing intestinal hypoxia and mucosal injury. Transfusion-related reperfusion gut injury (TRAGI) of the hypoxaemic gut has been postulated to predispose anaemic preterm infants to NEC. Probiotics with or without prebiotics to help promote normal gut flora have been studied extensively; their benefit remains unproven.

Current management of NEC is to stop feeds and place a large bore naso/orogastric tube for intestinal decompression, start broad spectrum antibiotics and provide supportive care. Surgical intervention may be required for bowel perforation or failure of medical treatment, with peritoneal drainage at the bedside or resection of non-viable bowel and anastomosis or ileostomy or colostomy.

Question 11.3

Intraventricular haemorrhage

Which of the following is the single most important risk factor for intraventricular haemorrhage (IVH)? Select ONE answer only.

A. Extreme prematurity
B. Low platelet count
C. Mechanical respiratory support
D. Pneumothorax
E. Respiratory distress syndrome

Answer 11.3

A. Extreme prematurity.
   All are risk factors but extreme prematurity is of overriding importance.

Question 11.4

Risk of cerebral palsy and cranial ultrasound abnormalities

Which of the following abnormalities in isolation confers the greatest risk of cerebral palsy in a preterm infant? Select ONE answer only.

A. Anterior cystic periventricular leukomalacia (PVL)
B. Grade III intraventricular haemorrhage (IVH)
C. Grade IV intraventricular haemorrhage (parenchymal)
D. Occipital cystic PVL
E. Ventricular dilatation

Answer 11.4

D. Occipital cystic PVL.
   Whilst imaging alone cannot confidently exclude or determine the risk of cerebral palsy, there are several large cohort studies that report on the relative values of imaging abnormalities in predicting neurodisability. In particular, bilateral, occipital or parietal cystic periventricular leukomalacia confers a very high risk of cerebral palsy, with two thirds to three quarters developing cerebral palsy.

Periventricular-intraventricular haemorrhage

Periventricular-intraventricular haemorrhage (PVH-IVH) is the most common neurological complication of preterm infants (the incidence is inversely related to gestational age) and is an important risk factor for neurodevelopmental impairment and death. It is caused by rupture of the fragile capillary network in the subependymal (also called germinal) matrix of the developing brain, which overlies the head of the caudate nucleus. The haemorrhage may be confined to the subependymal region (germinal matrix haemorrhage; GMH) or may extend into the body of the lateral ventricles (intraventricular haemorrhage) or involve the cerebral cortical parenchyma (parenchymal haemorrhage). The parenchymal lesion is not an extension of the haemorrhage as previously thought, but is a venous infarct related to obstruction to the venous drainage of the white matter. The parenchymal lesion subsequently undergoes cystic degeneration and by term there is a porencephalic cyst. Intraventricular haemorrhage is typically classified by grade (1–4) based on ultrasound appearances (Box 11.2). Serial cranial ultrasound is used to detect intraventricular haemorrhage, porencephalic cysts and ventricular dilatation or hydrocephalus, a complication of intraventricular haemorrhage. The agreement between ultrasound and autopsy diagnosis has been reported to be >90%.

The pathogenesis is multifactorial but key factors are thought to be the immature germinal matrix capillary network, impaired cerebral autoregulation (failure to maintain cerebral blood flow within the normal limits in spite of wide fluctuations in blood pressure), and abnormal coagulation. This is summarized in Figure 11.5.

Preterm infants with GMH-IVH have a higher mortality compared to those without. Uncomplicated IVH (grades I and II) can also cause motor and cognitive sequelae, with about 9% risk of developing cerebral

palsy. About a quarter of infants with grade III and half with grade IV develop cerebral palsy (CP) at two years of age.

Periventricular leukomalacia

Periventricular leukomalacia (PVL) is periventricular white matter injury, which usually results from a

combination of ischaemia from hypoperfusion of the periventricular white matter and inflammation resulting in oligodendroglial injury and failure of myelination (see Fig. 11.5). In cystic PVL, there are focal macroscopic areas of necrosis in the periventricular white matter leading to small bilateral periventricular cysts which may be visible on cranial ultrasound from about two weeks of birth. The incidence of cystic PVL is 3% of very-low-birth-weight babies. It has a significant impact on neurodevelopmental outcome with a high incidence of diplegic CP, poor visual spatial skills and low IQ scores. More commonly, the focal lesions are microscopic in size and evolve to small glial scars, which are not usually detected on ultrasound but can be identified on MRI scan. It may well be responsible for some of the characteristic cognitive difficulties many extremely preterm babies have at school age, rather than cerebral palsy.

Osteopenia of prematurity

Preterm infants are prone to poor bone mineralization. This is caused by phosphate deficiency and results in reduced bone mineralization with widening and cupping of the wrists, knees and ribs on X-ray (as with rickets), a failure in linear growth and fractures, particularly of ribs and long bones.

Investigations show a low phosphate with calcium being either normal or elevated initially in conjunction
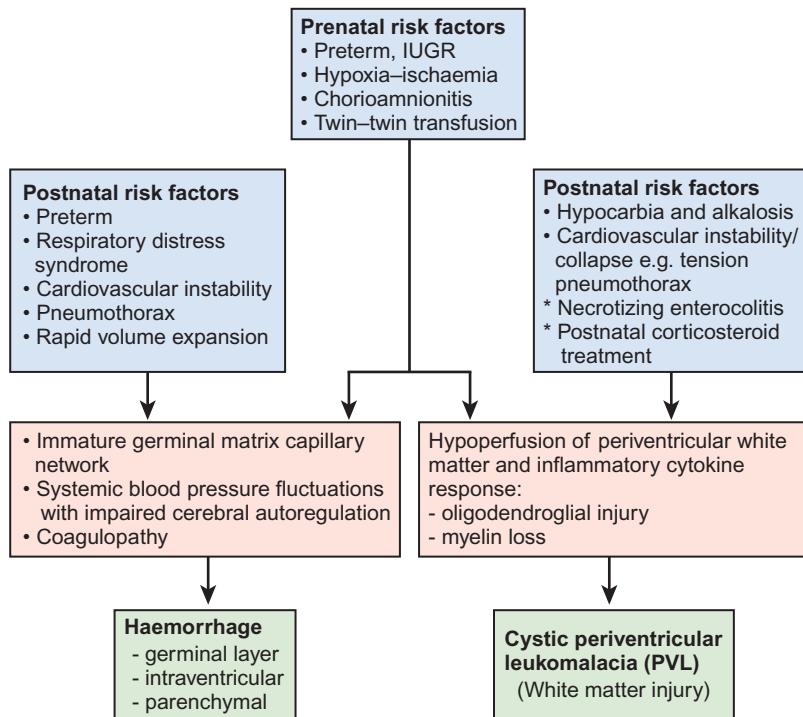
Fig. 11.5 Pathogenesis of periventricular-intraventricular haemorrhage (PVH-IVH) and cystic periventricular leukomalacia (PVL). *(Adapted from Neonatology at a glance, 3rd ed, Tom Lissauer, Avroy Fanaroff, Lawrence Miall, Jonathan Fanaroff. Oxford: Wiley-Blackwell, 2015.)*

with a markedly elevated alkaline phosphatase (a marker of bone turnover). It can be prevented by giving additional phosphate in parenteral nutrition and by giving oral phosphate or using preterm milk forti-fier. Providing sufficient phosphate if on long-term parenteral nutrition can be difficult. Treatment is with oral phosphate and vitamin D supplements.

Retinopathy of prematurity

Retinopathy of prematurity (ROP) is an important cause of visual impairment and blindness in the preterm newborn (see Chapter 30, Ophthalmology). The risk of its development should be minimized by avoiding hyperoxaemia (maintain oxygen saturation 91–95%), hypoxaemia and wide fluctuations in oxygen saturations.

Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) is defined clini-cally on the basis of clinical signs and dependence on ambient oxygen either at 28 days or more usually at 36 weeks post menstrual age. Although oxygen sup-plementation has routinely been used as a surrogate for assessing the severity of the underlying lung disease, this is subjective and it is not surprising that prevalence of BPD varies markedly between units and this variation has hampered epidemiological research. To rectify this, a stricter physiologic definition has been proposed in which infants receiving less than 30% supplemental oxygen are subjected to a stepwise 2% reduction of supplemental oxygen until they are breathing room air. The outcome of this allows the identification of:

- No BPD – oxygen saturation >90% for 60 minutes in room air
- BPD – if saturation <90% during the observation period

Babies undergoing an oxygen challenge test are monitored for apnoea, bradycardia and increased oxygen requirement. If any of these events occur and require treatment, this is considered a test failure and categorized as BPD. This method provides an objective assessment of the presence and severity of underlying lung disease. Using this physiological definition, the incidence of BPD is only about 10% of very-low-birth-weight infants compared to 25% using the standard criteria.

Its pathogenesis is multifactorial and includes:

- Underdeveloped lungs due to prematurity
- Initial injury to the lung due to primary disease process, e.g. RDS
- Ventilator-induced lung injury mediated through barotrauma (high pressure)
- Volutrauma (inappropriately high or low tidal delivery)
- Oxygen toxicity
- Inflammatory cascade
- Inadequate nutrition

The pathophysiology and underlying pulmonary mechanics in infants with BPD includes reduction in lung compliance as well as increased airway resistance leading to increased work of breathing. Later, expira-tory flow limitation may become more significant. Functional residual capacity may be reduced initially because of atelectasis but can increase in later stages from air trapping and hyperinflation. More recent findings in extremely premature infants reveal alveolar simplification, a reduction in the overall surface area for gas exchange, and failure of secondary alveolar crest to form normal alveoli (epithelial and endo-thelial cell growth abnormalities).

Once BPD has developed, treatment is only sup-portive. Most infants ultimately achieve normal lung function and thrive. They are at higher risk of death in the first year of life and long-term complications such as reactive airway disease, increased susceptibility to viral infection, particularly RSV (respiratory syncytial virus) infection, growth failure and neurodevelop-mental abnormalities.

Outcomes in preterm infants

This includes survival to discharge from hospital, key morbidities and neurodevelopmental outcomes. With advances in perinatal medicine such as use of ante-natal steroids, advanced ventilation techniques, good intensive care and decreased sepsis, the survival rate of extremely premature infants has increased markedly. However, they are at increased risk of medical prob-lems at and following discharge and of neurodevelop-mental problems. Medical problems at and following discharge include increased risk of:

- Poor growth – at discharge, over 90% of VLBW infants are below the 10th centile for weight, length and head circumference. Many show some catch-up growth in the first 2–3 years
- Pneumonia/wheezing/asthma
- Bronchiolitis from RSV (respiratory syncytial virus) infection (hospitalization is reduced by giving RSV monoclonal antibody, palivizumab)
- Bronchopulmonary dysplasia – may require supplemental oxygen therapy at home
- Gastro-oesophageal reflux – especially with bronchopulmonary dysplasia
- Complex nutritional and gastrointestinal disorders – following necrotizing enterocolitis or gastrointestinal surgery
- Inguinal hernias – require surgical repair.
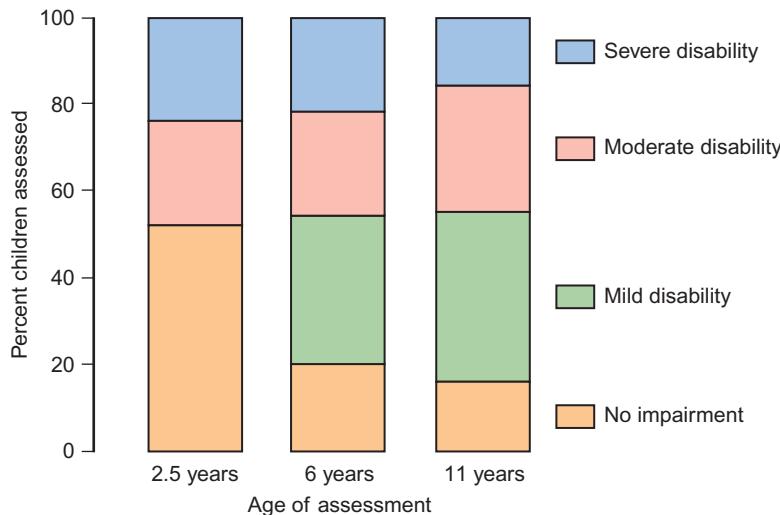
Fig. 11.6 Evolution of disability from birth to 11 years in births at 22–25 weeks of gestation in the UK (EPICure 1). About 55% have moderate or severe impairment at 11 years. *(Source: Johnson S, et al. Pediatrics 2009;124:e249–e257.)*

Readmission to hospital during the first year of life is increased approximately four-fold, mainly for respiratory disorders and surgical repair of inguinal hernias.

About 5–10% of VLBW infants develop cerebral palsy, but the most common impairments are learning difficulties. The prevalence of cognitive impairment and of other associated difficulties increases with decreasing gestational age at birth, and is greatest if born at very early gestational age (<26 weeks' gestation). It becomes increasingly evident when the individual child is compared to their peers at nursery or school. In addition, children may have difficulties with:

- fine motor skills, e.g. threading beads
- concentration, with short attention span
- behaviour, especially attention deficit disorders
- abstract reasoning, e.g. mathematics
- processing several tasks simultaneously.

A small proportion also have hearing impairment, with 1–2% requiring amplification, or visual impairment, with 1% blind in both eyes. A greater proportion have refraction errors and squints and therefore require glasses.

Focusing on preterm babies born at 22–25 weeks' gestation, the most recent population-based outcome study from all those births in England in 2006 (EPICure 2) found that of 3133 deliveries, there were 2034 live births, 1686 neonatal admissions and 1041 discharges from hospital.

Survival rates of live-born infants were:

22 weeks' gestation	2%
23 weeks' gestation	19%
24 weeks' gestation	40%
25 weeks' gestation	66%
26 weeks' gestation	77%

The evolution of disability up to 11 years of the babies born at 22–25 weeks in the UK in 1995 (EPICure 1) is shown in Figure 11.6. This outcome data is important to inform debate about ethical decisions concerning babies born at gestational age at the limit of viability (see Chapter 35, Ethics).

Respiratory system

Extremely premature infants are born at an early stage of lung development, before the development of alveoli, and have deficient surfactant production for extrauterine life (see Chapter 17, Respiratory medicine, for a description of the embryology). There are a number of factors that influence fetal lung growth or maturation, including physical (e.g. fetal respiration and fetal lung fluid), hormonal (e.g. glucocorticoids, prolactin and insulin), and local (cAMP, methylxanthines).

Airways are heterogeneous, conduct airflow, and do not participate in gas exchange. Stable pressure balance between collapsing forces and the dilator forces of supporting musculature help to maintain upper airway patency. Conducting airways of intrathoracic trachea (lower airway), however, do participate in respiratory gas exchange in portions of the terminal and respiratory bronchioles and alveolar ducts. Narrowing of the airways, from inflammation, excessive secretions or reactive airways, leads to increased resistance to airflow, thereby causing increased work of breathing.

Thoracic and respiratory muscles which are involved in respiratory function include the diaphragm, intercostal and accessory muscles and abdominal muscles.

Question 11.5

A 2-day-old infant with respiratory distress

A 2-day-old male infant is rushed to the paediatric emergency department because his mother found him to have gasping respirations and looking pale and mottled. He has respiratory distress, a respiratory rate of 80 breaths/min, heart rate of 164 beats/min and oxygen saturation (right foot) of 70%. He is given oxygen. What would you do next?

Select ONE answer only:

A. Blood gas

B. Blood culture

C. Chest X-ray

D. ECG

E. Move the pulse oximeter probe to the right hand

Answer 11.5

E. Move the pulse oximeter probe to the right hand
    A higher pre-ductal oxygen saturation would suggest critical congenital heart disease and giving prostaglandin to maintain ductal patency would be life-saving. (See Fig. 39.3 for details on oxygen saturation screening for detecting critical congenital heart disease.)

Respiratory distress

The clinical features of respiratory distress in newborn infants are tachypnoea (respiratory rate >60/min), nasal flaring, grunting, chest recession with variable cyanosis depending upon severity of illness. The differential diagnosis is wide (Table 11.3).

Transient tachypnoea of the newborn

This is by far the most common cause of respiratory distress in term infants. It is more common following elective caesarean section. Although absence of thoracic squeezing of lung liquid from the chest during delivery is thought to be a factor, clearance of fetal lung fluid is largely dependent on reabsorption of alveolar fluid via sodium channels in the lung epithelium, which is influenced by the level of circulating catecholamines. The lower concentration of circulating catecholamines following elective delivery results in reduced absorption of lung liquid. At birth, the baby generates marked negative pressures ($-60\,cmH_2O$), which fill the lungs with air. With the first two or three breaths, much of the fetal lung fluid is expelled. This is enhanced by positive end expiratory pressure (PEEP), which is generated by the baby crying

Table 11.3 Causes of respiratory distress

Common	Less common	Rare
Transient tachypnoea of the newborn	Pneumonia/ sepsis	Surfactant deficiency in term infants
Respiratory distress syndrome in preterm infants	Meconium aspiration	Congenital diaphragmatic hernia
	Pneumothorax	Tracheo-oesophageal fistula
	Congenital heart disease/heart failure	Pulmonary hypoplasia
	Persistent pulmonary hypertension of the newborn (PPHN)	Pleural effusion (chylothorax)
	Hypoxic– ischaemic encephalopathy	Milk aspiration
		Airway obstruction (e.g. choanal atresia)
		Lung anomalies (congenital pulmonary airway malformation – CPAM, lobar emphysema, pulmonary sequestration)
		Neuromuscular disorders
		Severe anaemia
		Metabolic acidosis (inborn error of metabolism)

(against partially closed vocal cords). The remainder is absorbed into the pulmonary lymphatics and capillaries over the first 6–12 hours. Delay in the absorption of lung liquid may result in respiratory distress and for several days.

Question 11.6

A baby with meconium-stained amniotic fluid at birth

A male infant is born at 41 weeks' gestation in poor condition through meconium-stained amniotic fluid (MSAF). He is intubated and ventilated. He requires 90% oxygen and his oxygen saturation remains between 80% and 85%. Arterial blood gas shows a pH 7.31, PaO_2 3 Kpa, $PaCO_2$ 4.5 Kpa and base deficit of 3. Which of the following is likely to be contributing to his hypoxia? Answer with true (T) or false (F).

A. Airway obstruction

B. Alveolar hypoventilation

C. Intrapulmonary shunt

D. Persistent pulmonary hypertension of the newborn

E. Systemic hypotension with R to L shunt through arterial duct

Meconium aspiration syndrome

Meconium stained amniotic fluid (MSAF) occurs in around 13% of all deliveries, but meconium aspiration syndrome (MAS) occurs only in only a small percentage of them. Aspiration most commonly occurs *in utero* and with thick MSAF consistency. Of affected infants, 30–60% require mechanical ventilation, 10–25% develop pneumothoraces and 2–5% die. Some 50–70% of infants with persistent pulmonary hypertension of the newborn have MAS as an underlying disorder.

The pathophysiology of MAS is complex, with proximal and distal airway obstruction and air trapping. There is also pulmonary parenchymal injury due to inflammatory cascade, which in turn can lead to surfactant inactivation. Those babies who suffered from chronic hypoxaemia before delivery may also have remodelling of their pulmonary vasculature leading to persistent pulmonary hypertension of the newborn (PPHN).

Of the various management strategies, few have been adequately evaluated. The mainstay is to provide adequate respiratory support to maintain oxygenation in the normal range, prevent air leaks using newer styles of ventilation including high frequency ventilation and treatment of PPHN with inhaled nitric oxide or extracorporeal membrane oxygen (ECMO). Most babies who survive have normal outcome unless MAS was a result of antenatal or intrapartum asphyxia. Such babies are at risk of subsequent neurodevelopmental delay.

Thoracic air leaks

This refers to a collection of gas outside the pulmonary space and includes pneumothorax, pneumomediastinum, pneumoperitoneum, and subcutaneous emphysema.

Several conditions increase the risk of pulmonary air leaks:

- Respiratory distress syndrome (incidence 5–20%, the commonest cause)
- Meconium aspiration syndrome (incidence 20–50%)
- Congenital diaphragmatic hernia (14%)
- Previous pneumothorax (risk of developing contralateral pneumothorax 45%)
- Pulmonary hypoplasia
- Pulmonary interstitial emphysema

Air leak syndrome arises via a common pathway that involves damage of the respiratory epithelium, which in turn allows air to enter the interstitial space, causing pulmonary interstitial emphysema. With continued high transpulmonary pressures, air dissects towards the visceral pleura and/or hilum by the peribronchial or perivascular space. Pneumothorax occurs when the pleural surface is ruptured resulting in the leakage of air into the pleural space. Acute pneumothorax is a serious complication causing collapse of the underlying lung, mediastinal shift and cardiovascular compromise due to reduced venous return and cardiac output. Diagnosis is made on suspicion from deterioration of clinical condition or increased oxygen requirement, clinical signs (reduced air entry, mediastinal shift), positive transillumination and chest radiograph. Needle aspiration can be used to treat a symptomatic pneumothorax. However, chest tube drainage (thoracostomy) is usually needed for continuous drainage of pneumothoraces that develop in infants receiving positive pressure ventilation, because the air leak may be persistent.

Persistent pulmonary hypertension of the newborn (PPHN)

Under normal circumstances, pulmonary vascular resistance (PVR) falls rapidly after birth. If this does not occur, PPHN ensues and this leads to a variable degree of right-to-left shunt of blood through the foramen ovale and ductus arteriosus, which together with intrapulmonary shunting results in severe

hypoxaemia. A similar clinical picture can arise from decreased systemic vascular resistance (SVR) or any condition in which the PVR : SVR ratio is more than one. PVR may be elevated as a result of an 'appropriate' response to an underlying acute pathological state (for example, pneumothorax or pneumonia), or as a result of structural abnormalities of the pulmonary vascular bed.

A number of non-structural (and therefore more reversible) factors may also impact on pulmonary vascular reactivity and pressure. Hypoxia, hypercarbia and acidosis cause vasoconstriction and elevate pulmonary artery pressure, and their presence may lead to failure of adaptation from fetal to neonatal (adult type) circulation. Conditions which cause increased pulmonary vascular resistance are of two types:

- Where the pulmonary vascular morphology is normal, as seen in association with asphyxia, meconium aspiration syndrome, severe parenchymal lung disease, and sepsis/pneumonia
- Increased pulmonary vascular resistance associated with morphologically abnormal pulmonary vasculature in association with pulmonary hypoplasia, congenital diaphragmatic hernia and congenital pulmonary airway malformations (CPAM). It may also occur in structurally abnormal heart disease, as for example in left ventricular outflow tract obstruction and anomalous pulmonary venous drainage.

Differential diagnosis of persistent hypoxaemia in the term/near term infant includes:

- Primary lung disease
- Cyanotic congenital heart disease
- PPHN, with or without lung disease.

Echocardiography is helpful in confirming the presence of PPHN and identifying congenital heart disease. Treatment includes general supportive measures, mechanical ventilation and pharmacotherapy including pulmonary vasodilators, mainly inhaled nitric oxide. If there is an inadequate responsive to these measures, extracorporeal membrane oxygenation (ECMO) has been shown to significantly reduce death without causing any increase in adverse neurological outcome in later life.

Developmental anomalies

Congenital anomalies in the lung can be categorized as malformations in:

- The tracheo-bronchial tree
- Distal lung parenchyma
- Abnormalities in the pulmonary arterial and venous trees and the lymphatics

Most pulmonary malformations arise during the embryonic and the pseudoglandular stages of lung development. However, acute lung injury in the neonatal period may alter subsequent alveolar and airway growth and development. The most common pulmonary and extra pulmonary malformations are congenital diaphragmatic hernia (CDH), congenital pulmonary airway malformations (CPAM), tracheo-oesophageal fistula (TOF), bronchopulmonary sequestration (BPS) and congenital hydrothorax.

Congenital diaphragmatic hernia

Congenital diaphragmatic hernia (CDH) occurs in 1 in 2000–3000 births. In roughly two thirds, it is an isolated lesion. The remainder are complex and it can be part of a syndrome including chromosomal anomalies. It results from failure of normal development of the diaphragm during first trimester and has different types:

- Posterior lateral defect, more often on the left than right
- Anterior or central portion defect
- Complete absence of diaphragm
- Eventration, which is not a true hernia but results from failure of muscle development in the primitive diaphragm.

Diaphragmatic hernia produces a spectrum of pathology from very mild pulmonary hypoplasia (causing minimal clinical compromise) to severe (incompatible with life).

Pathophysiology

The compression of the fetal lungs results in lung hypoplasia, especially in the ipsilateral lung. In severe cases, there may be compromised cardiac function. Cardiorespiratory function is further compromised by gaseous distension of the intrathoracic gut following delivery. This is a particular hazard if babies are given bag-valve-mask ventilation.

Pulmonary hypoplasia (including abnormalities of the pulmonary vasculature) and poor oxygenation following delivery commonly result in severe persistent pulmonary hypertension of the newborn (PPHN). In mild cases, the clinical presentation may be delayed.

Management

This may comprise:

- Fetal surgery – fetal endoscopic tracheal occlusion (FETO), which is reserved for severe CDH to promote lung growth and limit pulmonary hypoplasia. It may not alter the lung parenchyma and pulmonary arterioles qualitatively. Using fetal tracheoscopy, a balloon is inserted (ideally at 26–28 weeks) and the occlusion is reversed

in utero at 34 weeks. Overall fetal surgery for CDH offers little benefit, and its use should be limited to clinical trials.

- At delivery, if diagnosed antenatally:
  - Face mask ventilation is avoided as it distends the gastrointestinal tract
  - Intubation and artificial ventilation is instituted as soon as possible
  - Continuous drainage (decompression) of gas from abdomen is started
- Factors that could precipitate PPHN and lung injury are minimized
- Adequate ventilatory support is provided
- Pulmonary vasodilators are given if PPHN is present
- Surfactant – there is no evidence to support its recommendation except in premature infants with coexisting surfactant deficiency
- Surgical repair is clearly essential but should be performed when the baby is stable
- ECMO (extracorporeal membrane oxygenation) is able to provide stability and control PPHN but its benefit in CDH is unclear.

Tracheo-oesophageal fistula

This occurs in 1 in 3000–4500 live births and results from failure of the process of separation of the primitive foregut into the respiratory and gastrointestinal tract at 3–6 weeks of gestation (Fig. 11.7). It is usually found in combination with various forms of oesophageal atresia, the most common combination being oesophageal atresia with distal tracheo-oesophageal fistula (about 91%). Tracheo-oesophageal fistula without oesophageal atresia (H-type fistula) is extremely rare and usually presents after the neonatal period.

Tracheomalacia and bronchomalacia

Absence of softening in the cartilaginous rings causes the trachea to collapse on expiration. There is a reduction in the cartilage to soft tissue ratio. The anomaly may be segmental or diffuse.

Bronchopulmonary sequestration

This develops as a mass of non-functioning lung tissues, not connected to the tracheo-bronchial tree. It receives its blood supply from one or more anomalous systemic arteries arising from the aorta. Bronchopulmonary sequestration can be either within (intralobar) or outside (extralobar) the visceral pleural lining. On chest X-ray it appears as triangular or oval-shaped lung tissue on one side of the chest, usually the left. Diagnosis is confirmed by CT or MRI scan of the chest.

Congenital lobar emphysema

This may result from malformation in the bronchial cartilage with absent or incomplete rings resulting in
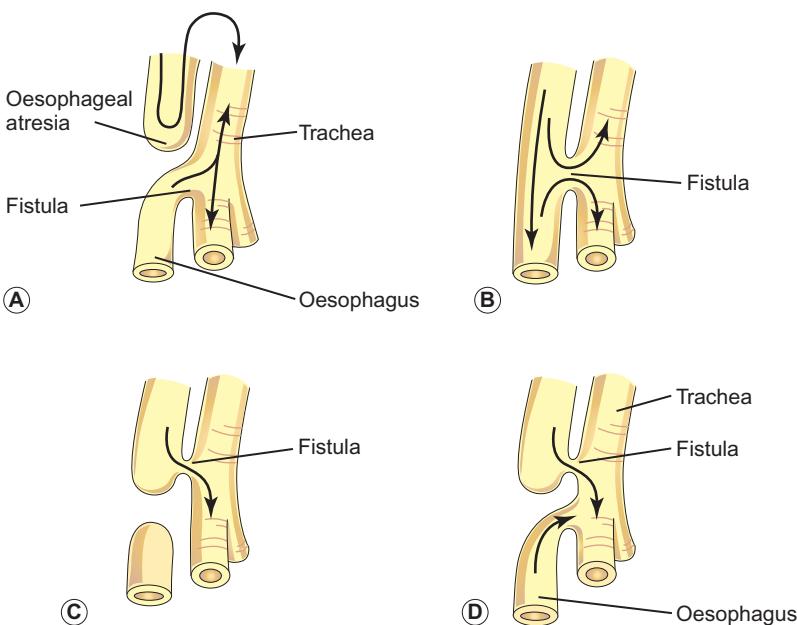
Fig. 11.7 The main varieties of tracheo-oesophageal fistula, shown in order of frequency. Possible directions of the flow of the contents are indicated by arrows. A. Oesophageal atresia associated with distal tracheo-oesophageal fistula (91%). B. H-type fistula between the trachea and the oesophagus, no oesophageal atresia (4%). C. Atresia with proximal oesophageal fistula with distal oesophagus as blind pouch. Air cannot enter the distal oesophagus or stomach (4%). D. Atresia with fistulas between the trachea and both the proximal and the distal segments of the oesophagus (1%). *(From Moore KL, Persaud TVN, Torchia MG. Before we are born, 8th ed, Saunders 2013, with permission.)*

lobar or segmental over-inflation and thus causing compression of the remaining ipsilateral lung or lobes.

Pulmonary hypoplasia

This is frequently secondary to other anomalies in the developing fetus, such as renal agenesis, oligohydramnios, diaphragmatic hernia, large pleural effusion and congenital anomalies of the neuromuscular system. These anomalies restrict either physical growth or expansion of the peripheral lung.

Congenital pulmonary airway malformations (CPAM)

This was previously called congenital cystic adenomatoid malformation (CCAM). It is pulmonary maldevelopment with cystic replacement of smaller airways and distal lung parenchyma. There are several types of CCAM classified on the basis of the gross appearance and histological features, but they are broadly divided into two major types: macrocystic and microcystic. In the macrocystic type, the cysts are more than 5 mm in diameter and are visible on fetal ultrasonography. This carries a good prognosis. In the microcystic type, the cysts are smaller and the mass has a solid appearance. The prognosis is worse, especially if the mass is large and associated with mediastinal shift, polyhydramnios, pulmonary hypoplasia or hydrops fetalis. Because the multiple cysts are connected to the airways, they fill with air and produce a further mass effect causing compression of the adjacent lungs. Fetal surgery is limited to severe cases with hydrops with some success. The main concern with this procedure is the onset of preterm labour.

Congenital pulmonary lymphangiectasis

Congenital pulmonary lymphangiectasis (CPL) is characterized by marked distension of pulmonary lymphatics, either generalized or localized, and presents with a pleural effusion which is typically chylous. If identified antenatally, a catheter shunt between the chest and amniotic cavity can be inserted. The condition has been associated with a number of syndromes, such as Noonan's and Down's syndrome.

Respiratory failure

Respiratory failure is present when there is a major abnormality of gas exchange (Fig. 11.8). The oxygen tension (PaO$_2$) in adults is expected to be >8 kPa. In the newborn, oxygen tension of 5.3–8 kPa is needed to maintain arterial saturation above 90% depending upon proportion of fetal haemoglobin (HbF) and arterial pH. The left shift of oxyhaemoglobin dissociation curve due to 70% HbF is eliminated by a 0.2 drop in pH, hence respiratory failure is better defined in

Determinants of gas exchange
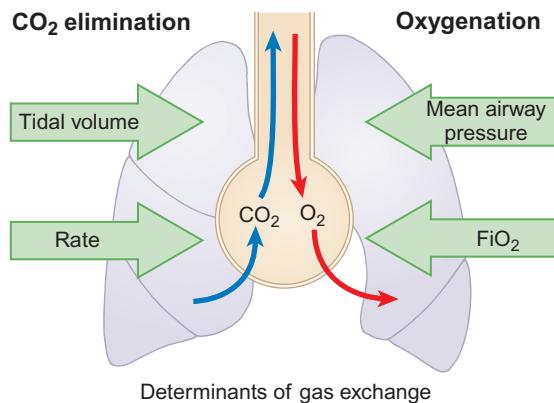
Fig. 11.8 Determinants of gas exchange. Oxygenation is determined by mean pressure and the FiO$_2$, whereas CO$_2$ elimination is determined by tidal volume and rate of ventilation.

terms of arterial oxygen tension than oxygen saturation.

Hypoxaemia in newborn infants can result from a number of causes, including:

- Ventilation–perfusion (V/Q) mismatch:
  - Distinguished by a good response to supplemental oxygen (intrapulmonary shunting)
  - Increased physiologic dead space
  - From parenchymal lung disease e.g. respiratory distress syndrome, pneumonia, meconium aspiration syndrome and bronchopulmonary dysplasia
- Extrapulmonary (right-to-left) shunts – cause relatively little improvement with supplementary oxygen and are found in conditions such as pulmonary hypertension and cyanotic congenital heart disease
- Tissue hypoxia – when oxygen transport is reduced below a critical level (i.e. below the metabolic demand), at which point metabolism must be maintained anaerobically or tissue metabolic rate must be reduced. Evaluation of tissue oxygenation is imprecise, and includes:
  - Mixed venous saturation – identifies global tissue hypoxia but local tissue hypoxia can exist with a normal mixed venous saturation
  - Blood lactate levels – but may be elevated in the absence of tissue hypoxia, e.g. sepsis
  - Fractional oxygen extraction (FOE) – increases with compromised oxygen transport to organs and tissues and can be measured using near-infrared spectroscopy (NIRS). It is now also possible to measure regional tissue oxygen saturation using new NIRS methods.

Fetal haemoglobin (HbF) has higher oxygen affinity and lower p50 (oxygen tension at which 50% of

haemoglobin is saturated at standard pH and temperature). This favours oxygen uptake from placenta to fetus, as adequate transport of oxygen is achieved at relatively low pO_2. However, the high oxygen affinity of HbF has a disadvantage in oxygen delivery to the fetal tissue, but this is offset to some extent by the fact that dissociation of oxygen from haemoglobin can occur with a relatively small decrease in oxygen tension at the tissue level.

Changes in both oxygen affinity and oxygen-carrying capacity occur postnatally, and in an infant born at term, p50 reaches adult levels by about 4–6 months of age.

Indices of oxygenation

Different indices have been used to describe oxygenation at tissue level, but there is no significant difference in their efficacy in predicting death and adverse respiratory outcome. Oxygenation index (OI) is most frequently used clinically as well as in research studies, and is calculated as:

$$OI = \text{mean airway pressure (cmH}_2\text{O)} \times FiO_2$$
$$\times 100/PaO_2 \text{ (mmHg)}$$

Monitoring of tissue oxygenation

Pulse oxygen saturation (pulse oximetry) is the most user-friendly method and is therefore used most frequently for monitoring oxygen therapy (see Chapter 3, History and examination, for more details). However, it has a major limitation in preterm infants – its failure to detect hyperoxia.

Hypoxia may be associated with hypercarbia ($PaCO_2 > 6.5$ kPa or > 55 mmHg), where:

$$PaCO_2 = CO_2 \text{ production/alveolar ventilation}$$

$$\text{Alveolar ventilation (L/min)} = (\text{tidal volume} - \text{dead space}) \times \text{frequency}$$

Respiratory failure associated with hypercarbia will occur, therefore, in situations associated with reduction in tidal volume (VT) and/or frequency. Ventilatory failure resulting in hypercarbia occurs in conditions associated with:

- Reduced central drive
- Impaired ventilatory muscle function
- Increased respiratory muscle workload
- Intrinsic (inadvertent) positive end expiratory pressure (PEEP)
- Diffusion abnormalities affecting alveolar–capillary interface

Artificial respiratory support

Artificial respiratory support can be provided in a variety of ways, which can be classified as:

- Non-invasive respiratory support
- Mechanical ventilation via a tracheal tube

In either method, the respiratory support can be given as a single level support, such as in CPAP (continuous positive airway pressure) or HFNC (high flow nasal cannula). These are essentially a form of distending pressure and do not provide mechanical breaths. Therefore, these methods are suitable only for those babies who are breathing spontaneously and have sufficient central drive. On the other hand, if babies are not breathing spontaneously and show signs of respiratory failure they require intermittent positive pressure ventilation either via a tracheal tube or nasal prong.

Question 11.8

The principles of mechanical ventilation

From the following list, select ONE answer only. The time constant is:

A. Equal to the airway compliance divided by the airway resistance
B. Higher in babies with stiff lungs
C. Made shorter by downsizing the endotracheal tube
D. The time taken for alveolar pressure to reach 95% of the airway pressure
E. Typically shorter in infants with RDS than in those with normal lungs

Answer 11.8

E. Typically shorter in infants with RDS than in those with normal lungs. See below for discussion.

Principles of mechanical ventilation

The ventilatory needs of a patient depend largely on the mechanical properties of the respiratory system and the type of abnormality in gas exchange. The pressure gradient between the airway opening and the alveoli drives the flow of gases. The pressure gradient necessary for adequate ventilation is largely determined by compliance and resistance.

Compliance describes the elasticity or distensibility of the lungs or respiratory system (lungs plus chest wall), and is calculated as compliance = volume/pressure.

Compliance in infants with normal lungs ranges from 3 to 5 mL/cmH$_2$O/kg. Compliance in infants with RDS is lower and often ranges from 0.1 to 1 mL/cmH$_2$O/kg.

Resistance describes the ability of the gas-conducting parts of the lungs or respiratory system (lungs plus

chest wall) to resist airflow. It is calculated as resistance = pressure/flow. Resistance in infants with normal lungs ranges from 25–50 cmH$_2$O/L/second. Resistance is not markedly altered in infants with RDS but can be increased to 100 cmH$_2$O/L/second or more by small endotracheal tubes.

The time constant is the time (milliseconds) necessary for the alveolar pressure (or volume) to reach 63% of a change in airway pressure (or volume). It is calculated as time constant = compliance × resistance. Duration of inspiration or expiration equivalent to 3 to 5 time constants is required for a relatively complete inspiration or expiration. Thus, in an infant with a lung compliance of 3 mL/cmH$_2$O/kg and resistance of 25 cmH$_2$O/L/second, the time constant is 75 milliseconds and inspiratory and expiratory duration should be around 225 to 375 milliseconds each (or 0.225 to 0.375 seconds), whereas a premature infant with RDS may have a time constant that is much shorter enabling inspiratory times of less than 0.2 seconds to be effective. The time constant will be shorter if compliance is decreased, as in patients with RDS, or if resistance is decreased. Time constant will be higher if compliance is high, as in large infants with normal lungs, or if resistance is high, as in infants with bronchopulmonary dysplasia.

A number of mechanical ventilation devices are used on the neonatal unit and their nomenclature often causes confusion. Broadly speaking, ventilators can be classified by the variables that are controlled (for example, pressure or volume), as well as those that start (or trigger), sustain (or limit), and end (cycle) inspiration and those that maintain the expiratory support (or baseline pressure).

- *Pressure controller*: This type of ventilator controls airway pressure, making it rise above the body surface pressure (i.e. positive pressure ventilator), or making it fall below the body surface pressure (i.e. negative pressure ventilator).
- *Volume controller*: This type of ventilator controls and measures the tidal volume generated by the ventilator despite changes in loads.
- *Flow controller*: This type of ventilator controls the tidal volume but does not measure it directly. The ventilator is a flow controller if the gas delivery is limited by flow.
- *Time controller*: This type of ventilator controls the timing of the ventilatory cycle but not the pressure or volume. Most high frequency ventilators are time controllers.

Monitoring of ventilated infants

Infants on assisted ventilation require close monitoring to assess the underlying lung pathology, response

to treatment and surveillance for associated complications. Monitoring may be considered in five broad categories:

- Clinical evaluation
- Assessment of gas exchange
- Chest imaging
- Pulmonary function and pulmonary mechanics testing
- Cardiac monitoring with echocardiography and imaging.

Clinical evaluation includes observation for general physical condition and complications of mechanical ventilation, such as gas trapping and air leaks.

Rapid shallow breathing and the presence of subcostal/intercostal retraction may suggest air hunger or increased work of breathing, which can be corrected by augmentation of ventilator parameters. A hyperactive precordium and presence of cardiac murmur may be indicative of a left-to-right shunt through patent ductus arteriosus (PDA). In contrast, right-to-left shunting causing cyanosis and desaturation on pulse oximetry suggests persistent pulmonary hypertension of the newborn (PPHN). Bedside transillumination with a fibre-optic light source applied to the chest wall is a useful and effective way to detect pneumothorax, which may require urgent attention.

Assessment of gas exchange with blood gas assessment must be interpreted in the clinical context, taking into account factors such as work of breathing, recent trends, stage of illness. For example, a PaCO$_2$ of 8.7 kPa (65 mmHg) is a genuine source of concern in an infant in the first few hours of life, but may be perfectly acceptable in an infant who is chronically ventilated for BPD. There is also a wide range of 'normal' blood gas values depending upon gestational age, postnatal age, source (arterial, venous or capillary) and disease status.

Analysis of gas exchange also requires an understanding of respiratory physiology. Oxygenation is dependent on ventilation–perfusion matching, whereas elimination of CO$_2$ from the blood into the alveoli is dependent on alveolar ventilation (tidal volume × respiratory rate). The pH of arterial blood is determined primarily by PaCO$_2$, lactic acid (produced by anaerobic metabolism) and buffering capacity, particularly serum or plasma bicarbonate and plasma haemoglobin concentration.

In the healthy term infant, the base deficit is usually 3 to 5 mEq/L. However, base deficit can vary widely. In babies with a base deficit between 5 and 10 mEq/L, assuming reasonable tissue perfusion, no acute intervention is needed. However, a base deficit of >10 mEq/L should prompt a careful assessment for evidence of hypoperfusion. Usually, correcting the underlying

cause of metabolic acidosis is more effective and less dangerous than administering sodium bicarbonate.

Chest radiography is the most commonly used imaging modality on neonatal intensive care units, both for diagnosis and following the course of the disease process. However, the specificity of chest radiography is poor and should always be interpreted in context with the clinical information. The findings on chest radiographs are mostly suggestive of pathology rather than being diagnostic.

Pulmonary function and pulmonary mechanics testing using the pulmonary graphics on the ventilator can help clinicians in determining dynamic compliance, airway resistance, inspired and expired tidal volumes, etc., in real time and forms a useful tool in practising 'gentle ventilation' with a view to minimizing ventilator induced lung injury (VILI).

Cardiac monitoring with echocardiography and imaging is helpful to confirm the diagnosis of patent ductus arteriosus and assess ductal shunting, to identify PPHN and congenital heart disease.

Question 11.9

Jaundice

A term baby presents with clinically very severe jaundice at day 3 of life. He is irritable. Which ONE of the following treatments is most likely to increase his risk of kernicterus?

A. Ceftriaxone

B. High flow nasal cannula oxygen

C. Immediate provision of phototherapy

D. Intravenous fluid bolus (0.9% sodium chloride solution)

E. Paracetamol

Answer 11.9

A. Ceftriaxone.

This will displace bilirubin from albumin and increase the risk of kernicterus. Whilst paracetamol will not cause a problem, ibuprofen might (see below).

Jaundice

Jaundice is common in the neonatal period. Over 60% of term and 80% of preterm infants develop jaundice in the first week, and up to 10% of breastfed infants are still jaundiced at 1 month. Neonatal jaundice is important because:

- It may indicate an underlying disease such as infection, haemolytic anaemia, liver and metabolic disease

- Severe unconjugated hyperbilirubinaemia can lead to neonatal encephalopathy and long-term neurodevelopmental problems

Bilirubin encephalopathy

Acute bilirubin encephalopathy or bilirubin-induced neurologic dysfunction (BIND) is used to describe the acute clinical CNS manifestations of bilirubin toxicity. It is caused by free bilirubin in the blood (unconjugated fraction of bilirubin unbound to albumin). Kernicterus was originally used to describe the histologic findings of bilirubin toxicity within the brain that include staining and necrosis of neurons. Key areas involved include basal ganglia (particularly the globus pallidus and subthalamic nuclei), nuclei of oculomotor, vestibulocochlear and facial cranial nerves, cerebellar nuclei (particularly the dentate), and anterior horn cells of the spinal cord, but the cerebral cortex is usually spared. Overall there is good correlation between yellow staining and the distribution of neuronal necrosis. However, the brainstem nuclei and the basal ganglia involvement is more obvious clinically.

Factors that increase the risk of bilirubin neurotoxicity include:

- High levels of free bilirubin either due to low albumin or high bilirubin–albumin ratio, abnormal bilirubin–albumin binding or competitive displacement by certain drugs (ceftriaxone, salicylates, ibuprofen, aminophylline)
- Disruption of the integrity of the blood–brain barrier due to sepsis, meningitis, seizures, shock, hypoxia–ischaemia
- Hypercapnoea, hyperosmolality, acidosis

The threshold when bilirubin toxicity occurs depends on coexisting risk factors, but the risk is increased when:

- Serum bilirubin level is >340 μmol/L in term infants
- Rate of rise of serum bilirubin is >8.5 μmol/L/ hour.

The mechanism of bilirubin neurotoxicity remains uncertain. The passage of bilirubin across the blood–brain barrier is thought to be a dynamic and potentially reversible process. Hypercapnoea leads to vasodilatation and increased cerebral blood flow and lower pH, thus increasing both influx and efflux of free bilirubin across it and results in high-level but brief exposure. This contrasts with hyperosmolality which slows the efflux but not the influx of bilirubin, so causes a longer low level exposure.

The initial signs of acute bilirubin encephalopathy are lethargy, hypotonia and decreased suck. This is

followed by an intermediate phase characterized by stupor, irritability, hypertonia manifested by arching of the neck and of the trunk (opisthonus) and a high-pitched cry. Without intervention, this is followed by coma, fever, apnoea, seizures and sometimes death. If infants with advanced encephalopathy survive, they may develop the cardinal clinical features of kernicterus: choreoathetoid type of cerebral palsy, sensorineural deafness, gaze abnormality (particularly upward gaze) and dental enamel dysplasia.

Answer 11.10

C. Carbon monoxide (see below).

All of these volatiles can be measured on the breath and may be elevated in respiratory failure (carbon dioxide), liver failure (ammonia), asthma in older children (nitric oxide) or Pseudomonas infection (hydrogen cyanide).

Bilirubin metabolism

This shown in Figure 11.9. Understanding it provides a rational basis of the causes of neonatal jaundice.

i. Production of unconjugated (indirect) bilirubin

Bilirubin is produced by the breakdown of haem that is present in haemoglobin, myoglobin and cytochromes. Eighty per cent of bilirubin is derived from haemoglobin. Each molecule of haem produces one molecule of bilirubin. Red cell breakdown is increased by the high concentration of haemoglobin at birth (150–220 g/L) in response to the relative hypoxic environment of the fetus. The increased oxygen concentration in postnatal life induces breakdown of haemoglobin. The neonatal production rate of bilirubin is 100–120 µmol/kg/day as compared to

Question 11.10

Bilirubin metabolism

Which ONE of the following volatiles is a useful biomarker of bilirubin production?

A. Ammonia
B. Carbon dioxide
C. Carbon monoxide
D. Hydrogen cyanide
E. Nitric oxide
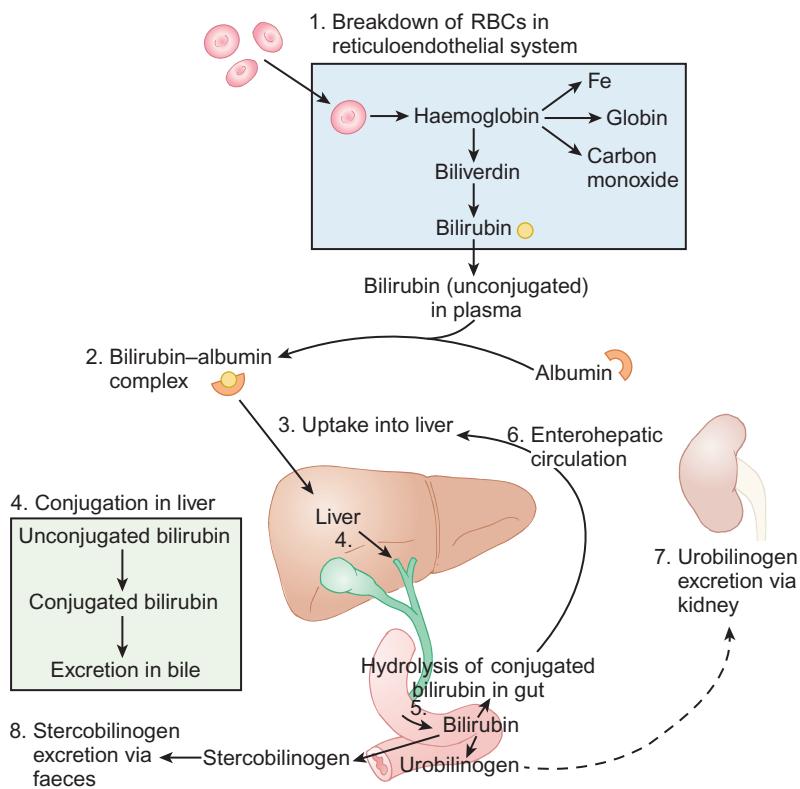
Fig. 11.9 Bilirubin metabolism.

adult production of 50–70 μmol/kg/day. In addition, fetal haemoglobin has a shorter half-life than adult haemoglobin. Neonatal red cell mass is also increased by delayed cord clamping.

The haem molecule is broken down in reticulo-endothelial cells to biliverdin by the enzyme haem oxygenase. Biliverdin is converted into bilirubin by biliverdin reductase enzyme.

Released iron is used in haem synthesis again. An equimolar amount of carbon monoxide (CO) is also released. Between 80% and 90% of endogenous CO is derived from haem. This end-tidal CO is a surrogate measurement for bilirubin production.

Red cell breakdown produces unconjugated (indirect) bilirubin, which is mostly bound to albumin.

ii. CNS toxicity

If the albumin binding capacity of exceeded, free bilirubin is released into the circulation. As this is lipid soluble, it can cross the blood–brain barrier and result in acute encephalopathy or kernicterus.

iii. Uptake by liver cells

Unconjugated bilirubin, bound to albumin, is transported to the liver for conjugation. The albumin–bilirubin compound is dissociated and the bilirubin is transported into hepatocytes. This process is mainly passive but is dependent on certain transporter proteins.

iv. Conjugation in the liver

Bilirubin is bound to cytosolic proteins known as glutathione S-transferases or ligandins within hepatocytes. Conjugation of bilirubin by uridine diphosphate glucuronyltransferase (UGT) enzyme mainly produces bilirubin diglucuronide but also some bilirubin monoglucuronide.

v. Excretion of bilirubin and enterohepatic circulation

Excretion of conjugated bilirubin into the biliary system is an active and energy-dependent process mediated by specific carrier proteins. Conjugated bilirubin is water-soluble and therefore cannot cross the blood–brain barrier. Most of the conjugated bilirubin excreted in the bile is hydrolysed back to unconjugated bilirubin by β-glucuronidase present in the intestinal mucosa. This is then reabsorbed in the terminal ileum and transported back to the liver via the portal circulation. This enterohepatic circulation plays an important role in bilirubin metabolism by allowing bile acids to be recycled. Active enterohepatic circulation is due to prolonged gut transit time, delayed passage of meconium, poor enteral feeding, prematurity or antibiotic treatment. Some of the

conjugated bilirubin is converted to stercobilinogen by colonic bacteria. This is further oxidized to stercobilin, which give faeces its brown colour. A small amount of reabsorbed urobilinogen (about 5%) is excreted in the urine following further oxidation to urobilin, which gives urine its colour.

Pathogenesis

The causes of hyperbilirubinaemia are listed in Box 11.3.

Physiological jaundice

Physiological jaundice refers to the common, generally harmless unconjugated hyperbilirubinaemia seen

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Box 11.3 Causes of hyperbilirubinaemia

1. Increased bilirubin production due to high red cell turnover

- High haemoglobin and red cell mass at birth and short RBC lifespan
- Polycythaemia
- Immune haemolysis due to Rh/ABO/other isoimmunization
- RBC enzyme defects – glucose-6-phosphate dehydrogenase (G6PD) and pyruvate kinase (PK) deficiency
- RBC membrane abnormalities – hereditary spherocytosis and elliptocytosis
- Other causes of haemolysis, e.g. sepsis
- Haematomas – extensive bruising, cephalhaematoma
- Maternal diabetes

2. Delayed bilirubin clearance (conjugation, biliary excretion, and faecal/urinary elimination)

- Poor uptake of bilirubin by hepatocyte – Gilbert's syndrome
- Decreased activity of glucuronyltransferase enzyme (genetic – Crigler–Najjar syndrome, hypoxia, infection, thyroid deficiency, hypothermia, prematurity)
- Drugs needing conjugation for excretion – compete for transferase enzymes
- Increased enterohepatic circulation – prolonged gut transit time, delayed passage of meconium, poor enteral feeding, prematurity or antibiotic treatment

3. Conjugated hyperbilirubinaemia

- Congenital infections
- Neonatal hepatitis
- Obstructive – biliary atresia, choledochal cyst
- Parenteral nutrition induced cholestasis

in a high proportion of newborn babies in the first weeks of life and for which there is no underlying cause. The cord blood level of unconjugated bilirubin is normally 20–35 μmol/L and usually rises at less than 85 μmol/L/day. Jaundice becomes clinically apparent when serum bilirubin is 80–90 μmol/L on day 2–3, and peaks on day 4–5. Peak jaundice is on day 7–8 in preterm infants.

Breastfed babies are more likely to develop physiological jaundice than formula-fed infants. Its pathogenesis is unclear. Proposed mechanisms include:

- Increased β-glucuronidase in breast milk can increase enteric absorption of bilirubin and hence the hepatic bilirubin load
- High free fatty acid in breast milk may compete for albumin binding sites for transport to liver
- Certain factors in breast milk may inhibit the enzyme responsible for conjugation in liver.

An additional but separate reason is inadequate milk intake, when sluggish gut action leads to an increase in the enterohepatic circulation of bilirubin. Formula-fed babies have lower bilirubin levels due to increased clearance of bilirubin from the gut.

Jaundice in term infants usually resolves by 2 weeks of age; by 3 weeks in preterm infants. However, it may persist for 4–10 weeks in some breastfed infants. Breastfeeding should be continued irrespective of the bilirubin levels.

Haemolytic disease of the newborn (Rh or ABO incompatibility)

In Rhesus haemolytic disease there is incompatibility of the Rh blood group (D, c or Kell antigens) between the mother and fetus. It may occur when a Rhesus-negative mother has a Rhesus-positive fetus, the child having inherited the antigen from the father. The mother develops antibodies in her blood stream against fetal red cells which are IgG and can cross the placenta causing fetal red cell haemolysis. This may cause jaundice, anaemia, hydrops and hepatosplenomegaly. It usually occurs in a second or subsequent pregnancy, as the mother needs to be sensitized to the Rhesus-positive antigen, which usually occurs during her first pregnancy due to feto-maternal haemorrhage (usually during delivery, but also miscarriage, placental abruption, amniocentesis or chorionic villous biopsy). It may occasionally occur with the first pregnancy if the mother has been sensitized, e.g. from blood transfusion and occasionally during normal pregnancy.

Prenatal management is with monitoring of antibody levels and referral to a specialist centre if indicated. Fetal rhesus genotype can now be determined non-invasively by cell free fetal DNA analysis in maternal serum. Fetal anaemia can be monitored with serial ultrasound scanning of middle cerebral artery Doppler waveform and measurement of fetal haematocrit from cordocentesis. Intrauterine blood transfusion may be given if necessary. The Rhesus D-positive infant will need close bilirubin and haemoglobin monitoring after birth, as the bilirubin level may rise very rapidly to dangerously high levels.

Rhesus D alloimmunization has become rare as maternal blood group and antibody status is routinely tested and if Rhesus negative mothers are given anti-D IgG immunoglobulin, which clears any fetal red blood cells (RBCs) that may have leaked into the maternal circulation. In developed countries, this has transformed Rhesus D disease from a major neonatal problem to one that is very uncommon. Most cases of alloimmunization are now anti-Kell and anti-c, which usually results in much less severe fetal anaemia and hyperbilirubinaemia.

Haemolytic disease of the newborn can also be caused by an ABO blood group incompatibility. It arises when a mother with blood type O has a fetus with a different blood type (type A, B, or AB). The mother's serum may contain anti-A and anti-B IgG antibodies, which can cross the placenta and haemolyse fetal RBCs. The hyperbilirubinaemia is less severe than Rh incompatibility as fetal RBCs express low ABO blood group antigens compared with adult levels. Onset of haemolysis and jaundice is after birth. Direct antibody test is positive.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked recessive disorder characterized by low levels of glucose-6-phosphate dehydrogenase, the enzyme involved in red blood cell metabolism. This is the most common cause of severe neonatal jaundice and kernicterus worldwide. Due to its X-linked inheritance, males are mainly affected, however carrier females may have a milder form as a result of lyonization. Those affected tend to be Mediterranean or Middle or Far Eastern or African in origin. They may develop haemolytic anaemia in response to a number of stressors, e.g. infection, certain medications, fava beans when older. It is diagnosed by measuring G6PD activity in red blood cells. (See also Chapter 23, Haematology and Chapter 21, Hepatology).

Crigler–Najjar (type 1 and 2) syndrome is due to deficiency of enzyme uridine diphosphate glucuronyltransferase (UGT). It is inherited as an autosomal recessive disorder and is described in Chapter 21, Hepatology. Both types present in the early neonatal period with a rapid rise in serum bilirubin to very high levels despite phototherapy. Kernicterus can develop. Type 1 is more severe, with peak bilirubin levels rising up to 850 μmol/L.

Gilbert's syndrome is thought to be a contributory factor in some infants with severe unconjugated

hyperbilirubinaemia. It is common, with 5–10% of the population being homozygous and about 40% heterozygous (see also Chapter 21, Hepatology).

Clinical assessment

Jaundice first appears in the sclera and face and progresses cephalocaudally, appearing last on the feet and soles. Examination of blanched skin in natural light may be helpful. It is more difficult to detect in preterm and dark-skinned infants. An infant who is not jaundiced clinically is unlikely to have significant hyperbilirubinaemia. However, once an infant becomes jaundiced, its severity cannot be reliably assessed by clinical examination and term infants who become jaundiced should have transcutaneous bilirubin measured.

The transcutaneous bilirubinometer can be used in babies of 35 weeks' gestation or more after 24 hours of age. It uses multiwavelength reflectance. There is good correlation with serum bilirubin level (correlation coefficient of 0.9) up to 250 μmol/L. It is a useful screening tool and can be helpful in community and postnatal wards.

A serum measurement should be obtained if:

- The infant is jaundiced and is <24 hours old
- Transcutaneous bilirubinometer measurement is >250 μmol/L
- Transcutaneous bilirubinometer (TcB) is not available
- The infant is jaundiced and is ≤35 weeks' gestational age
- The infant is on or has had phototherapy – as this lowers the cutaneous bilirubin levels more readily than serum bilirubin

Case history

An infant with birth weight of 3.6 kg at 37 weeks is discharged home, breastfeeding, at 18 hours. She is not jaundiced.

Is monitoring for jaundice indicated? This is considered below.

Monitoring for jaundice

The risk of developing significant hyperbilirubinaemia is increased if:

- Birth gestation is <38 weeks
- There is a history of jaundice requiring phototherapy in a sibling
- Visible jaundice develops in the first 24 hours after birth
- Exclusive breastfeeding.

Infants with any of these risk factors, such as the infant described in the Case history should have a clinical examination for jaundice before 48 hours of age; if present, it should be checked with a transcutaneous bilirubinometer measurement.

Visible jaundice in the first 24 hours of life is a risk factor for later significant hyperbilirubinaemia. A serum bilirubin >102 mmol/L in the first 24 hours of life is predictive of serum bilirubin of >290 mmol/L on days 3–5.

Predischarge transcutaneous bilirubin plotted on hour-specific nomograms has good accuracy in predicting subsequent hyperbilirubinaemia. However, significant hyperbilirubinaemia is not predicted by umbilical cord blood bilirubin or direct antiglobulin testing, nor by end-tidal CO measurement, though this shows good negative predictive value.

Investigations

Investigations to determine the cause of jaundice should be performed if:

- It appears within the first 24 hours
- Rate of rise is more than 85 μmol/L/day or 8.5 μmol/L/hour
- The serum bilirubin is more than 200 μmol/L after 72 hours of age in term infants
- Jaundice persists beyond 14 days in term and 21 days in preterm infants
- Conjugated fraction is more than 35 μmol/L at any time

The initial investigation should include:

- Serum bilirubin
- Haematocrit
- Blood group and Rh type of mother and baby
- Direct agglutination (Coombs) test – the result should be interpreted taking account of the strength of reaction and whether the mother received prophylactic anti-D Ig during pregnancy.

Investigations to determine the underlying pathology should include:

- Full blood count
- Peripheral blood film
- Sepsis work-up to include culture of blood, urine, and cerebrospinal fluid (as indicated)
- G6PD levels depending on ethnicity of parents.

Treatment

The type of treatment depends on the bilirubin level and its rate of rise, gestational age, and if other risk factors are present. Current treatment thresholds are based on consensus guidelines (NICE 2010 and AAP) and are not evidence-based.

The albumin–bilirubin ratio is not used as most laboratories overestimate albumin, especially at low

concentrations. Also, management is based on total bilirubin measurements. Conjugated bilirubin is not subtracted from total serum bilirubin. There are rare cases of kernicterus with high conjugated bilirubin levels and a theoretical risk that conjugated bilirubin can elevate free bilirubin levels by displacing unconjugated bilirubin from the binding sites.

Phototherapy

This works through geometric photoisomerization of unconjugated bilirubin (4Z, 15Z isomer). The light of a specific wavelength (peak 460 ± 10 nm) is used for phototherapy which is absorbed by bilirubin and it undergoes Z to E isomerization. The E-isomer is more polar and water-soluble than the Z-isomer and can be excreted without conjugation. A small amount of structural isomer (lumirubin) is also formed as well as photo-oxidation.

The effectiveness of phototherapy depends upon its wavelength, irradiance (dose of light) 30–40 mwatts/ cm^2/nm, exposed body surface area, distance from light source and duration of treatment. Blue or blue-green light spectrum is most effective (430–490 nm band). Intensive phototherapy is achieved by using more than one light source with blue or blue-green spectrum bulbs held at a close distance from well-exposed body. This maximizes the effectiveness of phototherapy by increasing irradiance. With increased use of LED lights that have a lower heat output, insensible water loss is less of an issue than it was in the past.

Pharmacological treatment of jaundice

Phenobarbitone

Phenobarbitone induces hepatic UGT enzyme and hence the conjugation of the bilirubin. It may also increase the hepatic uptake of bilirubin. However, it acts very slowly and does not lower serum bilirubin levels fast enough to be clinically helpful.

Metalloporphyrins

Tin and zinc protoporphyrins inhibit haem oxygenase, which is the rate-limiting step in the production of bilirubin from haem. They are under investigation for clinical use and currently not recommended.

Intravenous immunoglobulin

High-dose intravenous immunoglobulin (IVIG) has been shown to be effective in reducing the bilirubin levels and reduces the need for exchange transfusion in neonates with Rhesus or ABO immune haemolytic disease. It is used as an adjunct to intensive phototherapy if the serum bilirubin continues to increase more than 8.5 μmol/L/hour. In isoimmune haemolysis, red blood cells are destroyed by an antibody-dependent cytotoxic mechanism mediated by Fc

receptor-bearing cells of the neonatal reticuloendothelial system. The mechanism of IVIG action is non-specific blockade of Fc receptors, which reduces red cell breakdown. Maternal IVIG administration also reduces fetal haemolysis.

Exchange transfusion

This is performed to reduce severe hyperbilirubinaemia to prevent kernicterus, to remove haemolytic antibodies and correct anaemia. It involves removing aliquots of neonatal blood and replacing it with donor blood. The serum bilirubin concentration is usually reduced by 50% after a double volume exchange transfusion. The need for exchange transfusion has been markedly reduced by prevention or prenatal treatment of Rhesus disease and early treatment of jaundice with phototherapy. When required, there is a morbidity of 5% and mortality of 0.3% from biochemical and haematological disturbances, vascular accidents, cardiac complications and sepsis.

Infection

Infection in the newborn can be divided into three broad categories according to the time during pregnancy or postnatally when the infection is acquired or presents:

- Congenital (see Chapter 10, Perinatal medicine)
- Early-onset (<72 hours after birth)
- Late-onset (>72 hours after birth)

Newborn infants are particularly vulnerable to bacterial infection because of their immature immune

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Question 11.11

Early-onset group B streptococcal infection

Regarding early-onset group B streptococcal (GBS) infection, which of the following babies is MOST at risk? Select ONE answer only.

A baby born at:

A. 32 weeks' gestation with intrapartum antibiotic prophylaxis

B. 34 weeks' gestation without intrapartum antibiotic prophylaxis

C. Term following prolonged rupture of membranes without intrapartum antibiotic prophylaxis

D. Term following maternal intrapartum fever of 38.3°C with intrapartum antibiotic prophylaxis

E. Term following a positive GBS swab during a previous pregnancy without intrapartum antibiotic prophylaxis

B. 34 weeks' gestation without intrapartum antibiotics prophylaxis.

Prematurity overrides all other risk factors. The risks for each scenario are given in Table 11.4.

system. They are more dependent on their non-specific innate immune system than older infants because their adaptive immune system is both immunologically naïve and is relatively slow to function with overall reduced T-cell, B-cell and neutrophil function.

Neonates are particularly susceptible to pathogens with polysaccharide capsules, such as group B streptococcus (GBS) and E. coli because they have relatively low levels of complement and impaired opsonization. Overall activity of the alternative complement pathway is diminished and classical complement pathway activation cannot take place due to lack of specific antibodies.

Early-onset infection

The infant is exposed to bacterial organisms from maternal ascending infection or during passage through the birth canal. By far the commonest cause is GBS infection, but Gram-negative organisms and occasionally *Listeria monocytogenes* and *Staphylococcus* are other pathogens.

Maternal risk factors for early-onset infection are:

- Group B streptococcal (GBS) colonization or bacteriuria during pregnancy
- Prolonged rupture of membranes (>18–24 hours)
- Preterm prolonged rupture of membranes (<37 weeks' gestation)
- Prolonged labour (>12 hours)
- Maternal sepsis or chorioamnionitis (temperature >38°C, leucocytosis, tender uterus, purulent liquor)

- Frequent pelvic examinations
- History of early-onset GBS sepsis in previous infant.

The risk of early-onset infection in an infant can be assessed according to the presence of maternal risk factors and clinical indicators, some of which are considered to be 'red flag' (NICE Neonatal Sepsis guidelines, 2012).

Group B streptococcus sepsis

GBS sepsis has a fatality rate of up to 6% in term but up to 20% if preterm. In the UK, GBS colonization rate in pregnant women is 21%, however early-onset infection only occurs in fewer than 1% of colonized women and the overall incidence of early-onset infection is 0.5 per 1000 live births. Universal screening of pregnant women for GBS colonization is currently practised in the US, Canada, and Australia and intrapartum antibiotic prophylaxis (IAP) given to colonized mothers between 35 and 37 weeks' gestation (or before this if in labour). This approach has led to significant reduction in culture positive early-onset disease and sepsis-related mortality in the first week in the US. Late-onset disease has been unaffected. However, this approach is controversial and currently less than 1% of UK maternity units practise universal screening. In the UK, a risk factor-based approach has been adopted (to give intrapartum antibiotic prophylaxis if there is a history of invasive GBS infection in a previous baby, GBS bacteriuria or positive vaginal swab in the current pregnancy, pyrexia (>38°C) in labour or chorioamnionitis, but not if delivering by pre-labour lower segment caesarean section with intact membranes).

The risk of early-onset group B streptococcal disease with individual antenatal risk factors is shown in Table 11.4. The presence of a single risk factor increases the risk of proven sepsis by 1% and in isolation is not an indication to start antibiotics or undertake a full sepsis

Table 11.4 Risk of early-onset GBS sepsis (EOGBS) with individual antenatal risk factors, with and without intrapartum antibiotic prophylaxis (IAP)

Risk factor	Risk of EOGBS disease if IAP not given	Risk of EOGBS disease if full IAP given	Risk of death from EOGBS disease if IAP not given	Risk of death from EOGBS disease if full IAP given
Intrapartum fever (>38°C)	1:189	1:943	1:1783	1:8915
Prolonged rupture of membranes (>18 hours) at term	1:556	1:2777	1:9754	1:48,772
Prematurity (<37+0 weeks of gestation)	1:435	1:2173	1:2377	1:11,885
Prematurity (<35+0 weeks of gestation)	1:357	1:1786	1:1566	1:7829
Positive GBS swab in a previous pregnancy	1:1105	1:5525	1:10,424	1:52,122
Positive GBS swab in current pregnancy	1:434	1:2170	1:4094	1:20,471

Source: RCOG green top guideline 36, 2nd edition, 2012.

screen. The presence of two risk factors increases the risk by 5%, and three risk factors increases the risk to 25 times above the baseline. Some are considered major risk factors (maternal septicaemia or chorioamnionitis or GBS bacteriuria, invasive GBS infection in a previous infant). Antepartum antibiotics are given to the mother based on the risk factors described above.

Data from an infection surveillance network in the UK showed that 94% of infants with early-onset disease present on day 1. Two thirds have one or more risk factors before or during labour. A significant proportion have signs of fetal distress, an emergency delivery and low Apgar scores. The majority present with sepsis (79%), 12% have meningitis, 8% pneumonia and 1% focal infection.

Diagnosis of sepsis is confirmed on blood culture. It is recommended that at least 1 mL of blood should be added to the culture medium, as a smaller blood sample volume reduces the test sensitivity.

Undertaking lumbar puncture (LP) as a routine part of full septic screen remains controversial. The overall incidence of neonatal meningitis is low (0.25/1000 live births). However, up to 23% of neonates with bacteraemia have meningitis and a negative blood culture does not rule out meningitis. It is therefore recommended to only perform a lumbar puncture in infants with clinical and laboratory tests suggestive of sepsis, those with clinical deterioration on antibiotic treatment, and those with a positive blood culture. Routine lumbar puncture in the absence of any of the above is only likely to yield a positive result 1 in 1000 cases and is not recommended. The diagnosis of meningitis is important, as a prolonged course of antibiotic treatment is indicated.

A raised C-reactive protein (CRP) depends on an inflammatory response with the release of IL-6 and is rarely helpful in the initial evaluation of possible infection. In early-onset sepsis, a single raised CRP 24 hours into illness has a 93% sensitivity for 'probable' sepsis. Particularly helpful is a negative (<10 mg/L) result after 18–24 hours as it is 99% predictive of a non-infected infant. It has also been used to guide the duration of antibiotic treatment in neonatal sepsis but there is no evidence that this approach is any better than giving antibiotics for a set number of days. The NICE guidelines (2012) are to consider stopping antibiotics at 36 hours if the CRP concentration and trend is reassuring, blood culture is negative, risk factors for infection were not strong and the baby has no clinical indicators for infection.

There is no added value from routine superficial swabs or gastric aspirates, so they should not be taken. Management relies on early recognition from high levels of clinical suspicion and prompt initiation of antibiotics and supportive treatment. The use of intravenous immunoglobulin as adjunctive therapy is of no proven benefit in neonatal sepsis or meningitis (International immunotherapy study, INIS).

Late-onset infection

In contrast to early sepsis, which is acquired vertically from the mother, this is nosocomial (hospital-acquired) or community-acquired infection from the environment or caregivers. Group B streptococcal infection is still by far the commonest cause in term infants. It is more often associated with meningitis than early-onset sepsis and causes recurrent infections in 1% of cases.

Coagulase negative staphylococcus (CONS) is the most common cause of late-onset sepsis in VLBW infants. It is known to produce a biofilm that facilitates adherence to lines and catheters and diminishes host immune response and antibiotic effectiveness.

Strategies to reduce late-onset sepsis in preterm infants include:

- Strict infection control measures, including strict compliance with hand hygiene
- Scrupulous asepsis during invasive procedures, including insertion and subsequent care of central lines and catheters
- Minimizing breaches of skin integrity with electrodes, tape, venepuncture, heel pricks, etc.
- Judicious use of parenteral nutrition, as prolonged use increases infection risk as it requires central vascular access and intralipids enhance the growth of lipophilic organisms as they impair the phagocytic function of white cells
- Promotion of enteral feeding with mother's milk
- Rational use of antibiotics – curtailing the use of broad-spectrum antibiotics as they encourage the emergence of antibiotic resistance and fungal sepsis. Antibiotic choice should be narrow spectrum and guided by culture sensitivity results
- Limiting dexamethasone and H_2 blocker therapy.

The newborn gut plays an important role in the development of normal immune defences through a complex interaction between gut flora and mother's milk with secretory IgA and other immunological factors and gut-associated lymphoid tissue. The establishment of normal gut flora following vaginal birth and breastfeeding is thought to protect against invasion of gut mucosa by pathogenic organisms. Gut colonization is abnormal following caesarean section, formula milk feeding and antibiotic treatment. This is the rationale behind the use of pre- and probiotics as well as other immunological components, such as lactoferrin to reduce neonatal sepsis and necrotizing enterocolitis in preterm infants. However, whilst breast milk is protective against sepsis and necrotizing

enterocolitis, a causal link between altered gut flora and neonatal sepsis remains to be established. Although many studies have been conducted, probiotics have not been adopted for standard use as different bacterial components have been used in various preparations and they have not been shown to be beneficial.

Herpes simplex virus infection

Herpes simplex virus (HSV) infection is uncommon, with an incidence of only 2–30 per 100,000 live births, but is one of the most serious infections in the newborn. The risk of infection is high (25–60%) if the mother has primary infection at delivery, as the infant is exposed during passage through the infected birth canal and the infant will not have received passively-acquired maternal antibody. The risk is low (2%) for mothers with recurrent HSV infection or where primary infection has happened well before delivery. There is also a small risk of infection from a parent or caregiver with cold sores. Scrupulous hand hygiene will reduce this risk.

In the majority of neonates with HSV infection, the mother is asymptomatic or becomes unwell but the condition is not diagnosed. If diagnosed, risk of transmission may be reduced by delivery by caesarean section, maternal aciclovir (acyclovir) therapy and avoidance of invasive obstetric procedures during delivery (mechanically-assisted deliveries, fetal scalp electrodes). The portal of entry may be through skin, eyes or mouth and this can disseminate to the brain and other organs.

There are three modes of presentation:

- Localized – skin manifestations with a rash or conjunctivitis or mouth, usually presents in the second week of life with vesicles; this is the mildest form, prognosis is generally good but neurodevelopmental complications may arise.
- Encephalitis – carries 10–15% mortality
- Systemic – presents at 10–12 days with respiratory failure, circulatory collapse, shock and deranged clotting. May also be accompanied by encephalitis. Mortality is up to 50%, with a high neurodisability rate amongst survivors.

Early suspicion and antiviral treatment with intravenous aciclovir and supportive care remains at the core of clinical management. Vesicles are present in only two thirds of those with systemic disease or encephalitis, which often delays diagnosis. Diagnosis is made with PCR of blood, CSF or local lesions.

Infants born by vaginal delivery in mothers with primary HSV infection at the time of delivery are at greatest risk and empirical treatment with intravenous aciclovir is recommended until active infection is ruled out. In contrast, infants delivered by caesarean section are observed but no active treatment is indicated. Similarly, for infants born to mothers with recurrent HSV with or without active lesions at delivery, no active treatment is recommended unless the infant becomes symptomatic.

Glucose homeostasis and hypoglycaemia

Glucose is the primary fuel for the brain. Neonates have a threefold greater glucose requirement than adults because of their larger brain to body size ratio. To meet these needs, they have higher hepatic glucose production rates of up to 6 mg/kg/minute.

Energy metabolism in the newborn involves three processes:

- Glycogen production and glycogenolysis mainly in the liver and muscle. Liver glycogen is rapidly available for breakdown to glucose.
- Gluconeogenesis, the process of glucose synthesis from substrates such as amino acids, lactate, pyruvate and glycerol.
- Lipolysis, the breakdown of lipids into fatty acids and triglycerides, which can then be metabolized to ketone bodies, an important substrate for the brain.

Glycerol metabolized from adipose tissue can be directly utilized through gluconeogenesis. Glucose homeostasis involves close control from endocrine hormones such as insulin, glucagon, cortisone and growth hormones. Insulin lowers blood glucose by stimulating the formation of glycogen and glucose uptake into tissue cells; glucagon raises blood glucose by stimulating glycogen breakdown.

The fetus does not make glucose from glycogen, and is wholly dependent on glucose via the placenta. It does make glycogen, but the liver stores at term are sufficient for only a number of hours of fasting. At birth, the fetus is disconnected from the continuous supply of glucose and has to adapt to intermittent feeding; glucose levels fall and there is a surge of glucagon and a fall in insulin level. It takes some hours for the newborn baby to switch on gluconeogenesis. During the first few days of life, the infant's food intake is very low, with only a small volume of colostrum, and the baby relies on alternative energy substrates, such as ketone bodies.

Risk factors

At particular risk of transient hypoglycaemia are infants:

- of maternal diabetes mellitus, who have hyperinsulinaemia secondary to their exposure to high blood glucose levels *in utero*

- with decreased glycogen stores (IUGR, preterm, etc.)
- with increased requirements and impaired metabolism (sepsis, etc.)

There is lack of consensus about the definition of hypoglycaemia in the newborn. Severe and prolonged symptomatic hypoglycaemia has poor prognosis in terms of abnormal neurodevelopment or death. An 'operational threshold' of 2.6 mmol/L is generally used, but is the subject of controversy as many normal breastfed infants tolerate lower glucose levels in the first few days of life, as they are able to utilize ketones and other energy substrates, and unnecessary intervention should be avoided. Most babies with hypoglycaemia are asymptomatic but, when present, clinical features include jitteriness, irritability or a high-pitched cry variably accompanied by depressed consciousness, lethargy and hypotonia. Severe hypoglycaemia can result in apnoea, coma and seizures.

Management

Infants with risk factors need to be identified, and hypoglycaemia prevented by provision of energy by enteral (early and frequent feeds) or parenteral route, good temperature control and treatment of any underlying cause, e.g. infection. Their blood glucose should be monitored until it is >2.6 mmol/L. Extra feeds and intravenous glucose infusion may be required to achieve this. Symptomatic hypoglycaemia requires urgent correction and investigation. If hypoglycaemia is identified using a bedside glucometer, laboratory measurement is required as they do not measure low blood glucose levels accurately.

Persistent or symptomatic hypoglycaemia

Prolonged, persistent or refractory hypoglycaemia in the face of glucose intake of over 8–10 mg/kg/min requires detailed investigation. The causes are listed in Table 11.5. At the time of hypoglycaemia, glucose, urea and electrolytes, pH, liver function tests, lactate, pyruvate, free fatty acids and β-hydroxybutyrate, acylcarnitine, ammonia, insulin and c-peptide, cortisol, ACTH and growth hormone should be measured. Definitive diagnostic studies can then be undertaken based on abnormal results of the above tests.

Prolonged and refractory hypoglycaemia due to hyperinsulinism may require insulin suppression with diazoxide, somatostatin analogue (octreotide), pancreatic resection or glucagon. Specific endocrine deficiencies may require hormone replacement therapy. This is described in detail in Chapter 26, Diabetes and endocrinology.

Table 11.5 Causes of hypoglycaemia

Transient	Persistent	
	Reduced glucose availability	Increased glucose consumption
Antenatal: Maternal diabetes mellitus (insulin-dependent or gestational) **Neonatal:** IUGR (intrauterine growth restriction) Large for gestational age Preterm Infection, sick infant Iatrogenic (reduced feeds with inadequate intravenous glucose) Polycythaemia Perinatal asphyxia Rhesus disease Hypothermia	IUGR (intrauterine growth restriction) Prematurity Panhypopituitarism Cortisol deficiency Growth hormone deficiency Glucagon deficiency Accelerated starvation (ketotic hypoglycaemia) Inborn errors of metabolism	Congenital hyperinsulinism Transient neonatal hyperinsulinism Maternal diabetes Persistent hypoglycaemic hyperinsulinism of infancy (PHHI/nesidioblastosis) Beckwith–Wiedemann syndrome Rhesus haemolytic disease Perinatal asphyxia

Fluid, electrolytes, feeding and nutrition

Fluid distribution

The total body fluid in neonates is distributed among three major fluid spaces: plasma, interstitial and cellular space. The proportion of fluid in each of these compartments differs markedly in neonates from adults (Fig. 11.10), so a different approach to fluid management is required.

Question 11.12

Weight loss in a breastfeeding infant

A community midwife reviewed a 6-day-old male infant at home because of poor breastfeeding and weight loss of 13%. He was born at term, birth weight 3.8 kg. There are no abnormalities on clinical examination. What electrolyte abnormality is this infant most at risk of developing?

Select ONE answer only:

A. Hyperkalaemia

B. Hypernatraemia

C. Hypokalaemia

D. Hypomagnesaemia

E. Hyponatraemia
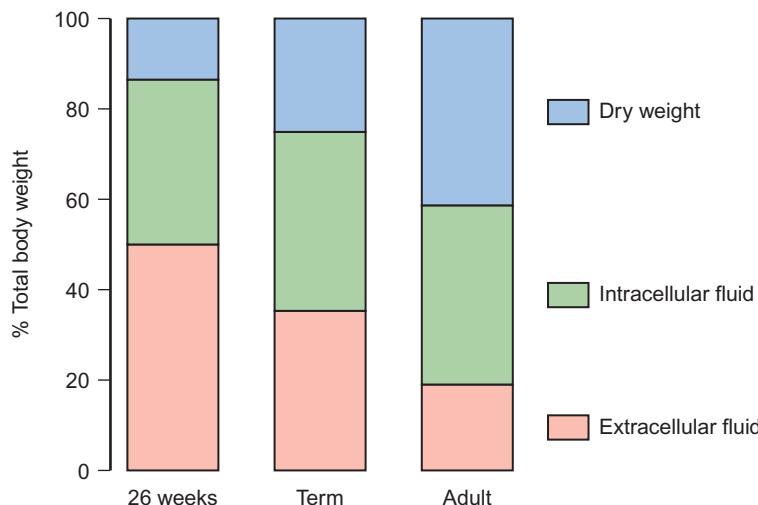
Fig. 11.10 Extracellular fluid expressed as a percentage of body weight. *(Data from Dear (1964) Reed Business Publishing, with permission.)*

In the early fetal period, water comprises 95% of the total body weight. This gradually decreases to 75% at term. As the fetus grows, the amount of fluid in the extracellular spaces also decreases gradually, whereas there is slow increase in the intracellular fluid. This change in the fluid distribution in body compartments continues throughout the neonatal period and affects decision-making about fluid changes, especially in the sick preterm infant.

Factors affecting neonatal fluid balance

The *glomerular filtration rate* in the extremely preterm infant is only a quarter that of the term infant. This makes them vulnerable for fluid overload and hyponatraemia as well as dehydration and hypernatraemia. Similarly, their immature renin–angiotensin mechanism increases the risk of hypernatraemia following rapid correction. All babies undergo a diuretic phase in the immediate postnatal period, regulated by an increase in atrial natriuretic peptide, leading to physiological contraction of the extracellular volume. A negative sodium balance early on, followed by sodium retention by the kidney, is important for growth. Term infants and preterm infants >30 weeks, gestation are able to maintain an adequate water balance over a wide range of fluid intake, but in extremely preterm infants, administration of fluid boluses, infection, hypotension and mechanical ventilation also affect their fluid homeostasis.

Preterm infants with *respiratory distress syndrome (RDS)* have a delayed diuretic phase and their

Table 11.6 Fluid and energy requirements in term and preterm infants

Gestation	Day 1	Day 7
Term	~50 mL/kg	150 mL/kg
Preterm	60–70 mL/kg	Up to 175 mL/kg
Energy requirement by day 7		
Term infant	100 kcal/kg	
Preterm infant	120 kcal/kg	
IUGR infant	Up to 140 kcal/kg	

IUGR, intrauterine growth restriction.

extracellular volume is not decreased; hence, it is important not to give extra fluids and sodium before the diuretic phase.

There is high *transepidermal water loss (TEWL)* in preterm babies due to their large surface area and thin, permeable, non-keratinized skin. This loss can be up to 15 times higher in infants at 25 weeks' gestation compared to term infants and can be reduced by nursing inside an incubator with high humidity (up to 80%) to prevent evaporative water loss. It can also be reduced by humidification of respiratory gases and good skin care.

The sick preterm with complications such as pneumothorax, intraventricular haemorrhage and surgery may develop hyponatremia due to diminished capacity to excrete a free water load, increased sodium loss in the urine and iatrogenic fluid administration of hypotonic, low sodium solutions. True inappropriate secretion of anti-diuretic hormone (ADH) is probably rare.

Fluid (feed) requirements

These are summarized in Table 11.6.

Electrolyte balance

The Na$^+$/K$^+$–ATPase mechanism, responsible for maintaining sodium and potassium balance, is affected during intensive care for sick babies. In addition, the infants have limited ability to handle solute load in administered fluid due to renal impairment. Hence, most infants are given solute-free dextrose solution in the first 2–3 days as sodium, potassium or chloride is not required.

Serum sodium level reflects both sodium and water balance. In hypernatraemia (>145 mmol/L) there is an absolute or relative deficit of body water in relation to body sodium. Similarly, in hyponatraemia (<135 mmol/L), there is relative or absolute excess of body water. Total body sodium may be increased, decreased or unchanged in both hypernatraemia and hyponatraemia. The change in weight and clinical context need to be assessed when determining the cause of hyponatraemia or hypernatraemia. Weight gain in the first few postnatal days with normal serum sodium indicates isotonic expansion of extracellular space and a positive sodium and water balance, at a time when it should be negative. Hyponatraemia with weight loss or inadequate weight gain indicates sodium depletion and requires supplemental sodium. Hyponatraemia due to water excess responds to fluid restriction, along with treatment of the underlying cause. Similarly, hypernatraemia with weight loss suggests dehydration; hypernatraemia with weight gain indicates sodium and water overload.

Most of the potassium in the body exists in the intracellular compartment and the blood levels usually do not reflect total body potassium. The Na$^+$/K$^+$–ATPase maintains the high intracellular potassium concentration by pumping sodium out and potassium into the cell. Potassium is necessary for the electrical responsiveness of muscle cells and also for the contractility of cardiac, skeletal and smooth muscles. Potassium-rich fluids must be avoided if there is oliguria or anuria due to renal compromise.

The mineral requirements of term and preterm infants are shown in Table 11.7.

Table 11.7 Mineral requirements (mmol/kg/day) of term and preterm infants

Mineral	Term	Preterm
Sodium	2.5–3.5	3–4
Potassium	2.5–3.5	2–3
Chloride	5	1.5–4.5
Phosphorus	1.0–1.5	1.9–4.5
Calcium	1.2–1.5	3–5.5
Magnesium	0.6	0.3–0.6

Neonatal weight loss and gain

Physiologic contraction of extracellular water volume and catabolism secondary to low caloric intake leads to a weight loss of about 5–7% in healthy term infants in the first week, most marked on day 2–3. They regain birth weight within 2 weeks. Weight loss may be more marked in breastfed infants. Weight loss in excess of 10% may lead to hypernatraemic dehydration; its incidence in the UK from recent studies ranges from 7–14 per 10,000 infants.

There is average weight gain of about 30 g per day during the first 6 months. Infants double their birth weight by 4–5 months and treble it by 1 year of age.

Breastfeeding

Breastfeeding offers benefits to both mother and baby, as human milk is ideal for meeting the nutritional requirements of the term infant for the first six months of life. The evidence on the health effects of breastfeeding is considered in detail in Chapter 13, Nutrition, but is briefly summarized here.

Benefits to the baby include:

- Most suitable source of nutrition
- Reduced risk of infection from gastroenteritis and otitis media, probably of severe lower respiratory tract infection requiring hospitalization
- May be protective in eczema in infants with positive family history
- Beneficial effect on later 'cardiovascular' health outcomes such as plasma lipid profile, blood pressure and risk of obesity
- May improve later cognitive function
- May provide protection against SIDS (sudden infant death syndrome); although this may be through maternal education, socio-economic status and birth weight.

In the preterm infant, it provides:

- Better gastrointestinal tolerance
- Reduced incidence of necrotizing enterocolitis (NEC) and systemic infection
- Improved cognitive outcome
- Lower blood pressure, more favourable plasma lipid profile and higher bone mass during childhood and adolescence.

Benefits to the mother include:

- Better mother–infant bonding
- Sense of personal achievement
- More rapid weight loss for nursing mothers
- Readily available without any preparation
- Easy to express and store
- Delayed return to menses (increased time-interval to next child is important when alternative birth control not available)

- Uterine involution through oxytocin
- No cost
- Some protection against osteoporosis, ovarian and breast cancer.

There is marked increase in the number of breast ducts and alveoli during pregnancy in response to progesterone, oestrogen and placental lactogen. Prolactin from the anterior pituitary causes glandular tissue to secrete small amounts of colostrum in the last trimester. The let-down reflex, mediated by afferent impulse from baby rooting at the nipple and oxytocin secretion from the posterior pituitary, controls milk flow after birth. Oxytocin squeezes milk into large ducts through smooth muscle fibre stimulation around alveoli. Milk production is maintained by prolactin secretion as well as effective suckling and emptying of breast milk (Fig. 11.11).

Breast milk energy content is 67 kcal/100 mL with fat (54%), carbohydrate (40%) and protein (6%). It has a relatively low amount of protein (0.9 g/100 mL) but with a high whey:casein ratio of 0.7. A large amount of nitrogen is derived from non-protein sources. It has twice as much lactalbumin as cows' milk but no lactoglobulin. There are high levels of amino acids such as taurine, aspartic acid, glutamic acid and aspargine. Human milk fat is better absorbed due to the smaller size of fat globules and lipase content. There is a higher amount of unsaturated fatty acids as well as vitamins A, C, E and nicotinic acid but less of vitamins B and K. There is low renal solute load. Calcium and phosphate levels are lower but better absorbed.

There are very few contraindications to breastfeeding. These include conditions in the mother such as severe acute illness (septicaemia), breast abscess, chemotherapy, some mental health conditions (medication, e.g. lithium), active tuberculosis and HIV; and conditions in the infant such as metabolic conditions, e.g. galactosaemia, phenylketonuria and lactose intolerance. Breastfeeding may be difficult to establish with severe cleft lip/palate.

Artificial or formula feeding

In the absence of breastfeeding, this is an alternative option to meet the nutritional demands without compromising normal growth, body metabolism and composition. It is difficult to detect certain small but important differences, variations in body systems or long-term complications. Although aiming to mimic human milk constituents, there are key differences, such as high casein protein content and relatively low whey:casein ratio, low lactose content and none of the components that offer immunological benefits to human milk. Although higher in calcium, phosphates and iron content, there is less absorption and bioavailability.

Central nervous system

Embryology

The timeline for major events in the development of the central nervous system is shown in Fig. 10.7 and described in detail in Chapter 28, Neurology. Failure of fusion of the neural tube may result in neural tube defects and of the complex events of neural proliferation, migration and myelination in a wide range of CNS abnormalities. The head itself may be abnormal in size, microcephaly or macrocephaly (more than two standard deviations below or above the mean), or be of abnormal shape from craniostenosis.

Craniostenosis (craniosynostosis)

Distortion of the head shape results from premature fusion of skull sutures. In mild cases, its effect is cosmetic, but if severe, it may require surgical intervention because of arrested brain growth and raised intracranial pressure as well as for cosmetic reasons.
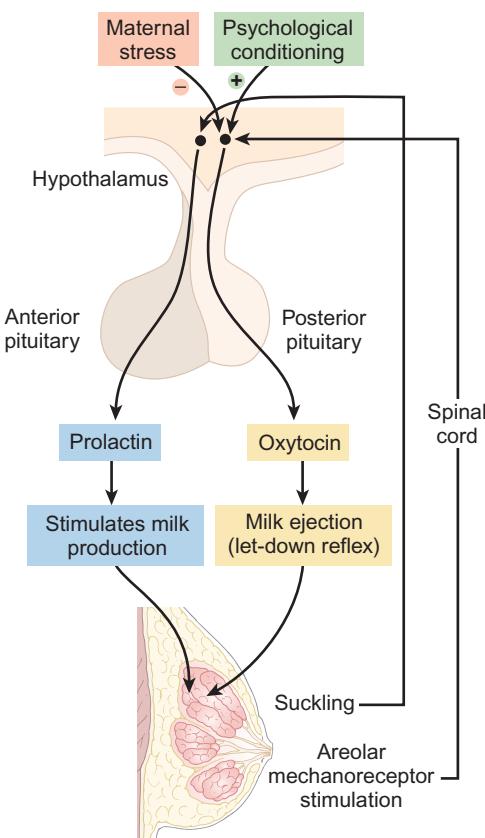
Fig. 11.11 Hormonal maintenance of lactation.

Infant skull deformity
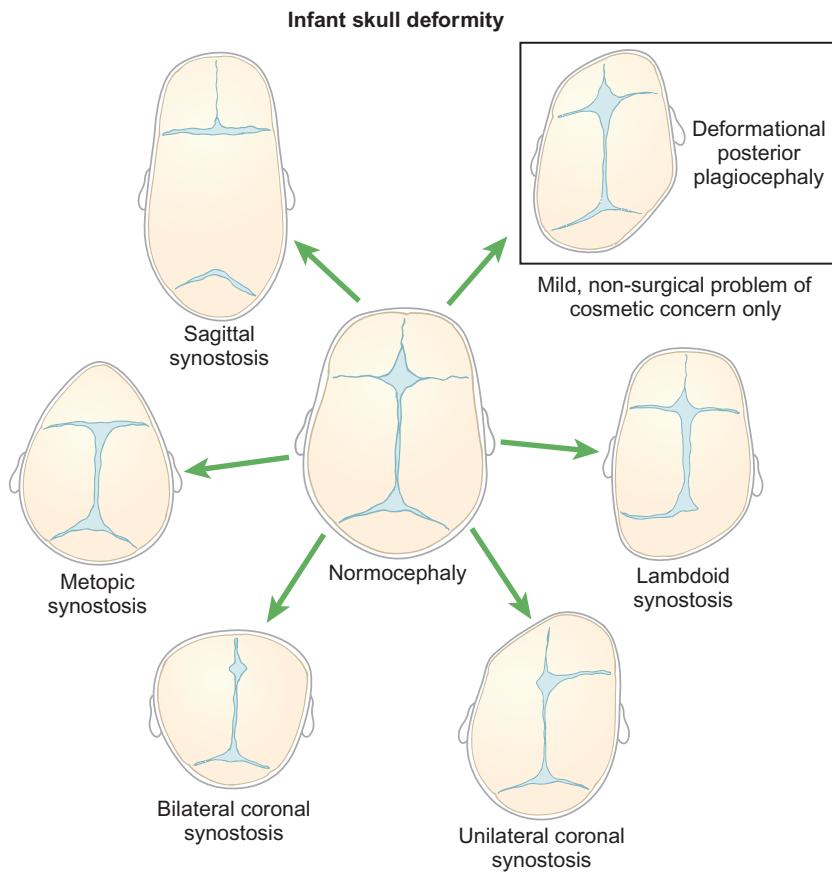
Fig. 11.12 Different types of craniostenosis.

The common forms of craniostenosis (Fig. 11.12) include:

- Closure of sagittal suture (scaphocephaly)
- Closure of one lambdoid suture (occipital plagiocephaly)
- Coronal synostosis leading to wide head (brachycephaly)
- Triangular forehead due to involvement of metopic sutures (trigonocephaly).

Very severe forms of craniostenosis can also be inherited as certain rare autosomal dominant disorders (e.g. Alport's syndrome, Crouzon's syndrome (craniofacial dysostosis) and Carpenter's syndrome).

The incidence of positional plagiocephaly later in infancy has increased because of babies lying and sleeping on their back to reduce the risk of sudden infant death syndrome (SIDS). The prognosis is excellent and does not warrant investigation or intervention, only parental reassurance.

Hypoxic–ischaemic encephalopathy

Hypoxic–ischaemic encephalopathy (HIE) in term and late preterm infants is a significant cause of mortality and neurodisability. Its incidence in the UK is 1–1.5 per 1000 live births and it accounts for up to 30% of cerebral palsy. Its incidence in low-income countries may be up to 10 times higher. Globally, it is a major problem for families and provision of healthcare.

It is important to define terms in common use such as perinatal hypoxia, ischaemia, asphyxia. These denote lack of oxygen, blood flow and gas exchange to the fetus and newborn, respectively. Ischaemia is more damaging than hypoxia since it also leads to glucose depletion, which is important in the causation of neuronal injury. Asphyxia leads to impaired respiratory gas exchange, thus producing hypercarbia-associated acidosis and increased cerebral blood flow.

HIE is a specific type of encephalopathy due to low oxygen and blood delivery to the brain. Other causes of neonatal encephalopathy are listed in Box 11.4.

A clinical diagnosis of HIE should only be considered in the presence of all of the following criteria:

- Evidence of intrapartum asphyxia, such as a sentinel event (Box 11.5)
- Respiratory depression at delivery
- Encephalopathy in the immediate postnatal period

> **Box 11.4 Causes of neonatal encephalopathy**
>
> - Hypoxic–ischaemic encephalopathy
> - Infection (neonatal sepsis, meningitis, herpes meningoencephalitis)
> - Trauma and haemorrhage (subgaleal, extradural and subdural haematomas)
> - Metabolic (non-ketotic hyperglycinaemia, mitochondrial myopathies, aminoacidaemias)
> - Neuronal migration defects (e.g. lissencephaly)
> - Congenital myotonia (myasthenia gravis, peroxismal disorders, Prader–Willi syndrome)
> - Neonatal stroke

> **Box 11.5 Sentinel events during labour and delivery which may cause acute brain injury**
>
> - Cord prolapse
> - Uterine rupture
> - Abruption of placenta
> - Amniotic fluid embolism
> - Acute maternal haemorrhage
> - Maternal circulatory failure
> - Acute neonatal haemorrhage due to vasa praevia, acute loss from cord and feto-maternal haemorrhage

Intrapartum asphyxia and respiratory depression at birth may be indicated by at least one of the following parameters:

- Apgar score of ≤5 at 10 minutes after birth
- Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth
- Acidosis within 60 minutes of birth, as defined by umbilical cord, arterial or capillary pH of <7.0
- Base deficit ≥16 mmol/L in umbilical cord or any blood sample within 60 minutes of birth.

Moderate to severe encephalopathy may be indicated by at least one of the following:

- Early-onset seizures
- Altered sensorium (reduced or absent response to stimulation)
- Abnormal tone (hypotonia or flaccidity)
- Abnormal primitive reflexes (weak or absent suck or Moro reflex)

The presence of these objective parameters in addition to moderate or severe abnormalities in the background electrical activity on cerebral function monitoring (aEEG) is required for case selection for treatment or interventions for HIE. Indicators of intrapartum asphyxia alone (abnormal cardiotocography, reduced fetal movements, cord pH ≤7.0, or base deficit ≥16 mmol/L) without moderate to severe encephalopathy should not meet the requirements for such an intervention. Adherence to these criteria is also important because of the potential medico-legal consequences in relation to maternal care during labour and delivery.

Pathophysiology

Fetal responses to hypoxia–ischaemia

This is described in Chapter 10, Perinatal medicine.

Mechanisms of brain injury during severe hypoxia–ischaemia

Hypoxic–ischaemic injury leads to neuronal death in two phases. Primary neuronal necrosis due to cellular hypoxia and primary energy failure following depletion of cellular high-energy compounds may happen immediately after a severe insult, and is not amenable to any treatment or intervention. This is followed by a secondary phase of delayed neuronal death, usually after a latent period of at least six hours. The mechanisms responsible for delayed neuronal death include reperfusion and hyperaemia, cytotoxic oedema, programmed apoptotic cell death, mitochondrial failure, free radical damage, accumulation of excitotoxins, nitric oxide synthesis and cytotoxic actions of microglia. This delayed phase of neuronal damage is associated with seizures and encephalopathy and leads to a large proportion of neuronal necrosis following a severe and global insult. The latent period before secondary neuronal necrosis offers a therapeutic 'window of opportunity' for interventions like cooling.

Postulated mechanisms for the neuroprotective effects of moderate hypothermia include:

- Decreased number of apoptotic but not necrotic cells
- Reduction in cerebral metabolic rate and oxygen consumption
- Attenuation of excitatory amine release such as glutamate
- Improving the uptake of glutamates in neuronal cells
- Reduction in the synthesis of toxic nitric oxide and free radicals.

Patterns of brain injury

There are mainly three types of brain injury (Fig. 11.13):

1. *Basal ganglia and thalamus (BGT)* is associated with a sentinel event, such as placental abruption. The deeper structures of the basal ganglia and thalamus are most susceptible to hypoxic–ischaemic type injury because of their high metabolic rate and high
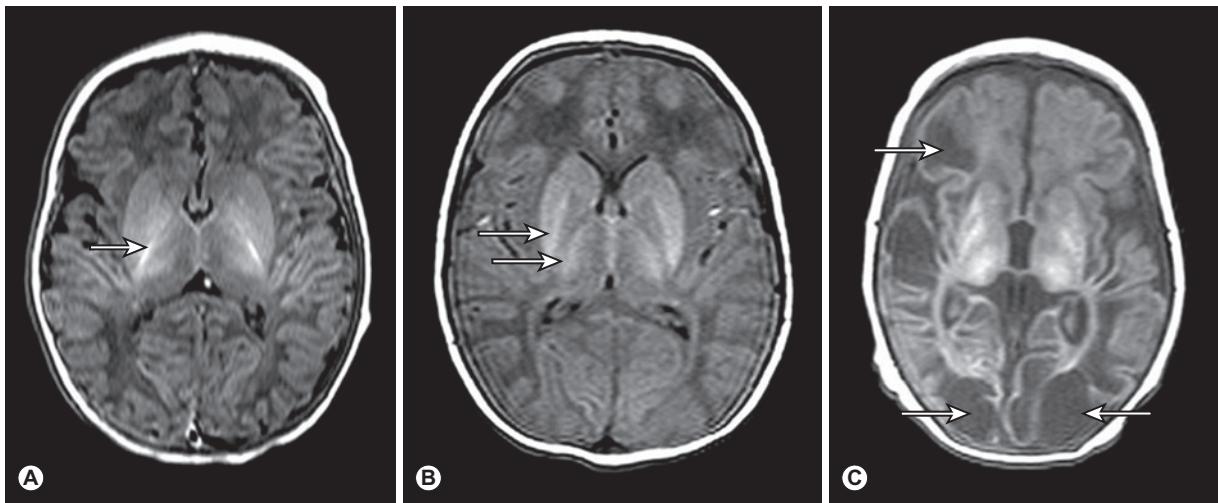
Fig. 11.13 Types of brain injury. A. Basal ganglia and thalamus (BGT) lesions. B. Watershed pattern of parasagittal cerebral injury. C. Global pattern involving subcortical white matter and cortex.

concentration of NMDA receptors. This is often accompanied by brainstem injury, with lesions in the midbrain, pons and cerebellar vermis. These may be of varying severity from mild/focal to involving the whole of the BGT area. There is also associated involvement of the posterior limb of the internal capsule (PLIC). Outcomes include death in up to 50% of cases in the first 2–3 years. Survivors have a range of impairments including cerebral palsy in 75%, speech and language difficulty, visual and hearing impairment. BGT lesions are the best predictor of motor problems. PLIC involvement is the best predictor for inability to walk at 2 years.

2. *Watershed pattern* involves parasagittal cerebral injury or watershed injury, mainly due to chronic partial hypoxia. Similar lesions are associated with hypertension, infection and hypoglycaemia. These areas of necrosis relate to border zones between major cerebral arteries. Watershed injuries may lead to communication problems.

3. *Global pattern*, involving subcortical white matter and cortex, is seen in severe neonatal encephalopathy and is usually fatal.

Assessment

Clinical
The most commonly used scoring system for grading the severity of acute neonatal encephalopathy is the Sarnat stages, as this is brief and objective and has good correlation with outcomes.

Stage 1: Characterized by irritability, lethargy or hyperalertness, hyperreflexia, tachycardia, dilated pupils and abnormal tone that improve within 24–48 hours. Mild encephalopathy has no risk of death or significant disability.

Stage 2: Seizures and EEG abnormalities are prominent features along with abnormal tone, proximal weakness and loss of consciousness. This is associated with 5% mortality and 25% neurodisability.

Stage 3: Severe encephalopathy with deep coma and unresponsiveness, flaccid tone and areflexia, abnormal EEG with discontinuous background electrical activity or burst suppression pattern. This is associated with up to 80% mortality and most survivors have severe disability.

Alternatively, the Thompson scoring system can be used for an objective assessment and system of monitoring, and is simpler to use (Table 11.8). Problems with these scoring systems include difficulties in reliably measuring some clinical parameters soon after birth (e.g. assessing primitive reflexes, breathing, and seizures in a sedated or ventilated infant). Also, many infants have signs intermediate between the stages and assessment is complicated by anticonvulsant therapies, paralytic agents and co-morbidities.

Amplitude modulated EEG (aEEG) or cerebral function monitor
This is helpful for clinical assessment at the bedside, grading the severity of encephalopathy, and seizure detection. It is easy to obtain a trace and interpret, hence it has been used for case-selection criteria for therapeutic hypothermia. It provides robust, objective bedside monitoring with excellent correlation with neurodevelopmental abnormality. Severely abnormal patterns such as low voltage patterns persisting for more than about 48 hours after birth are associated

Table 11.8 Thompson HIE score

Sign	0	1	2	3	Score
Tone	Normal	Hyper	Hypo	Flaccid	
LOC	Normal	Hyper alert, stare	Lethargic	Comatose	
Seizures	None	Infrequent <3/day	Frequent >2/day		
Posture	Normal	Fisting, cycling	Strong distal flexion	Decerebrate	
Moro	Normal	Partial	Absent		
Grasp	Normal	Poor	Absent		
Suck	Normal	Poor	Absent / bites		
Respiration	Normal	Hyperventilation	Brief apnoea	Apnoeic	
Fontanelle	Normal	Full, not tense	Tense		
Total Score					

LOC, level of consciousness.

with a poor neurodevelopmental outcome in about 70% of infants. Normal aEEG within 6 hours of birth is a good predictor of normal outcome.

Cranial ultrasound

This is helpful to exclude other causes of encephalopathy, such as metabolic causes and structural malformations. It is also useful in detecting calcification and cysts suggestive of viral infection and detecting atrophy suggestive of longstanding damage. It will also identify cerebral haemorrhage. Doppler cerebral flow velocity indices are commonly used as markers of cerebral perfusion and are also helpful in assessing the severity of HIE and predicting long-term outcome.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is the preferred neuroimaging method because of its sensitivity for detecting hypoxic–ischaemic injury, information about the timing of injury and ability to identify other causes. Ideally done between 5 and 14 days, as injury may be underestimated if performed during the first few days after birth. Magnetic resonance spectroscopy (MRS) is increasingly available and provides important prognostic data during the first week. Reduction in N-acetylaspartate (NAA), which reflects neuronal injury and elevation of lactate, which reflects tissue ischaemia and hypoxia, correlate with later neurological problems.

Management

Supportive treatment

This includes maintaining cardiorespiratory stability in intensive care, with due attention to biochemical normality of glucose, electrolytes, fluid and blood gases and management of renal failure, deranged clotting and seizure control. Fluids are initially restricted to prevent cerebral oedema.

Therapeutic hypothermia

The neuroprotective effects of hypothermia during cardiac surgery in animals were initially described in the 1950s. Similarly, it was shown to reduce cerebral blood flow, oxygen consumption and intracranial pressure during experimental traumatic injury in dogs. Resurgence of interest in therapeutic hypothermia followed the demonstration of beneficial effects of moderate hypothermia on mortality and neurological outcomes in out-of-hospital cardiac arrest. This led to a number of basic science studies trying to understand the cellular mechanisms of neuroprotection and the 'window of opportunity' for such interventions in perinatal brain injury (see Box 37.6).

Conducting clinical studies (RCTs) for HIE was complicated by ethical concerns about significant early intervention in a newborn infant born with a severe, unexpected condition. Strict case selection was necessary post-resuscitation. Infants with mild HIE do not need this intervention as they have an excellent prognosis and needed to be excluded. Those with the most extensive brain injuries where palliative care was indicated also had to be excluded. Clinicians were also concerned if this intervention reduced deaths at the expense of worsening neurodisability. The trials have shown that mild hypothermia (33–34°C), started within 6 hours and continued for 72 hours, leads to significant reduction in death or neurodisability at 18 months with a risk ratio of 0.75 (95% confidence interval (CI) 0.68–0.83), and the number needed to treat for an additional beneficial outcome was 7. With cooling, 6 out of 10 infants with moderate to severe insult have a normal outcome at 2 years of age (see Box 37.13 for further details). The UK TOBY study group recently published the outcomes at 7 years of age, which also showed a significant reduction in the risk of cerebral palsy (risk ratio of 0.59, 95% CI 0.37–0.95) and the risk of moderate to severe disability (risk

Table 11.9 Causes of neonatal seizures

Cerebral	Metabolic	Sepsis	Drugs	Other
Hypoxic–ischaemic: • hypoxic–ischaemic encephalopathy, birth trauma • focal ischaemia (arterial/venous) Subarachnoid or subdural haemorrhage Parenchymal haemorrhage in preterm infants Cerebral malformations of the brain, including vascular anomalies	Hypoglycaemia Hypocalcaemia Hypomagnesaemia Hyponatraemia Hypernatraemia Inborn errors of metabolism	Septicaemia Meningitis Encephalitis	Drug withdrawal: • maternal abuse • following neonatal narcotic therapy Side-effect of drugs	Kernicterus Pyridoxine deficiency Idiopathic benign neonatal seizures (familial and non-familial)

ratio of 0.59, 95% CI 0.37–0.94). Significantly more children survived without neurological abnormalities in the hypothermia group (45% vs 28%, relative risk 1.60, confidence interval 1.15–2.22).

Although the treatment has been successful, the rate of death or moderate to severe disability in infants with moderate to severe HIE after cooling is 46% (95% CI 40–53%). There is still an urgent need for additional therapies to improve outcomes and achieve maximal neuroprotective effect. Other drugs currently being researched are magnesium sulphate, melatonin, N-acetylcysteine, topiramate, erythropoietin and xenon inhalation.

Neonatal seizures

Seizures occur more often during the neonatal period than at any other time during life. Their incidence is estimated at 1.5–3.5 per 1000 term live births and 10–130 per 1000 preterm live births.

Seizures occur when a large group of neurons undergo excessive, synchronized depolarization. Depolarization can result from excessive excitatory amino acid release (e.g. glutamate) or deficient inhibitory neurotransmitter, e.g. gamma amino butyric acid (GABA).

The biochemical effect of neonatal seizures includes derangements of energy metabolism leading to compromise of energy-dependent ion pumps and consequent rise of adenosine diphosphate (ADP) levels. The rise in ADP stimulates glycolysis with the ultimate increase in pyruvate, which accumulates as a result of compromised mitochondrial function.

Another potential cause for seizures is disruption of adenosine triphosphate (ATP)-dependent resting membrane potentials, which cause sodium to flow into the neuron and potassium to flow out of the neuron. For example, hypoxic–ischaemic encephalopathy disrupts the ATP-dependent sodium–potassium pump and appears to cause excessive depolarization.

Although seizures in the neonatal period may present with chronic or tonic involuntary movements of one or more limbs, manifestations are often subtle with apnoea, transient cyanosis, episodes of oxygen desaturation, lip smacking, altered consciousness or floppiness. Seizures in the developing brain are poorly classified, frequently under-diagnosed and difficult to treat. In term infants, the most common cause of seizures is hypoxic–ischaemic encephalopathy (HIE); in preterm infants, seizures occur in up to 70% of preterm infants with intraventricular haemorrhage or periventricular leukomalacia, but are often unrecognized. The causes are shown in Table 11.9.

The current best practice is to attempt to recognize seizures early, which is assisted by aEEG or EEG monitoring, preferably with video recording. Investigations are likely to include comprehensive biochemical, infective and metabolic screening, as well as neurophysiological studies, such as EEG and neuroimaging with cranial ultrasound or CT to identify haemorrhage or traumatic injury, or MRI brain scans to identify ischaemia and malformations. Screening for inborn errors of metabolism and congenital infection may be indicated.

Seizures are treated if prolonged. No anticonvulsant has been shown to be superior to others. As few anticonvulsants as possible should be used. There is evidence that some anticonvulsant medication, while reducing the abnormal movements, do not reduce the electrical discharge (electroclinical dissociation).

Seizures are an independent risk factor for adverse neurodevelopmental outcome. Prognosis depends on the cause.

Perinatal stroke

Stroke is now recognized to occur perinatally in as many as 0.2–1 per 1000 live births. There are three distinct types recognized. They may be:

- Perinatal arterial ischaemic stroke (PAIS) – the most common site is left middle cerebral artery
- Haemorrhage – may be parenchymal, subarachnoid or intraventricular
- Cerebral sinovenous thrombosis (CSVT) – can cause venous infarction, often with haemorrhage.

Their aetiology is complex and often no risk factor is identified.

Perinatal arterial ischaemic stroke (PAIS) is typically from thromboembolism, from placental vessels, from venous thrombi that cross the patent foramen ovale, from right-to-left shunts in congenital heart disease and from thrombi from umbilical vessel catheters. Sepsis or meningitis, trauma and prothrombotic disorders, e.g. protein C, protein S deficiency, may also contribute.

Haemorrhagic stroke may result from intraparenchymal haemorrhage from vascular anomalies or haemorrhage into ischaemic infarction; periventricular haemorrhagic infarction is associated with intraventricular haemorrhage in extremely premature infants.

Perinatal stroke classically presents with focal seizures in the first 3 days of life but may be asymptomatic. Cranial ultrasound may be abnormal, but MRI is required for accurate diagnosis and prognosis. Investigations to rule out thrombophilic disorders – protein C, protein S deficiency, Factor V Leiden deficiency, MTFHR mutation in the family – may be indicated.

Nearly 50% of infants with perinatal stroke develop motor disability, often a hemiplegia on the contralateral side presenting in infancy or childhood, and cognitive dysfunction. Occipital lesions may be associated with visual impairment. Large lesions may lead to epilepsy.

Further reading

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John W Gregory

Growth and puberty

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Understand the basic principles underpinning normal growth
- Understand growth measurement and charts and their interpretation
- Be able to identify abnormal growth patterns
- Know about the genetic and environmental factors that influence growth
- Know the common causes and assessment and investigation of short stature
- Know the common causes of tall stature
- Understand the causes and how to investigate and manage abnormal timing in the onset of puberty

Normal growth

Embryology of the pituitary

The anterior pituitary is derived from the ectoderm, specifically Rathke's pouch, originally part of palatal development, whereas the posterior pituitary derives from the neuroectoderm. The anterior wall of Rathke's pouch develops to fill the pouch and form the pars distalis, which forms the bulk of the anterior pituitary, where most hormone production occurs, and the pars tuberalis, which forms a sheath which extends up to the pituitary stalk. The clinical importance of Rathke's pouch is that it is from this embryonic tissue that a craniopharyngioma is formed. The posterior wall of the pars distalis forms the poorly-defined pars intermedia, which separates the anterior from the posterior pituitary.

Mutations of at least eight genes encoding transcription factors involved in pituitary development have been associated with multiple pituitary hormone deficiency. Identification of an underlying genetic defect allows the clinician to anticipate likely pituitary hormone deficiencies that will arise and which will need monitoring. Some of these mutations are listed in Box 12.1.

Endocrine regulation of growth

Growth hormone (GH) exerts the major influence on postnatal growth. It is an amino-acid polypeptide, which circulates bound to a GH-binding protein, which is derived from the extracellular component of the GH receptor. GH is secreted from somatotroph cells under the dual regulation of hypothalamically-derived GH-releasing hormone and somatostatin, the combination of which is necessary to produce the episodic pulses, seen mostly overnight and which are essential for normal growth. These hypothalamically-derived regulators of GH secretion are themselves regulated by central neurotransmitters, which integrate input from a variety of stimuli including nutrition, sleep, exercise and stress (Fig. 12.1).

GH stimulates the synthesis from the liver and a number of other organs of insulin-like growth factors (IGF-1 and IGF-2), which share a degree of structural homology with proinsulin and may exert weak insulin-like effects. IGF-1 is thought to be a major regulator of GH action. It circulates bound to IGF binding protein-3 (IGFBP-3), whose concentrations are also regulated by GH. This complex associates with another GH-dependent glycoprotein known as acid-labile subunit, the combination forming a ternary complex.

Box 12.1 Genetic mutations associated with pituitary hormone deficiencies

- *PROP1* gene – the most common, autosomal recessive inheritance, associated with deficiencies of GH (growth hormone), TSH (thyroid-stimulating hormone), LH (luteinizing hormone), FSH (follicle-stimulating hormone), ACTH (adrenocorticotrophic hormone) and prolactin.
- *POU1F1* (previously known as *PIT1*) – autosomal dominant or recessive, causes deficiencies of GH, prolactin and the β-subunit of TSH.
- *HESX1* – autosomal dominant or recessive, is expressed in the oral ectoderm that gives rise to Rathke's pouch, causes GH deficiency in association with septo-optic dysplasia.
- *LHX3* and *LHX4* – regulate the proliferation and differentiation of pituitary specific cell lineages, associated with combined pituitary hormone deficiencies.
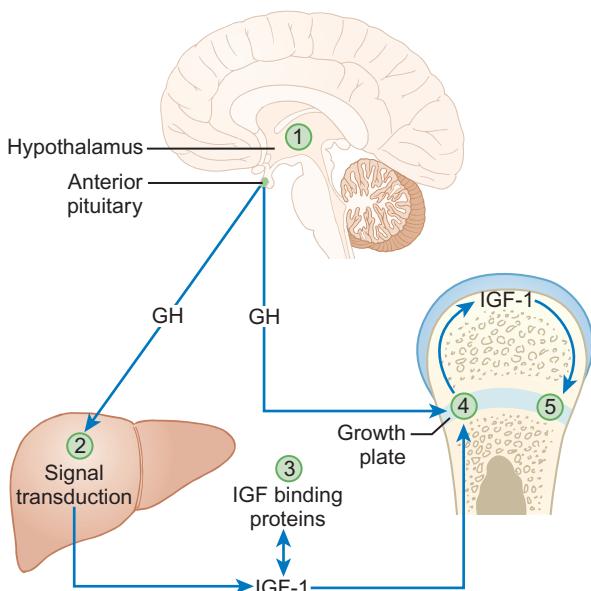
Fig. 12.1 The growth hormone/IGF-1 axis. Cytokines act on (1) appetite centres in the brain affecting appetite and calorie intake; (2) growth hormone signal transduction in the hepatocyte; (3) proteolysis of IGFBP-3; (4) IGF-1 expression in the growth plate; (5) proliferation of growth plate chondrocytes. GH, growth hormone; IGF, insulin-like growth factor. *(From Sanderson IR. Growth problems in children with IBD. Nature Reviews Gastroenterology & Hepatology (2014) doi:10.1038/nrgastro.2014.102, with permission.)*

Most IGF-1 circulates in bound or inactive forms and the IGF-binding proteins (IGFBPs) prolong the half-life of IGFs, allowing them to be transported to target cells such as in the growth plate, where they interact with IGF receptors to produce their biological effects. We will return to the issue of how IGF-1 can be useful in determining GH abnormalities later in this chapter.

Physiology

The pattern of normal growth can be subdivided into three phases, which correspond to the three main influences on growth. The infancy component, which is largely driven by nutritional factors, depends on normal placental function and nutritional intake in early life. It can be considered to start from conception and it persists through fetal life, ending during the first two years of postnatal life. The childhood phase, which is GH, IGF-1 and thyroxine dependent, starts postnatally and persists until the end of puberty. The final phase is the pubertal component, which is driven by increasing gonadal production of sex steroids, which stimulate GH secretion. These three phases, when superimposed, produce the normal growth pattern (Fig. 12.2) seen through childhood in which height velocity falls rapidly during the first two years of life from approximately 25 cm/year to a fairly steady state of 5–7cm/year through mid-childhood before the onset of the pubertal growth spurt. In girls, the pubertal growth spurt starts at the onset of breast development, peaking a year later at an average age of 12 years, whereas in boys the growth spurt is typically two years later, peak height velocity coincident with testicular volumes of 15 mL. The average difference of 12.5–14 cm in the adult height of men and women is caused by the longer prepubertal contribution to growth and greater peak height velocity seen in boys.

History

Growth failure can arise from genetic abnormalities, nutritional and endocrine problems and defects in almost any organ system. Therefore, when assessing a child referred with a possible growth disorder, a detailed and wide-ranging history is required. Details should be sought of:

- Family history, including parental heights and their timing of puberty, given the important influence of genetics on such factors
- Pregnancy, mode of delivery and birth weight, which may impact on the infant phase of growth
- Feeding history
- Development of signs of puberty
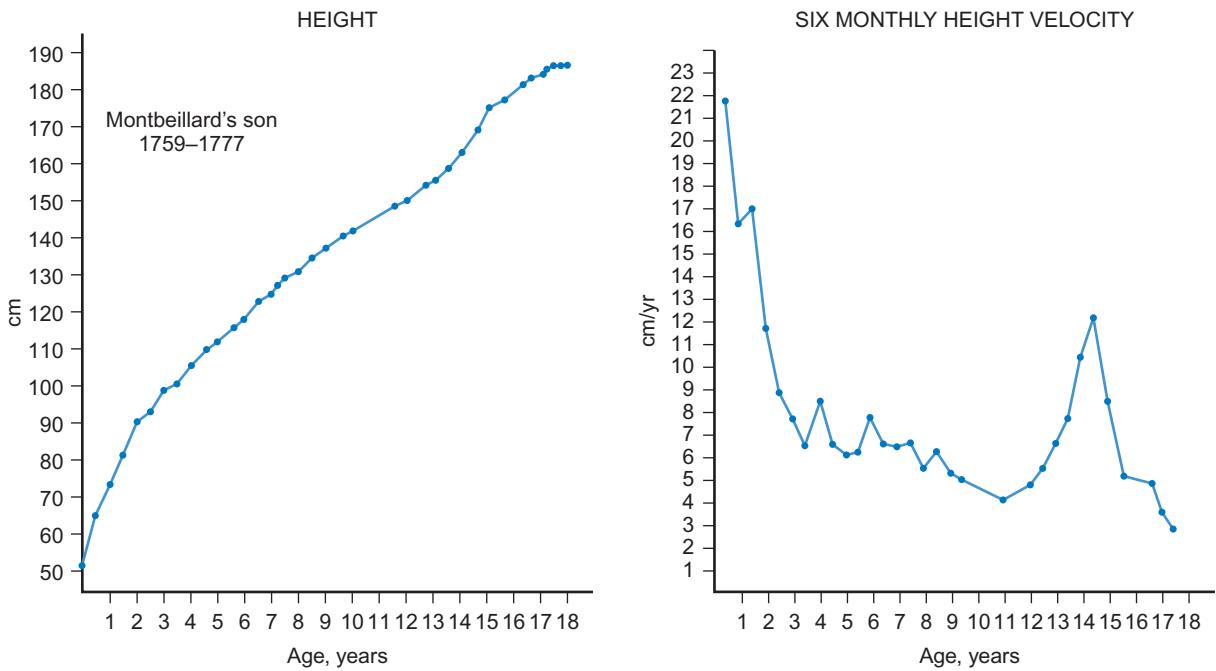
Fig. 12.2 Height and height velocity through childhood. These are the oldest known growth charts, of Count de Montbeillard's son.

- Headache, visual disturbance or symptoms to suggest pituitary dysfunction or intracranial disease
- Details of systemic symptoms that might suggest any coexistent medical disorder
- Social history, including details of how the short stature is affecting the child.

In a child with unusually tall stature, in addition to the family history, specific enquiry should be made for:

- Symptoms suggestive of precocious puberty
- Symptoms of thyrotoxicosis, Marfan's syndrome or other overgrowth syndromes.

Examination

A fundamental requirement when examining children with growth disorders is an accurate measurement of their growth. Because of the effect of time of day (human height shortens as the day progresses) and inter-observer variation on measurement, serial growth measurements should be undertaken at approximately the same time of day and preferably by the same measurer. Over the age of two years, a stadiometer (preferably wall-mounted) should be used and the child measured without shoes or socks, with heels, buttocks and shoulders against the backplate and the head in the Frankfurt plane (an imaginary line connecting the lower border of the eye socket with the external auditory meatus). There is no evidence that undertaking stretched measurements with upward pressure on the mastoid processes achieves greater consistency, but the same technique should be used when comparing sequential measures.

Under the age of two years, supine table measurements or a neonatometer and two observers are required to assess length, ensuring that the Frankfurt plane is vertical and that the child's head is in firm contact with the headboard and the foot dorsiflexed against the movable baseplate.

As skeletal dysplasias may impair growth of different parts of the skeleton differentially, the sitting height, which is a proxy for vertebral body growth, should be measured using a table-mounted stadiometer. Subtracting sitting height from standing height produces the sub-ischial leg length, which is a measure of long bone growth in the leg. Head circumference should be measured in children under the age of two years.

Height measurements should be compared with weight (assessed in a child wearing minimal clothing) by plotting measurements on a growth chart. In the UK, the UK-WHO growth charts are used. These are a composite of the UK90 charts derived from cross-sectional growth data and the WHO growth standards, which describe the growth of healthy breastfed children from six countries. Because of the association of weight with height (taller children tend to be heavier), interpretation of weight data requires adjustment for height. This should be done by calculating the body

mass index (weight in kilograms / (height in metres)^2) and plotting this on a centile chart. To help interpret the growth pattern, height measurements should be compared with other measurements taken in the past by plotting all available measurements on a growth chart to evaluate whether crossing of centiles has occurred, which implies an abnormal height velocity. The appropriateness of the child's height for their genetic background is assessed by calculating the target height range (requires parental height measurements), which is the mid-parental centile (the mid-point between the parents' centiles) +/− 8.5 cm.

Additional features that should be assessed on thorough physical examination of a child with abnormal growth include:

- General appearance and nutritional state
- Dysmorphic features, particularly of the craniofacial skeleton or suggestive of skeletal disproportion or an underlying syndrome
- Pubertal staging, which is important in evaluating the chronology of physical development which has major influences on growth (see section on puberty)
- A detailed systems review including blood pressure, visual fields and fundoscopy, as disease of almost any system may present with growth abnormalities.

Investigations

Before considering any investigations, the findings from the history and examination should be integrated into a differential diagnosis. The following investigations should be considered:

- If features suggestive of a defect in a clinical system have been identified, then appropriate further tests of the relevant system to confirm the diagnosis should be organized
- In a short or slowly-growing child with no obvious pathology, an X-ray of the left wrist to calculate a bone age should be performed to assess the degree of delay in physical development, along with a blood sample for:
  - Full blood count, blood film and ESR or C-reactive protein
  - Urea, electrolytes and creatinine
  - Calcium and phosphate
  - Thyroid function tests
  - IgA and anti-tTG (anti-tissue transglutaminase) antibodies or other screening test for coeliac disease
  - Karyotype in girls to exclude Turner's syndrome
  - IGF-1, though this is of limited sensitivity for screening for GH deficiency and may also be affected by nutritional state

  - Formal stimulation tests of GH secretion – only indicated once the above tests have been performed and (with the exception of IGF-1) found to be normal.

In a tall or rapidly-growing child, the following investigations may be necessary:

- Bone age, which is useful to assess physical maturation
- Karyotype in boys to exclude Klinefelter's syndrome
- Thyroid function tests for hyperthyroidism
- IGF-1 to exclude GH oversecretion
- Cardiac ultrasound if Marfan's syndrome is suspected
- *FMR1* gene analysis to exclude Fragile X syndrome in a boy with learning difficulties
- DNA for specific genetic syndromes (e.g. Marfan's, Beckwith–Wiedemann, Sotos syndromes).

Short stature and impaired growth

Familial short stature and constitutionally delayed growth and puberty

Familial short stature is the most common cause of short stature referred to clinical services. Calculating the target height range is required to demonstrate familial short stature, though if one parent is particularly short, one needs to consider whether they too may have a potentially inheritable underlying growth disorder. Children with familial short stature will have a height centile consistent with their short target height range and will demonstrate growth parallel to the centiles and consistent with a normal height velocity. Extensive investigations are not indicated but a careful explanation and reassurance for the child and parents is required to alleviate anxiety.

Short stature due to constitutionally delayed puberty is discussed in the section on puberty.

Small for gestational age

Short stature due to being small for gestational age is suggested when the birth weight is below the 10th centile. Symmetrical growth failure implies adverse influences on fetal growth that have operated throughout much of development, whereas asymmetric growth failure in which head circumference is preserved implies growth failure restricted to the last part of pregnancy, often due to placental failure. There are many other underlying causes including:

- Major fetal defects (such as chromosomal and genetic defects, major structural malformations and intrauterine infection)
- Maternal influences, including ill-health and excess cigarette and alcohol consumption.

Most (80–85%) small-for-gestational-age infants will show catch-up growth postnatally but those with symmetrical growth failure are least likely to do so.

Infants who are small for gestational age are at increased risk of hypoglycaemia in the first two days of life. In the much longer term, they have been shown to be at increased risk of a range of adult diseases, such as hypertension, cardiovascular disease, type 2 diabetes and obesity. A fetal programming hypothesis (the Barker hypothesis) has been proposed, which suggests that there are critical periods in fetal development when permanent adaptive changes occur in body structure and function to cope with nutritional insufficiency *in utero* and likely nutritional challenges postnatally. However, these adaptations place the individual at a disadvantage postnatally should calorie supplies become potentially unlimited.

Treatment of affected individuals involves ensuring an adequate supply of nutrition postnatally to facilitate catch-up growth. In those individuals who remain short, GH therapy at larger doses than those required to treat GH deficiency has been shown to increase final height, though whether this impacts on other risk factors for disease in later life is unknown.

Syndromic short stature

The more common syndromic causes of short stature which may present with growth concerns include Russell–Silver syndrome, fetal alcohol spectrum disorder, Turner's syndrome and Noonan's syndrome.

Russell–Silver syndrome

Russell–Silver syndrome is an example of an imprinted disorder, usually caused by maternal uniparental disomy of chromosome 7. Imprinted disorders are associated with assisted reproductive techniques and often cause abnormalities of growth. Russell–Silver syndrome is characterized by intrauterine growth restriction, increased risks of hypoglycaemia and sweating, asymmetry (one side of the body being shorter than the other) and short stature with failure to catch up growth, thinness, a triangular-shaped face with a small pointed chin and clinodactyly. Treatment involves optimal dietary support and, for some, GH therapy.

Fetal alcohol spectrum disorder

Alcohol is a teratogen and exposure *in utero* causes a number of problems, including impaired growth at any time point postnatally, brain damage leading to poor concentration, behaviour and learning difficulties and a characteristic facial appearance of microcephaly, a flat mid-face, low-set ears and micrognathia.

Turner's syndrome

This is caused by a loss or abnormality of one X chromosome, affecting 1 in 2500 girls. Although the phenotype is relatively mild for such a major chromosomal anomaly, reflecting the partial inactivation of the second X chromosome from early fetal life, 99% of conceptions result in miscarriage or stillbirth. About one third of genes on the short arm (Xp) are unsilenced, including the short stature homeobox (*SHOX*) gene, and these account for the characteristic features, which include: a skeletal dysplasia causing short stature; short fourth and fifth metacarpals; cubitus valgus; micrognathia; ovarian failure leading to pubertal failure and infertility; lymphoedema; neck webbing; a low hairline and increased naevi; congenital heart disease, particularly coarctation of the aorta; wide-spaced nipples; Madelung deformity (a focal dysplasia of the distal radial physis), middle ear problems; renal anomalies; specific learning difficulties related to numeracy and visuospatial tasks; social vulnerability; and an increased risk of autoimmune and inflammatory disease.

Many children with Turner's syndrome have few abnormal findings and so karyotyping is essential in any girl with impaired growth of unknown aetiology. Treatment requires GH therapy to improve growth, oestrogen induction of puberty and specific monitoring for cardiac, renal, autoimmune and hearing abnormalities.

Noonan's syndrome

Noonan's syndrome may affect as many as 1 in 1000 individuals. It is caused by mutations of genes involved in the RAS/MAPK signalling pathway (including the *PTPN11*, *SOS1*, *KRAS* and *RAF-1* genes) and is inherited in an autosomal dominant manner. Clinical features include short stature, scoliosis, low-set ears, ptosis, pectus excavatum, cubitus valgus, pulmonary stenosis, cryptorchidism and delayed puberty, lymphoedema, mild educational difficulties and a coagulation defect.

Skeletal dysplasias

A range of bony dysplasias may cause short stature. Depending on which part of the skeleton is involved, impacts on growth may lead to skeletal disproportion, which justifies the measurement and comparison of both sitting and standing heights. Many skeletal dysplasias are inherited in an autosomal dominant pattern and so the possibility of an affected parent of a short child should be considered. Achondroplasia

and hypochondroplasia cause rhizomelic (shortening of the proximal limb segment) short stature and are often found to be caused by mutations of the fibroblast growth factor receptor 3 (*FGFR3*) gene. The mutated receptor is constitutionally active and inhibits cartilage formation and thus bone growth. Spondyloepiphyseal dysplasia leads to markedly impaired trunk growth and less severely affected short limbs, causing a disproportionately short sitting height. In children with short-limbed forms of short stature, height may be improved by leg-lengthening surgery.

Chronic disease

Chronic disease of many systems may lead to impaired growth. Mechanisms involved include a negative energy balance due to:

- Inadequate calorie intake (feeding problems)
- Malabsorption (coeliac disease or cystic fibrosis)
- Excess calorie requirement (cystic fibrosis or congenital heart disease)
- Hypoxia (congenital heart disease)
- Electrolyte abnormalities (renal disease or mineralocorticoid deficiency or resistance)
- Inflammatory cytokines (inflammatory bowel disease or juvenile idiopathic arthritis)
- Steroid treatment (asthma, chronic inflammatory disease)
- Acquired partial resistance to GH (renal failure or Crohn's disease delaying the onset of puberty).

Treatment to improve growth in these circumstances will require attention to the underlying mechanism, such as improving nutrition, reduction in steroid dosages, etc., before considering other options such as GH therapy).

Psychosocial deprivation

Adverse psychosocial factors may lead to poor growth through well-recognized mechanisms that impair fetal growth, such as maternal smoking or alcohol consumption, or through an inadequate diet or increased illnesses linked to parental smoking. Emotional deprivation or abuse may also cause growth failure through these influences producing hypothalamically-mediated suppression of pituitary GH secretion. Appropriate treatment of the growth failure requires interventions to prevent further abuse and to ensure the child is raised in a loving and supportive environment.

Endocrine disorders

Growth hormone deficiency

GH deficiency is characterized by: growth failure (more severe forms tend to present earlier); delayed skeletal maturation and puberty; increased body fat; micropenis; and hypoglycaemia in infancy when severe. If caused by hypopituitarism, the following features may be present:

- Signs of TSH, ACTH and gonadotrophin deficiencies
- Midline craniofacial skeleton abnormalities
- Optic atrophy and visual impairment suggestive of septo-optic dysplasia
- Signs of raised intracranial pressure (papilloedema)
- Bitemporal hemianopia consistent with a pituitary tumour compressing the optic chiasm.

A family history of other similarly affected individuals would suggest a mutation in the *GHRH* or *GH-1* gene, or in genes that encode the transcription factors involved in pituitary development.

Investigation for possible GH deficiency is only indicated once baseline investigations for non-GH-related causes of short stature have been performed and found to be normal. GH is secreted in a pulsatile fashion and as levels are low throughout most of a 24 hour period, random blood samples to measure GH concentrations are generally unhelpful. Monitoring blood samples every 20 minutes to produce a 24 hour GH secretory profile is challenging both to organize and to interpret and so stimulatory tests of GH secretion are the most clinically useful way to diagnose GH deficiency.

The gold standard GH stimulation test involves insulin-induced hypoglycaemia, which promotes a counter-regulatory GH secretory response and also allows measurement of the ACTH-induced cortisol response. However, this test is potentially dangerous and should only be performed in children over five years old in units experienced in its use. Alternative GH secretagogues include glucagon, which also stimulates cortisol release, clonidine and arginine, which stimulate GH alone, and GHRH, which stimulates the pituitary directly. A GHRH stimulation test is poor at distinguishing hypothalamic forms of GH deficiency from a normal short child and is therefore rarely used in childhood testing. A high peak GH response (in excess of 8.3 ng/dL) excludes a diagnosis of GH deficiency whereas intermediate values (5–8.3 ng/dL) suggest GH insufficiency if the growth pattern is consistent with this diagnosis. Low values (<5 ng/dL) indicate more severe forms of GH deficiency. In the UK, because of the limited sensitivity and specificity of these tests to diagnose GH deficiency, two abnormal responses to GH testing are required to make a diagnosis unless there is radiological evidence of intracranial abnormalities consistent with the diagnosis. If a

diagnosis of GH deficiency is made, an MRI scan is mandatory to exclude an underlying tumour. Consideration of tests for wider pituitary dysfunction is then also necessary.

Prior to treating GH deficiency, it is important to obtain accurate growth data, preferably over a minimum one year period, against which the benefits of GH treatment can be assessed. GH produced by recombinant DNA technology is administered by daily subcutaneous injection. The growth response should be evaluated by measurements every four to six months. Large post-marketing surveillance studies of responses to GH therapy have shown that these are related to severity of GH deficiency, pre-treatment height velocity, age, difference in child's height from parents' heights, birth weight, current weight and dose of GH. Taking these factors together, it is now possible to predict response to GH and to 'personalize' the dose of GH for the child to ensure a maximal and cost-effective response. A maximum growth response to GH therapy occurs in the first year, with tachyphylaxis occurring thereafter, presumably due to down-regulation of the GH receptor. An increase in height velocity of at least 2 cm/year is indicative of a successful response. Values less than this would call into doubt adherence to therapy or a diagnosis of GH deficiency. If a poor response persists, consideration should be given to discontinuation of therapy in the longer term. Once growth is complete after puberty, GH testing should be repeated, as mild forms of GH deficiency do not require ongoing therapy into adult life, during which lower levels of GH are required for maintenance of normal body composition, bone health and avoidance of cardiovascular risk factors. Ongoing monitoring for wider defects in pituitary function is important in supervising GH therapy.

In the very rare circumstances of GH resistance, GH therapy is ineffective and recombinant IGF-1 treatment is indicated.

Other endocrine causes of growth failure

Both congenital and acquired hypothyroidism cause growth failure. Hypothyroidism suppresses GH secretion. Furthermore, in the absence of thyroid hormone action through its receptor sites, the growth and anabolic effects of GH and IGF-1 are down-regulated. The growth failure of hypothyroidism can be reversed by thyroxine treatment.

Cushing's syndrome is characterized by marked growth failure. Excess cortisol levels directly suppress both GH secretion and action as well as delaying the onset of puberty.

Questions 12.1 and 12.2

Growth

A 15-year-old girl was being followed up in the growth clinic, having been diagnosed with GH deficiency aged five years. At that time, in response to insulin-induced hypoglycaemia (minimum blood glucose 2.2 mmol/L), she had demonstrated a maximum GH response of only 1.5 ng/dL (normal >8.3 ng/dL). A diagnosis of idiopathic GH deficiency was assumed and she started treatment with GH therapy. Her height had initially increased from the 0.4th centile to the lower limit of the target height centile on the 9th centile, but in recent years this had fallen back to the 2nd centile and her adherence to therapy had been questioned. Her serum IGF-1 levels on GH treatment were within the normal range. Despite starting puberty aged twelve years, her Tanner stage 3 breast development had not progressed at all over the previous three years, causing her significant upset. She was otherwise well.

Question 12.1

Which of the following investigations is least likely to be helpful? Select ONE answer only:

A. Karyotype

B. LHRH stimulation test

C. MRI scan

D. Skeletal survey

E. Thyroid function tests

Question 12.2

What treatment is she most likely to require to optimize her final height? Select ONE answer only:

A. Calorie supplementation to her diet

B. Increasing the dose of GH

C. Oestrogen replacement

D. Oxandrolone

E. Parents to resume the responsibility of injecting her with GH

Answers 12.1 and 12.2

Question 12.1: Which of the following investigations is least likely to be helpful?

D. Skeletal survey.

A skeletal survey is unnecessary, as skeletal dysplasias are not associated with GH deficiency or pubertal failure. The failure of pubertal progression in the context of known GH deficiency suggests the development of a wider defect in pituitary function, which should be evaluated by an LHRH stimulation test and thyroid function testing, given that both hypogonadotrophic hypogonadism

and hypothyroidism may delay puberty. An MRI scan is important to exclude an intracranial tumour such as a craniopharyngioma. Turner's syndrome should be formally excluded in any short girl with pubertal failure, though a prior diagnosis of GH deficiency makes this diagnosis unlikely.

Question 12.2: What treatment is she most likely to require to optimize her final height?

C. Oestrogen replacement.

This girl has pubertal failure, most probably due to hypogonadotrophic hypogonadism and requires oestrogen therapy to complete puberty and the pubertal growth spurt. A normal IGF-1 level suggests good adherence to GH therapy and neither oxandrolone nor nutritional supplementation is appropriate treatment for oestrogen deficiency.

Tall stature

Familial tall stature and constitutional advance in growth and puberty

Familial tall stature is the commonest cause of tall stature (usually girls) referred to a growth clinic for assessment. The increased likelihood that tall parents will produce tall children reflects the polygenic inheritance of height. However, where one parent is exceptionally tall, the possibility of an autosomal dominant cause of tall stature should be considered. In familial tall stature, simple explanation and reassurance is usually sufficient. Rarely, suppression of final height can be attempted by early induction of puberty with high dose oestrogen to limit the prepubertal component of growth. However, this treatment has rather fallen out of fashion due to concerns about adverse longer term effects on fertility. A somewhat radical and rarely performed alternative involves surgical epiphysiodesis to fuse the growth plates.

Constitutionally advanced puberty is associated with rapid growth but puberty-induced oestrogen promotes early growth plate fusion, which prevents unacceptably tall final height. Likewise, simple obesity is associated with tall stature in earlier childhood but earlier onset of puberty.

Syndromic tall stature

Marfan's syndrome

This autosomal dominant condition is caused by mutations in the *FBN1* gene encoding the glycoprotein fibrillin-1, which form fibres in connective tissue. In addition to long-limbed tall stature, many of the features of Marfan's syndrome are linked to connective tissue defects, including aortic root dilatation, mitral valve prolapse, ligamentous laxity, lens subluxation, scoliosis and striae. Long-term monitoring of cardiovascular status is required.

Sotos syndrome

This overgrowth syndrome is caused by mutations of the *NSD1* gene and is associated with accelerated prenatal and infantile growth, tall childhood stature but advanced bone age leading to a normal adult height. Many have variable degrees of learning difficulties and a characteristic inverted 'pear-shaped' head with a prominent forehead.

Beckwith–Wiedemann syndrome

This largely sporadic condition is associated with defects in chromosome 11p15 including paternal uniparental disomy, another example of an imprinting disorder which affects growth. (These chromosomal abnormalities lead to overactivity of the gene that encodes the IGF-2 growth factor and absence of *CDKN1C*, which encodes an inhibitor of cell proliferation.) Apart from overgrowth, Beckwith–Wiedemann syndrome is associated with hemi-hypertrophy, defects in the anterior abdominal wall, macroglossia, hypoglycaemia, abnormal ear creases and an increased predisposition to tumours, particularly Wilms'.

Endocrine causes of tall stature

The commonest endocrine cause of tall stature is precocious puberty (see later). Thyrotoxicosis, familial glucocorticoid deficiency and GH-secreting tumours rarely also cause tall stature. The observation that the two very rare conditions of aromatase deficiency and oestrogen receptor defects lead to extreme tall stature has demonstrated the importance of oestrogen action in stimulating fusion of the growth plate even in males.

Questions 12.3 and 12.4

Tall stature

A 13-year-old girl whose height is above the 99.6th centile is referred for evaluation of tall stature. Her father is also tall, though the upper limit of the target height based on her mid-parental heights lies on the 90th centile. She is well in herself. The only family history is that a paternal uncle died unexpectedly in his early 20s. On examination, she has slender, long limbs and digits and her arm span exceeds her height. She has a pulse rate of 60/min and normal ankle jerks. She has Tanner stage 4 breast and pubic hair development.

Disorders of gonadal function and sexual development

This is described in Chapter 20, Genital disorders.

Endocrine regulation of puberty and normal pubertal development

Puberty is the process through which a child passes to achieve sexual maturity and reproductive capacity. Pubertal onset is precipitated by the secretion of hypothalamic pulses of gonadotrophin-releasing hormone (GnRH), which in turn stimulate pulses of LH. Precisely how this is regulated is unclear, though GnRH neurons are under the control of excitatory (glutamate) and inhibitory (GABA) neurons. Given the inherited pattern to the timing of onset of puberty, there are clearly important genetic influences in addition to leptin-mediated nutritional effects and other environmental influences that have been observed to affect the onset of puberty in girls.

In boys, increasing LH stimulates testicular Leydig cells to secrete testosterone, which in turn promotes development of secondary sexual characteristics, namely enlargement and maturation of the penis and scrotum, increased musculature, facial and other body hair and deepening of the voice. GH and IGF-1 levels rise to stimulate the pubertal growth spurt leading to increased resistance to insulin-mediated glucose metabolism, which in turn causes increased insulin secretion to help fuel anabolism during the growth spurt. Testosterone feeds back to modulate LH secretion. At the same time, increased FSH binds to Sertoli cells to enhance spermatogenesis. Inhibin B secreted by Sertoli cells exerts negative feedback on pituitary FSH release.

In girls, LH stimulates proliferation of follicular and thecal cells and androgen secretion during the follicular phase of the menstrual cycle. FSH stimulates proliferation of granulosa cells, supports aromatization of androstenedione to oestradiol and stimulates progesterone production. Oestrogens stimulate secondary sexual characteristics such as breast development and the growth spurt and they act on FSH receptors on granulosa cells to cause proliferation of follicular cells. Inhibin A is produced by large antral follicles and the corpus luteum and inhibin B by granulosa cells in small antral follicles. Inhibins may feedback on FSH secretion as well as being involved in the dominant follicle selection. The follicular phase of the menstrual cycle is variable in duration but typically lasts 14 days. Fifteen to twenty primordial follicles develop during each cycle, most becoming atretic, but one dominant Graafian follicle persists. FSH increases from the first day of the cycle to stimulate follicular production of oestradiol which leads to feedback inhibition of LH and FSH. Oestradiol feedback to the pituitary then switches from negative to positive,
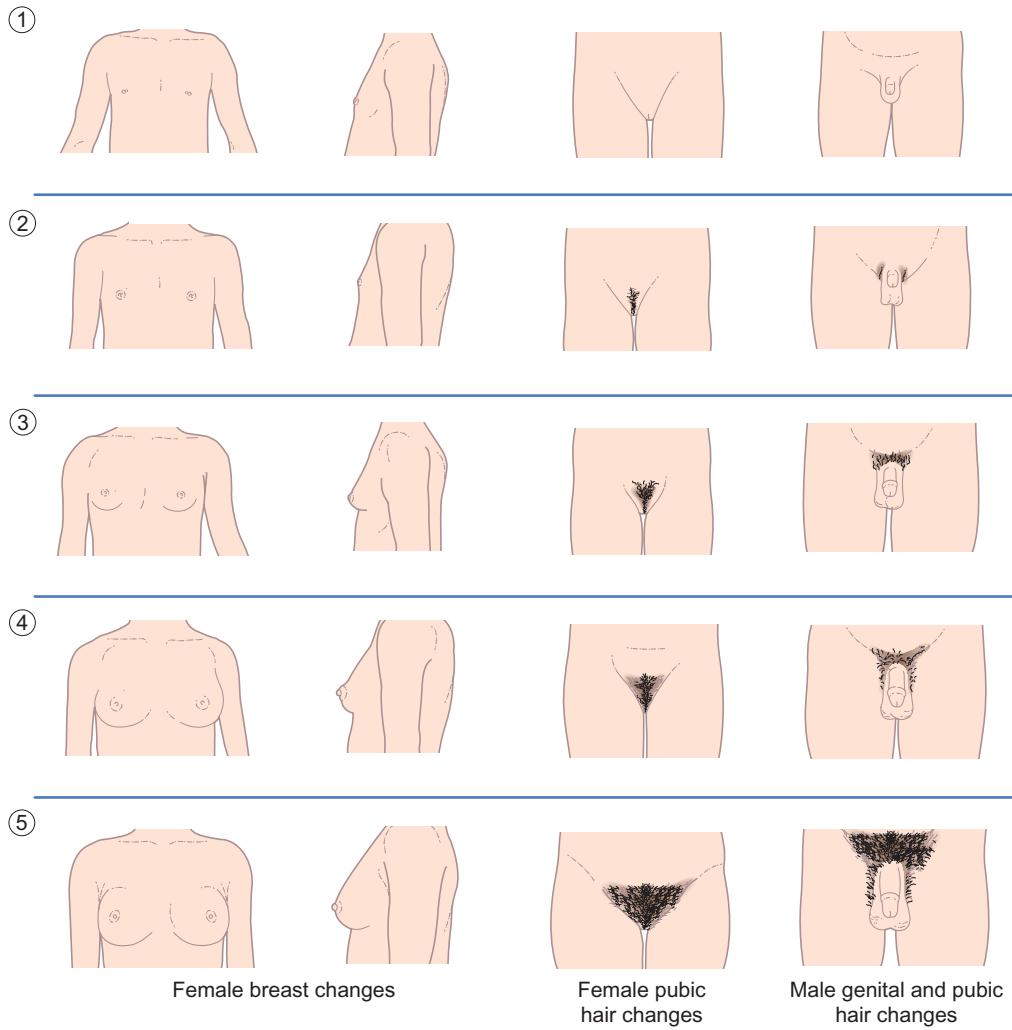
Fig. 12.3 **Tanner stages of puberty.** *(From Levene M. MRCPCH Mastercourse, 2007, Elsevier Churchill Livingstone, with permission.)*

causing a preovulatory LH surge. In the 14 day luteal phase of the menstrual cycle, LH stimulation causes the ovum to enter the final phase of the first meiotic division to become a secondary oocyte. The follicle swells, ruptures and releases the ovum into the fallopian tube. A corpus luteum is formed from the follicle resulting in progesterone-mediated swelling and secretion of the endometrium. Progesterone peaks five to seven days post ovulation, exerting a negative feedback on GnRH-regulated LH and FSH secretion, causing the corpus luteum to lose its receptors and become atretic, following which a new cycle starts.

In boys, the mean age for onset of puberty is 12 years, with anywhere between 10–14 years being regarded as normal. The first sign of normal puberty is the development of 4 mL testicular volumes, followed shortly thereafter by the development of pubic hair and genital changes, which can be progressively documented through puberty using the Tanner staging

methodology (Fig. 12.3). The pubertal growth spurt is a feature of the second half of puberty in boys. By contrast, in girls, the mean age for onset of puberty is 11 years with anywhere between 8–13 years being considered normal. The first sign of puberty is breast bud development followed thereafter by pubic hair growth, with the pubertal growth spurt occurring earlier than in boys. Typically, progression through puberty takes about three years, though there is considerable variation in the length of time that individuals will spend in each stage of puberty.

Precocious puberty

Precocious puberty may be defined as evidence of breast or pubic hair development in girls before the age of eight years, or signs of testicular volume increase to at least 4 mL or other evidence of virilization in boys occurring before the age of 9 years.

History

In the history, the following details are important:

- Details of the previous growth pattern and weight gain
- Timing of onset of features of puberty, including acne, body odour, breast, pubic hair and genital development, increased vaginal secretions or periods
- Presence of headache or other neurological symptoms suggestive of intracranial pathology
- Risk factors in the perinatal history (e.g. prematurity, intraventricular haemorrhage, small for gestational age) or the presence of other disorders associated with sexual precocity (e.g. McCune–Albright syndrome, neurofibromatosis)
- Drug history (e.g. oxymethalone)
- Family history of early onset of puberty, including timing of maternal menarche
- The extent to which the early onset of puberty is impacting on the child's psychosocial well-being.

Examination

The following should be noted:

- Measurement of height (and comparison with the target height range based on parental height centiles), weight, documentation of Tanner stages of puberty and, in boys, measurement of testicular volumes using a Prader orchidometer
- Café-au-lait patches and axillary freckling suggestive of neurofibromatosis
- Café-au-lait pigmentation with an irregular outline (which on occasions follow a dermatomal distribution along the lines of Blaschko, see Chapter 25, Dermatology) or other features of endocrine overfunction (e.g. hyperthyroidism) or suggestive of McCune–Albright syndrome
- Fundoscopy and visual field examinations for signs of raised intracranial pressure.

Investigations

The following investigations should be considered:

- A guide to the extent of physiological advance can be obtained by calculating a bone age from an X-ray of the left wrist
- A pelvic ultrasound to document the size of the uterus, extent of endometrial response and the size of the ovaries and the presence of ovarian follicles
- A basal blood sample for measurement of testosterone (boys) or oestradiol (girls) to confirm biochemical evidence of puberty, LH and FSH to distinguish between gonadotrophin-dependent

and independent causes, and adrenal androgens (DHEAS, androstenedione and 17-OH progesterone) to exclude a defect in adrenal hormone biosynthesis (a urinary steroid metabolite profile may be helpful in the latter circumstance)
- If basal gonadotrophins are low and sex steroids high, implying gonadotrophin-independent precocious puberty (Fig. 12.4), an LHRH stimulation test is indicated to confirm the lack of gonadotrophin response in this scenario
- In gonadotrophin-dependent precocious puberty (Fig. 12.4), an MRI of the hypothalamo-pituitary axis is required to exclude an intracranial tumour, especially in boys.

True central precocious puberty

This is defined as early-onset puberty which has been stimulated by activation of the hypothalamo-pituitary axis. It is a phenomenon that is more commonly seen in girls than in boys. In girls, the underlying cause is usually unknown, whereas in boys this is usually the consequence of intracranial pathology, including tumours in the region of the hypothalamus (e.g. gliomas, astrocytomas and benign hamartomas) and following previous cerebral trauma often incurred in the perinatal period, such as periventricular haemorrhage. Diagnosis requires measurement of serum oestradiol concentrations and usually an LHRH stimulation test to demonstrate activation of gonadotrophins. A wrist X-ray will show advanced bone development and in girls a pelvic ultrasound may show ovarian enlargement with follicles and uterine enlargement consistent with pubertal development. An MRI scan is important to exclude intracranial pathology.

Treatment requires GnRH analogue therapy to suppress gonadotrophin and oestradiol secretion to prevent the challenging psychosocial effects of advancing puberty and to maximize potential adult height. GnRH analogues bind to the GnRH receptors, initially stimulating them but thereafter achieving downregulation, and this may lead to a temporary episode of vaginal blood loss, which may also be precipitated by falling oestradiol levels. Treatment should be continued until the child and family are comfortable to allow puberty to progress or until the child has achieved the normal age-range for the stage of puberty that has been achieved.

Androgen-mediated precocious puberty

This form of early-onset puberty is precipitated by excess androgen secretion, which causes virilization
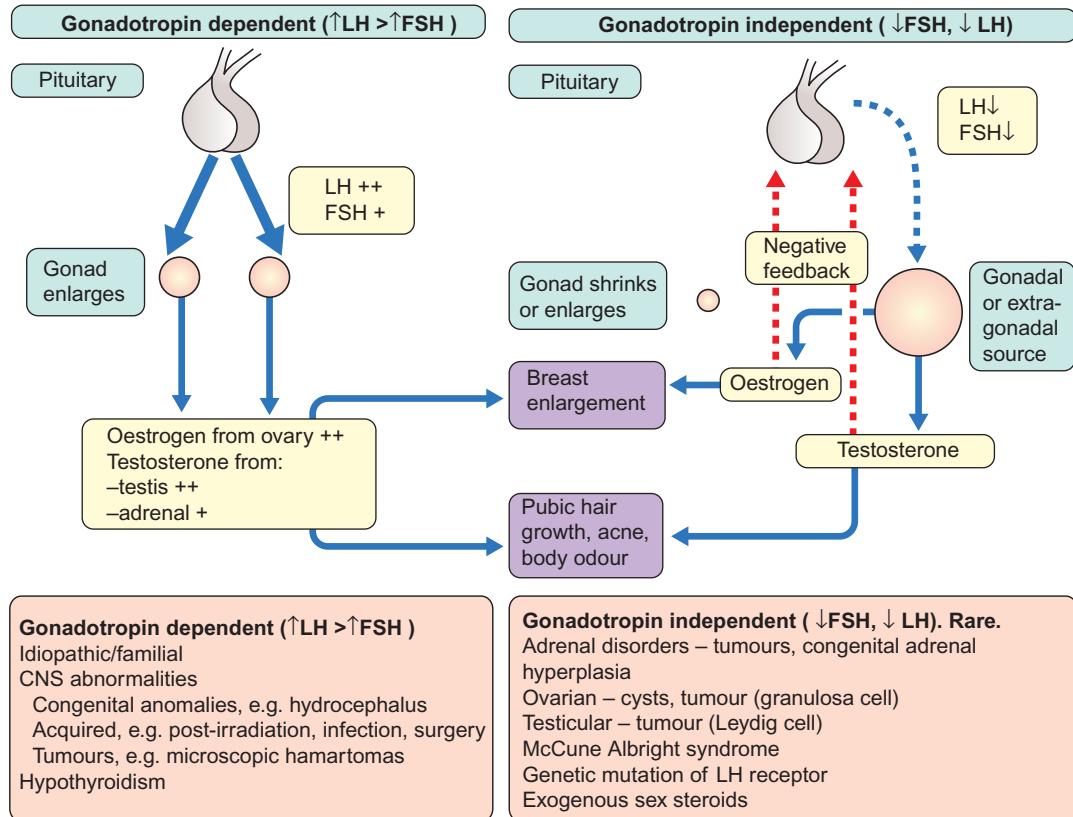
Fig. 12.4 Causes of precocious puberty. *(Courtesy of Dr Emma Rhodes. Adapted from Lissauer T, Clayden G. Illustrated Textbook of Paediatrics, 4th ed. Edinburgh: Mosby Elsevier; 2012.)*

including pubic and axillary hair development and, in more severe cases, genital maturation in boys and cliteromegaly in girls. The commonest form is *exaggerated adrenarche*, which is associated with the physiological activation of the adrenal gland from the age of six years, which produces relatively weak androgens such as DHEAS (dehydroepiandrosterone) and androstenedione. The physiological consequences of this pass unnoticed in most children, but in a proportion, small amounts of pubic or axillary hair are produced, sometimes associated with increased skin secretions and body odour. There is no specific therapy for exaggerated adrenarche and simple reassurance is all that is required. This condition has been shown to be associated with reduced birth weight and polycystic ovarian disease in later life.

It is important to distinguish exaggerated adrenarche from congenital adrenal hyperplasia (CAH). This requires measurement of 17OH-progesterone for the common 21-hydroxylase deficient variant or a urinary steroid metabolite profile for the less common virilizing forms. Virilizing forms of CAH are usually associated with significant virilization including cliteromegaly and evidence of a growth spurt with marked advance in bone age. Treatment of CAH to prevent precocious puberty is discussed elsewhere. Rarely, virilizing tumours of the ovarian or adrenal glands may cause androgen-mediated precocious puberty and will require surgery.

Other causes of early pubertal development

Gonadotrophin-independent precocious puberty, also known as testotoxicosis, is rare in boys and is due to autosomal dominant activating mutations of the LH receptor. In both genders, activating mutations of a gene involved in G-protein coupled signalling, as occur in McCune–Albright syndrome, may also lead to gonadotrophin-independent precocious puberty. In both these conditions, GnRH analogue therapy will not work as the defect lies distal to the action of GnRH. Therapy for gonadotrophin-independent precocious puberty requires the use of anti-oestrogens in girls or, in boys, androgen synthesis blockers (cyproterone, ketoconazole), aromatase inhibitors (testolactone) or androgen receptor blockers (spironolactone, ketoconazole, cyproterone, flutamide).

Premature thelarche is a relatively common condition in which isolated breast development presents in young girls aged about six to twelve months in the absence of any wider evidence of puberty or rising oestradiol concentration. An FSH response to LHRH stimulation testing occurs but the underlying mechanisms of breast development are not understood. This condition is benign and self-limiting and no therapy is required. A similar phenomenon may occur between the ages of five to eight years, sometimes associated with a slight increase in height velocity or a brief period of vaginal blood loss and is known as thelarche variant. At a similar age, through unknown mechanisms, cyclical vaginal bleeding may occur in the absence of wider signs of puberty, known as premature menarche. The differential diagnosis includes vulvovaginitis, vaginal trauma, foreign bodies, tumours and sexual abuse.

Questions 12.5 and 12.6

Breast development and vaginal blood loss in a two-year-old girl

A two-year-old girl is referred with concerns about breast development and an episode of vaginal blood loss. She is otherwise clinically well. Her length and weight are on the 97th centile, but there are no abnormal findings apart from the presence of Tanner stage 3 breast development. A bone age is advanced by one year and a pelvic ultrasound shows an enlarged uterus of 30 mL and enlarged ovaries with follicles. Basal blood sampling shows an LH <0.5 U/L, FSH 1.7 U/L and oestradiol of 84 pmol/L rather than undetectable levels, which would be regarded as normal in a two-year-old.

Question 12.5

Which is the most likely diagnosis? Select ONE answer only.

A. Hypothalamic hamartoma

B. Idiopathic central precocious puberty

C. McCune–Albright syndrome

D. Premature thelarche

E. Thelarche variant

Question 12.6

What is the next most appropriate investigation? Select ONE answer only.

A. GH suppression test

B. LHRH stimulation test

C. MRI scan of head

D. No further tests are indicated

E. Thyroid function tests

Answers 12.5 and 12.6

Question 12.5: Which is the most likely diagnosis?

B. Idiopathic central precocious puberty.

This girl presents with clear evidence of precocious puberty, including tall stature, breast development, periods and elevated serum oestradiol concentrations with uterine and ovarian enlargement, all of which together exclude premature thelarche or thelarche variant.

Question 12.6: What is the next most appropriate investigation?

B. LHRH stimulation test.

The lack of elevated basal gonadotrophins casts doubt on whether this is gonadotrophin-dependent or independent puberty, and an LHRH stimulation test is indicated to clarify the underlying mechanism, likely differential diagnosis and most appropriate therapy. Although McCune–Albright syndrome cannot be excluded at this point, the lack of pigmented skin lesions makes idiopathic central precocious puberty the most likely diagnosis. This would be confirmed by showing a gonadotrophin response to LHRH and normal findings on an MRI scan.

Delayed puberty

Is defined as lack of evidence of any breast development in girls by the age of 13 years and failure of testicular enlargement to at least 4 mL in boys by the age of 14 years.

History

When faced with a child with delayed onset of puberty, the following details should be sought in the clinical history:

- Details of the previous growth pattern
- Symptoms or the presence of other chronic disease, including details of medication such as steroids
- Features suggestive of gonadal impairment, such as cryptorchidism, need for orchidopexy, gonadal irradiation
- The presence of symptoms suggestive of hypopituitarism, including headache, visual disturbance, significant neonatal hypoglycaemia or prolonged jaundice
- An impaired sense of smell, which may suggest a defect in olfactory nerve development consistent with a diagnosis of Kallmann's syndrome
- Family history of delayed puberty, including timing of maternal menarche

Examination

In a child with delayed onset of puberty, the following should be noted:

- Measurement of height (and comparison with the target height range based on parental height centiles), weight, documentation of Tanner stages of puberty and, in boys, measurement of testicular volumes using a Prader orchidometer
- Dysmorphic signs consistent with syndromes associated with delayed puberty, such as Turner's or Klinefelter's syndrome
- Signs suggestive of an underlying chronic disorder (e.g. clubbing, hypertension, Harrison's sulci)
- Midline defects of the craniofacial skeleton, presence of optic atrophy or other features consistent with congenital hypopituitarism
- Fundoscopy and visual field examinations for signs of raised intracranial pressure.

Investigations

In children with delayed puberty, the following investigations should be considered:

- A guide to the extent of physiological delay can be obtained by calculating a bone age from an X-ray of the left wrist, evaluated (using either the Tanner–Whitehouse methodology in the UK, or the Greulich–Pyle method derived from US standards)
- A pelvic ultrasound to document the size of the uterus, extent of endometrial response and the size of the ovaries and the presence of ovarian follicles may be helpful
- Relevant tests of any system thought to be a cause of chronic disease impacting on the timing of puberty (e.g. thyroid function tests, screening for coeliac disease or inflammatory markers if occult inflammatory disease is suspected)
- Karyotype to exclude Turner's syndrome or Klinefelter's syndrome
- A basal blood sample for measurement of LH, FSH and testosterone (boys) or oestradiol (girls)
- Elevated basal gonadotrophins imply primary gonadal failure, but low gonadotrophins do not reliably distinguish constitutionally delayed puberty from hypogonadotrophic hypogonadism, for which an LHRH stimulation test is required
- Testicular function can be assessed by measuring the testosterone response to HCG (a specialist opinion is required for the different protocols for dynamic tests of pituitary–gonadal function).

Management

Delayed puberty may be subdivided into those causes that are mediated by abnormalities of hypothalamo-

pituitary function (central) or those which are a consequence of defects in gonadal function (peripheral).

Centrally delayed puberty

The most common cause of delayed puberty is where there are no underlying abnormalities of the hypothalamo-pituitary-gonadal axis and the delay in onset of puberty is regulated by genes as yet unknown. Boys are most likely to be referred for assessment. A family history of a similarly affected parent is common and the presentation is characterized by a slowing in height velocity in the years leading up to the delayed onset of puberty. No abnormalities will be identified in the history or on examination (apart from the delayed physical development). Management includes counselling of the child and parents that, given time, puberty will develop normally; in those who wish, puberty can be induced after the age of 13–14 years using low-dose testosterone or oestrogen, usually for six to twelve months to prime the hypothalamo-pituitary axis.

A range of chronic diseases, particularly those associated with chronic inflammation such as inflammatory bowel disease or with a negative energy balance due to impaired food intake or absorption (e.g. coeliac disease), are associated with delayed puberty, probably mediated through the effects of the disease on the hypothalamic function. Treatment of the delayed puberty usually requires correction of the underlying defect using appropriate anti-inflammatory measures in the former and nutritional support, including a gluten-free diet, in the latter. Sometimes, additional low-dose testosterone or oestrogen therapy can be added for six to twelve months to the disease-specific medication to accelerate the onset of puberty.

Impaired hypothalamo-pituitary function can also result in centrally delayed puberty due to hypogonadotrophic hypogonadism. Causes include local tumours, such as a craniopharyngioma, and congenital defects in pituitary development including Kallmann's syndrome, caused by mutations in a range of genes that encode proteins involved in the development, migration or activity of the GnRH-releasing neurons. Some of these genes also regulate the migration of olfactory neurons from the olfactory bulbs to the hypothalamus, which accounts for the frequent association of anosmia with hypogonadotrophic hypogonadism. Treatment of delayed puberty requires testosterone or oestrogen replacement at steadily increasing doses over two to three years to full adult replacement.

Primary hypogonadism

Primary hypogonadism in boys may occur when the testes have failed to descend normally, undergone

bilateral torsion, been damaged by radiotherapy or surgery or in association with Klinefelter's syndrome. If there is associated failure of puberty and virilization, then induction with low-dose testosterone, steadily increased over a three year period to adult replacement doses, is indicated.

In girls, primary hypogonadism may occur after radiotherapy or in association with Turner's syndrome (see previous section). Treatment of pubertal delay requires administration of oestrogen starting with a low dose, which should be steadily increased over a three year period to an adult replacement dose.

Questions 12.7 and 12.8

Delayed puberty

A 13-year-old girl was referred because she was upset about her delayed onset of puberty and poor growth in recent years. Her height was 5 cm below the 0.4th centile compared to a target height range that came down to the 2nd centile. She was reportedly clinically well. Her mother underwent menarche aged 13 years and her father did not recall experiencing a delayed puberty. There were no abnormal findings on examination apart from her lack of pubertal development. A basal blood sample demonstrated a serum LH of 2.4 U/L and FSH of 15.4 U/L with undetectable oestradiol concentrations. GH testing using insulin-induced hypoglycaemia demonstrated a maximum GH of 9 ng/dL (normal response).

Question 12.7

What is the most likely diagnosis? Select ONE answer only:

A. Constitutionally delayed growth and puberty
B. Craniopharyngioma
C. Familial short stature
D. GH deficiency
E. Turner's syndrome

Question 12.8

What treatment is indicated? Select ONE answer only:

A. GH
B. GH and low-dose ethinyloestradiol
C. Low-dose ethinyloestradiol
D. Oral contraceptive pill
E. Oxandrolone

Answers 12.7 and 12.8

Question 12.7: What is the most likely diagnosis?

E. Turner's syndrome

The elevated basal FSH concentrations suggest a primary defect in ovarian function most likely due to Turner's syndrome rather than constitutionally delayed puberty or hypogonadotrophic hypogonadism due to an intracranial tumour. The target height range and child's current height are not consistent with a diagnosis of familial short stature and the GH response to testing is normal (>8.3 ng/dL).

Question 12.8: What treatment is indicated?

B. GH and low-dose ethinyloestradiol

Given the severity of short stature and delay in onset of puberty, a combination of GH and low-dose ethinyloestradiol should be given to stimulate both growth and puberty in Turner's syndrome. Oxandrolone alone will not induce breast development and the oestrogen dose in the oral contraceptive pill is too large for initial induction of puberty even though it may be an appropriate form of hormone replacement once puberty has been completed.

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Mary Fewtrell
With contributions by
Hannah Tobin

CHAPTER

13

Nutrition

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Understand the principles of body composition in children and its assessment
- Understand the scientific basis of nutrition
- Understand the physiological basis of normal enteral nutrition and its variation throughout childhood
- Know the constituents of a healthy diet at all ages, including breastfeeding and formula feeding in infancy
- Know the constitution of infant feeds commonly used in health and disease
- Know the principles and methods of dietary supplementation, e.g. calories, vitamins, minerals
- Know the principles of nutritional management in childhood disease, e.g. neonates, sick children
- Understand the assessment of faltering growth
- Know about the assessment of being overweight or obese

Growth and body composition

The traditional measures of nutritional status and well-being during infancy and childhood are body weight and/or length or height, plotted on appropriate centile charts so that the individual child's growth can be compared with that of a child of the same age and gender from a 'reference' population.

Monitoring growth

Currently, five different growth charts are available in the UK (see Further reading for more information). The UK-WHO '0–4 years' is the growth chart most commonly used to monitor growth in healthy infants and young children. In addition to this, a Neonatal and Infant Close Monitoring chart (NICM) has been designed to monitor growth in very preterm infants and those whose growth may be affected by early health problems or chronic disease. This chart has low lines to monitor unusually short or underweight children and provides assistance with correction for gestational age. Two different charts are now available for school-aged children: the '2–18' chart, whose features include guidance on monitoring puberty, BMI and an adult height predictor; and the new Childhood and Puberty Close Monitoring chart (CPCM). This chart is for use in school-aged children with growth or nutritional problems and can be used until the age of 20. Separate charts are also available for children with Down's syndrome.

In May 2009, the new UK-WHO growth charts replaced the British 1990 (UK90) charts for children aged 0–4 years. These new charts combine data from the British 1990 reference at birth with data from the WHO Multicentre Growth Reference Study (MGRS; see Further reading) from 2 weeks to 4 years. The MGRS was conducted to provide data on the way that infants should grow (a standard) rather than how they do grow (a reference). It is conceptually different from older growth references and is based on the premise

that babies of all ethnicities grow similarly and to the same extent when receiving optimal nutrition – breast-feeding – and with no environmental constraints on growth. Therefore, the WHO MGRS collected anthropometric data from term infants exclusively breastfed for at least the first 4 months of life from the most advantageous backgrounds in six countries of differing ethnicity. By contrast, older growth charts (references) were based on data from a mixture of formula-fed and breastfed babies from a range of socio-economic backgrounds, generally in a single country or area.

Key differences between the new UK-WHO chart and the old UK90 chart are:

- It is designed for term infants (the MGRS did not include preterm infants)
- Birth measurements for term infants born between 37 and 42 weeks' gestation are plotted at a single point
- A separate UK preterm chart is available, incorporating older UK90 data until term age, and WHO data from 2 weeks
- No data are provided from 0–2 weeks, allowing for the expected dip in weight and regaining of birth weight up to 2 weeks
- The 50th centile is de-emphasized (it is no longer printed in bold type)

When values for the same infants are plotted on both charts, the apparent growth trajectory can vary significantly, especially for weight and head circumference. Plotting infants on the new charts after the age of 6 months will give twice as many above the 98th centile for weight and only 1/200 below the 2nd centile. Indeed, this was one of the aims of the new growth standard, since breastfed infants tend to grow more slowly than formula-fed infants during the second 6 months of life and were often diagnosed as having growth faltering when older charts were used. However, the expected trajectory of weight gain on the new charts is harder to achieve in the period up to 6 months (perhaps because of the highly selected nature of the reference population). This has the potential to result in mothers stopping breastfeeding or supplementing with infant formula if they think their infant is not gaining weight normally. Clinicians need to be aware of the changes to the growth charts and the apparent impact this can have on a child's growth, in order to advise mothers appropriately.

Body composition

'Body composition' refers to the amount of fat and fat-free mass in the body. There is increasing evidence that this is relevant both for nutritional management and for clinical outcome. For example, providing additional energy to chronically ill children whose linear growth is stunted may make them gain fat without improving linear growth or lean mass; similarly, underweight children with developmental handicaps may become fatter when given improved nutrition without beneficial effects on any clinical outcome. Theoretically, basing energy intake on lean mass, which is the metabolically active component, might be a more sensible approach.

Body Mass Index (BMI = weight/height^2) is widely used as a measure of 'adiposity' or fatness. However, this index is a composite of fat and fat-free tissue and does not provide information about the amount of fat or fat-free tissue in the body. In groups or populations, it is reasonable to regard BMI as a proxy for adiposity, since fat is the most variable component of body composition. However, this is not the case for individuals; children with the same BMI can have very different amounts of fat and fat-free mass. Indeed, the relative amount and accretion rates of fat and lean tissue differ between boys and girls.

Historically, the use of more detailed body composition measurements in clinical practice has been limited due to methodological problems in obtaining reliable measurements and to a lack of reference data for the paediatric age group. UK reference data for body composition are now available for children aged 5 and above, so individual children can be given a centile or SD score for fat and lean mass in the same way as for weight, height or BMI.

Measuring body composition

A number of different techniques are available to measure body composition ranging from simple measures such as skinfold thicknesses, waist circumference or mid upper arm circumference (see Fig 33.5) to more complex methods suitable only in a research setting. These methods are outlined below, and the advantages and disadvantages of individual methods are further summarized in Table 13.1.

'Two-component' models divide the body into fat mass (FM) and fat-free mass (FFM). Body composition is either 'predicted' (for example, by combining several skinfold thickness measurements in a prediction equation, or using bioelectric impedance (Fig. 13.1C) to predict body water and hence FFM) or 'measured' (for example, measuring body density (usually by air displacement plethysmography), body water using a stable isotope such as deuterium as a tracer, or by dual X-ray absorptiometry (DXA; Fig. 13.1B)). The main limitation of these two-component models is the need to assume a constant hydration of fat-free mass. In fact, hydration has been shown to vary with age and is altered by obesity as well as in many acute and chronic diseases.
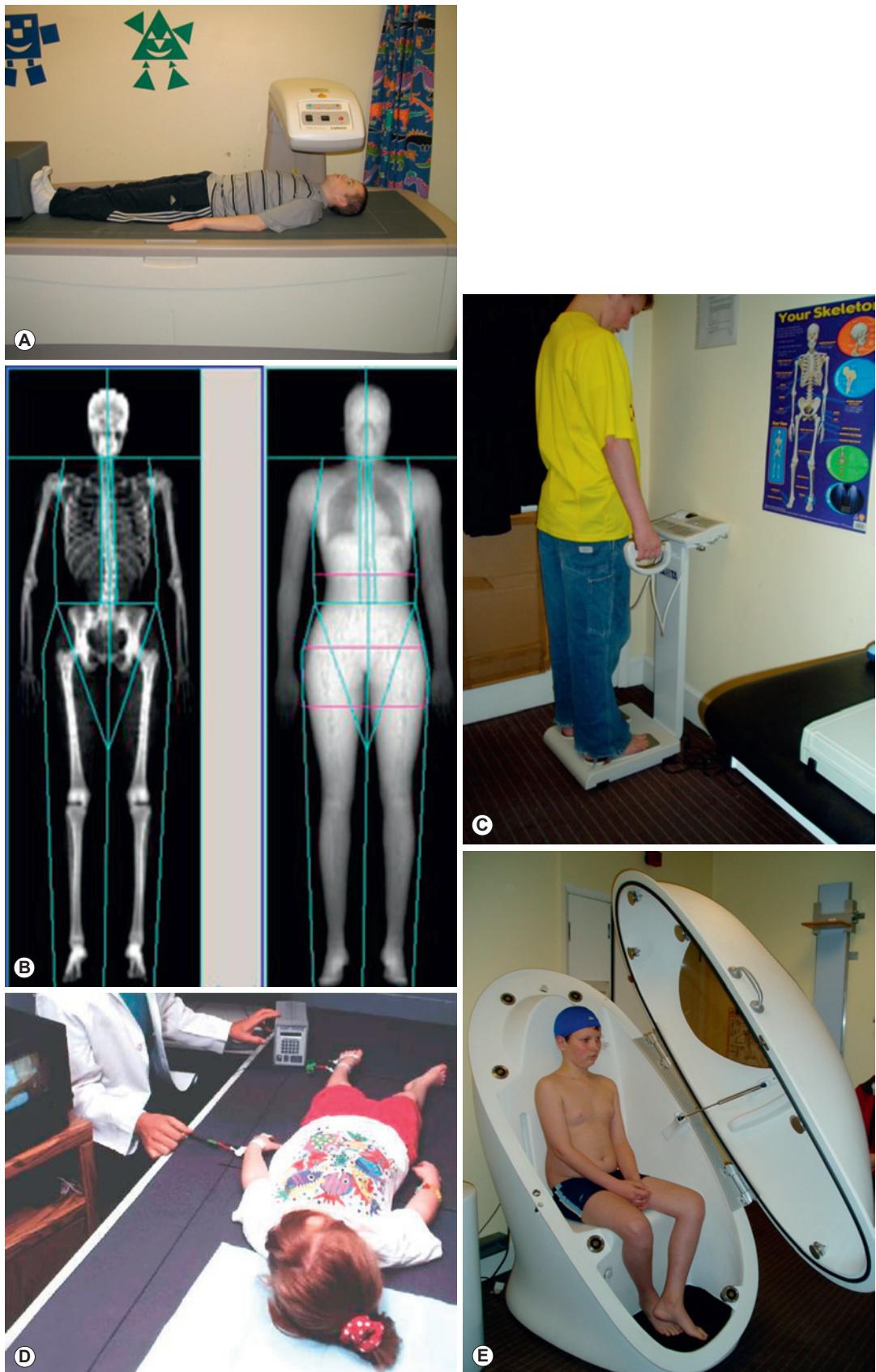
Fig. 13.1 Some techniques used to measure body composition in children. A,B. Child undergoing a dual energy X-ray absorptiometry (DXA) whole body scan and the image generated. C,D. Children undergoing bioelectric impedance analysis measurements with two types of machine (standing and supine). E. Air displacement plethysmography (BodPod), used to measure body volume by air displacement plethysmography.

Table 13.1 Summary of assumptions underlying different techniques for measuring body composition, their availability, and their main advantages and disadvantages

Technique	Assumptions made	Reference data	Availability*	Advantages/disadvantages
Skinfolds – raw	Constant skin protein content	Y	+++	For: simple measure of regional fat Against: no information on lean mass
	Skinfolds ∝ whole body fat	N	+++	For: simple and quick Against: population specific, poor accuracy in individuals and groups
Body mass index	Var weight = var fat	Y	+++	For: simple and quick Against: measures nutritional status not body composition
Waist circumference	Waist ∝ central fat	Y	+++	For: simple, quick, robust measure of abdominal fat Against: not so accurate as measure of internal visceral fat
Bioelectric impedance analysis (BIA)	Conductivity ∝ body water	N	++	For: simple and quick Against: population specific, poor accuracy in individuals and groups
DXA (dual X-ray absorptionometry)	Constant attenuations of FFM and F	Y	++	For: accurate for limb lean and fat Against: radiation exposure, whole body bias ∝ size, sex, fatness
Densitometry†	Constant D_{ffm} and D_f	N	+	For: acceptable two-component technique Against: effects of disease on lean mass reduce accuracy
Isotope dilution	Constant H_{ffm}	N	+	For: only technique acceptable in all age groups Against: delayed results, inaccurate if disease affects H_{ffm}
MRI	Electromagnetic properties	N	+	For: accurate for regional AT Against: expensive, limited availability, measures AT not fat

*Availability: +, low; ++, medium; +++, high. †Densitometry by air displacement plethysmography (BodPod). Abbreviations: AT, adipose tissue; D_f, density of fat; D_{ffm}, density of fat-free mass; D_{min}, density of mineral; F, fat; FFM, fat-free mass; H_{ffm}, hydration of fat-free mass; Var, variability.

More sophisticated models ('three- and four-component' models) reduce the number of assumptions made by performing more measurements. In the three-component model, the body is divided into fat mass, fat-free mass and water; whereas in the four-component model, fat-free mass is further divided into mineral mass and protein mass. The four-component model is regarded as the gold standard for measuring body composition *in vivo* since it makes the fewest assumptions. However, it requires the subject to undergo air displacement plethysmography (Fig. 13.1E), a DXA scan and a measurement of total body water using stable isotopes, so is not suitable outside a research setting. Furthermore, it is currently almost impossible to accurately measure body volume in children between the ages of about 8 months and 4 years.

A recent study comparing results from different body composition measurement techniques against the four-component model in children with a variety of underlying illnesses concluded that DXA and bioelectric impedance analysis (BIA) were likely to be the most accurate and feasible methods in clinical practice, although it is unlikely that a single method could be used in all patients on all occasions; DXA requires the child to be taken to the scanner and to lie still for a few minutes, whereas BIA is not suitable in children with significant abnormalities in hydration.

Scientific basis of nutrition

Historically, the main objective in feeding infants and children was meeting nutritional needs, preventing nutritional deficiencies and facilitating adequate growth and development. However, the increasing evidence that early nutrition has biological effects, with important implications for short-term health, clinical course and prognosis as well as for later health outcomes, has led to a shift in focus. Until recently, nutritional recommendations and practice were underpinned largely by observational or physiological studies, or by small clinical trials designed to test for the effects of specific products on nutritional status, growth and tolerance. However, the past 20 years have seen the application of randomized trials to nutritional interventions. These trials examine both short-term and long-term efficacy and safety and are increasingly regarded as an essential component of the development and testing of novel nutritional products by regulatory bodies.

Nutritional programming

The concept that there are sensitive periods in early life when insults or stimuli may have long-term or even lifetime effects has been defined as

'programming'. Evidence that nutrition could act as a programming agent was shown in a variety of animal species by McCance and Widdowson. For example, in the early 1960s, they showed that malnutrition during an early 'critical period' in rats permanently impaired their growth. In this experiment, rat pups that were malnourished during the suckling period by putting them in large litters showed later growth deficits which were not reversible even with an unrestricted food supply after weaning; whereas a similar period of malnutrition later in the growth period produced only a temporary effect on weight gain, which was rapidly reversed when adequate food was supplied. Since then, animal studies in a wide range of species, including non-human primates, have shown that nutrition during critical periods in early life can programme outcomes such as changes in metabolism, endocrine function, gut function, size, body fatness, blood pressure, insulin resistance, blood lipids, learning, behaviour and longevity. Over the past few years, findings from randomized intervention studies in human infants with later follow-up have confirmed that health outcomes in human infants, as in other species, can be programmed by early diet. Early diet has been shown to have long-term effects on blood pressure, insulin resistance, blood lipids, obesity risk, bone health, atopy, cognitive function and brain structure. The size of the effect on some outcomes is large enough to be of public health significance; for example, in the case of cardiovascular risk factors (blood pressure, blood lipids, insulin resistance), the programming effects of early nutrition are greater than non-pharmacological interventions in adult life, such as exercise and weight loss. The implication of these findings is that it is no longer sufficient to think about nutrition only in terms of short-term adequacy or outcomes; potential effects on later health must also be considered.

Physiological basis of nutrition

Nutritional requirements throughout infancy and childhood vary more than at any subsequent stage of life, due to changing requirements for growth and organ development. Hence, the potential for inadequate or excessive nutrition is also greatest during this period.

Nutrient requirements for healthy infants and children

Recommendations for nutrient intakes in the UK are provided as Dietary Reference Values (DRVs) for boys and girls (0–3, 4–6, 7–9, 10–12 months, 1–3 years,

4–6 years, 7–10 years), and for males and females (11–14 years, 15–18 years, 19–50 years, 50+ years). There are separate recommendations for pregnant and breastfeeding women.

In North America, recommendations for the intake of specific nutrients are provided in the Dietary Reference Intakes (DRIs; see Further reading for more information), a set of recommendations intended to provide guidance for evaluating nutrient intakes and planning diets for both individuals and population groups. Recommendations are provided for the following life stage groups: Infancy (first 6 months, second 6 months), Toddlers (1–3 years), Early childhood (4–8 years), Puberty/adolescence (9–13 and 14–18 years), Young adult/middle age (19–30 and 31–50 years), Adulthood and older age (51–70 and 70+ years), and pregnancy and lactation.

The DRVs and DRIs consist of different estimates, summarized and defined in Table 13.2 and Figure 13.2. They share a number of common features, which are important to consider when interpreting and using the recommendations:

- Recommendations are made for healthy populations. They are not appropriate for malnourished or sick populations, or for those with pre-existing deficiencies.
- Where available, data on the effect of nutrients on chronic health or disease are considered, so recommendations are not just based on preventing deficiency.
- Compared to older recommendations, there is a greater emphasis on the distribution of nutrient
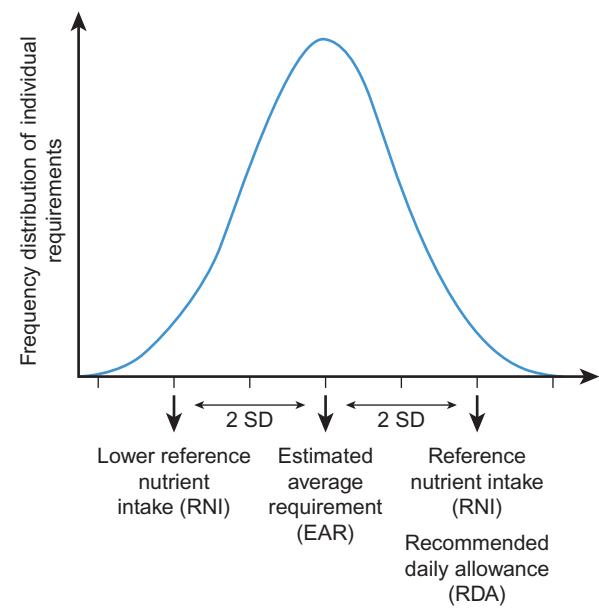
Fig. 13.2 Illustration of Dietary Reference Values.

Table 13.2 Dietary Reference Values (UK) and Dietary Reference Intakes (North America)

UK – Dietary Reference Values	North America – Dietary Reference Intakes
Estimated average requirement (EAR): The average requirement for a nutrient 50% of population require more and 50% require less	**Estimated average requirement (EAR):** Average daily nutrient intake level estimated to meet the requirements of half the healthy population
Reference nutrient intake (RNI): The amount of a nutrient needed to meet the requirements of 97.5% of the population	**Recommended dietary allowance (RDA):** The average daily nutrient intake sufficient to meet the requirements of 97.5% of the population
Lower reference nutrient intake (LRNI): The amount of a nutrient that is sufficient only for the 2.5% of the population with the lowest requirements	
Safe intake: Used where there is insufficient evidence to set EAR, RNI or LRNI. The amount at which there is judged to be no risk of deficiency, but below the level where there is a risk of undesirable effects.	**Adequate intake (AI):** Used where there is insufficient evidence to set EAR/RDA. The average daily nutrient intake based on observed or experimental approximations or estimates of intake by apparently healthy people that are assumed to be adequate.
	Tolerable upper intake level (UL): Highest daily nutrient intake likely to pose no risk to almost all individuals

requirements in a population, rather than on a single value.

- Where data exist, upper levels of intake are given, taking into account the potential for harmful effects, which is considered important given the increased use of food fortification and supplements.

The data used to formulate the recommendations for different nutrients varies in quality and quantity, and is often inconsistent over the different age groups specified. The types of data used include clinical, dose response, balance studies, depletion–repletion studies, and observational studies (for example, recording the intakes of apparently healthy individuals or those with clinical signs of deficiency); combined with theoretical estimations based on requirements for maintenance and growth, taking into account bioavailability, absorption and excretion. For ethical reasons, many of these approaches are difficult or impossible in infants and children and, consequently, many recommendations for toddlers and children are based on data extrapolated from adults, with consequent limitations.

Recommended nutrient intakes for infants are based on the estimated nutrient intakes of healthy breastfed infants growing normally during the first 6 months, and from 6–12 months on the nutrient intakes of infants who are receiving breast milk alongside complementary foods. Given the wide variation in breast milk intake and milk composition over time, between and within individuals, this approach has obvious limitations; and this is likely to be even more problematic in older infants, where the type of complementary foods consumed is also very variable.

Where data are considered to be sufficient in quality and quantity, an *estimated average requirement* (EAR) is determined; defined as the nutrient intake estimated to meet the requirements of half the population in a particular age group. From this figure, a *recommended daily allowance* (RDA) is calculated as the average nutrient intake sufficient to meet the requirements of nearly all subjects (97.5%; calculated as the mean + 2SDs). If the data are insufficient to establish an EAR, then an adequate intake (AI; US) or safe intake (UK) is provided. Recommended nutrient intakes for infants <12 months are provided as adequate intakes, reflecting the lack of data sufficient to determine an EAR for this population.

Important points to consider when using these recommended intakes in infants and children include:

- Recommendations are provided for individual nutrients rather than foods. In practice, it may be difficult or impossible to meet the theoretical requirements for all nutrients simultaneously using real foods for certain age groups; this is particularly the case during the complementary feeding period when recommended requirements for iron are very high and it is difficult to provide sufficient iron from foods without exceeding recommended intakes for other nutrients such as protein.
- Recommendations do not generally take into account the bioavailability of the nutrient from different foods. This is particularly important for nutrients such as iron, where the absorption of haem iron (e.g. from meat) is much better than that of non-haem iron (e.g. from fortified cereals

or supplements). Iron absorption is also affected by other foods and drinks; for example, vitamin C will increase absorption, whereas phytates (from cereals) or tea will decrease it.

Recommendations for energy intake in infants and children

The recommendations for energy intake in infants and children (see Further reading) require special consideration. EAR values are provided, since an RDA/RNI (representing the mean + 2SDs) would provide excess energy for the majority of the population. Historically, recommendations were based on observed energy intakes in different populations, but this approach has obvious flaws for populations experiencing increasing rates of overweight and obesity. The development and refinement of the doubly-labelled water technique, which uses stable isotopes to measure total energy expenditure (TEE) non-invasively in free-living subjects, has allowed the development of recommendations based on energy expenditure. New EARs for energy intakes were produced in 2011.

The main components of TEE are the basal metabolic rate (BMR), which makes up 40–70%, and physical activity, which makes up 25–50% in the majority of individuals and is the most variable component of energy expenditure. Infants and children have an additional energy requirement for new tissue deposition. The energy costs for growth make up about 35% of the total energy requirement during the first three months of life, about 17.5% in the next three months and reduce further over the next six months to only 3% at 12 months. Energy for growth falls to less than 2% of daily requirements in the second year, remains between 1 and 2% until mid-adolescence, and gradually disappears by 20 years of age.

Infant feeding

The natural biological food for a human infant is breast milk. Breastfeeding is the 'gold standard' for infant nutrition, and mothers should be encouraged and supported to breastfeed their infant. Although the beneficial effects of breast milk and breastfeeding (and the detrimental effects of not breastfeeding) are widely cited, there are considerable limitations of the evidence available on this topic, which apply both to the composition of breast milk and health effects of breastfeeding. These issues are relevant to the design of optimal breast milk substitutes for use when mothers cannot or choose not to breastfeed. One must also remember that the majority of infants in countries such as the UK receive an infant formula at some point even if they are initially exclusively breastfed, as

the use of cows' milk as the main drink is not recommended before 12 months.

Breast milk composition

The composition of breast milk has long been used as the basis for determining infant nutrient requirements during the first 6 months of life, and as a basis for regulations on the permitted composition of breast milk substitutes (infant formulas). Whilst this makes sense theoretically, in practice there are a number of problems associated with this approach, summarized in Table 13.3. Recognizing these problems, in recent years, there has been a greater focus on trying to achieve the performance (health and developmental outcomes) of breastfed infants rather than simply trying to mimic the composition of breast milk, which is in many ways impossible.

Developing evidence-based infant feeding guidelines

Data on the effectiveness and safety of any intervention can be obtained from observational studies or

Table 13.3 Issues to consider when using the composition of breast milk as a basis for recommended nutrient intakes or for the composition of breast milk substitutes

Issue	Consequence
Breast milk composition varies between mothers and changes over the course of lactation, during a day, during a feed The method used to obtain breast milk samples may affect the results (e.g. fore-vs hindmilk, hand- vs pump-expressed, single versus pooled samples)	It is difficult to define a single reference concentration for many nutrients
The composition of expressed milk may differ from that of the energy suckled by the infant direct from the breast	This probably resulted in an overestimation of human milk, which was then applied to infant formulas
Breast milk contains many bioactive substances (hormones, growth factors, etc.)	These are difficult or impossible to mimic in an infant formula
The milk from different mammals varies considerably not just in composition but in the configuration or quality of fat or protein, which can affect outcomes	Infant formulas may contain the same total fat or protein concentration as human milk, but there may still be significant differences in the type of nutrients, e.g. stereo-isomeric differences in triglycerides influence fat and calcium absorption; different protein composition (e.g. α-lactalbumin, β-lactoglobulin) can affect growth

from randomized controlled trials (RCTs). Randomized trials are regarded as the 'gold standard' in terms of demonstrating causal relationships between intervention and outcome and underpinning clinical practice. They are now accepted as the preferred approach for evaluating nutritional interventions. Observational studies, such as birth cohorts, have the advantage that the sample sizes are generally large and results can often be obtained rapidly. However, because the type of infant feeding is not randomly assigned, these studies can show *associations* between infant feeding and health outcomes but they cannot demonstrate *causation*.

Whilst accepted as the gold standard, there are a number of problems when it comes to conducting RCTs in the field of infant nutrition. The main one is that healthy term infants cannot be ethically or feasibly randomized to be breastfed or formula-fed, which prevents the use of an RCT for assessing the effect of any intervention against the 'gold standard' for infant feeding. It is also difficult in practice to randomize breastfeeding mothers to different breastfeeding practices – for example, altering the duration of exclusive breastfeeding (EBF). Given these problems, it is perhaps not surprising that there have been only two experimental studies designed to examine the health effects of breastfeeding (one in preterm infants randomized to banked donor breast milk versus preterm infant formula in the 1980s in the UK; the other a cluster-randomized trial of a breastfeeding promotion intervention in healthy term infants in Belarus), and three published experimental studies examining health effects of the duration of EBF (two in Honduras, one in Iceland). All other data on the health effects of breastfeeding come from observational studies.

Lack of randomization to the exposure variable (in this case, breastfeeding) inevitably introduces significant methodological issues, particularly in the case of infant feeding studies where the choice of feeding mode is strongly related to social and demographic factors such as educational achievement and socio-economic status, which are in turn related to many of the health outcomes of interest. The issue of confounding, together with a number of other methodological problems, have been recognized for many years and publications from the 1980s by Bauchner and Kramer highlighted many of these problems and proposed potential solutions. Despite greater awareness of these issues, there is still a lack of consistency both in the extent to which they are addressed and in the methods used to do so. This makes meta-analyses difficult or impossible. These issues are summarized in Table 13.4.

Table 13.4 Methodological problems with observational studies in infant nutrition research

Ascertainment of feeding behaviour (where are data obtained from?)	Often retrospective Different sources of data (e.g. mother, health professional)
Definition of breastfeeding	Definitions are very variable, especially for exclusivity Range from 'ever/never' to detailed prospective records
Outcomes	Assessment not always blind Lack of consistent definitions or measurement methods
Control for confounders	Variable definition and collection of data on confounders Direction of confounding differs in different populations and with time
Reverse causality	Alteration in feeding behaviour is a response to outcome rather than the cause (e.g. mothers with a family history of atopy may breastfeed for longer to prevent the infant developing atopy, but if the infant then develops atopy, this may be attributed to breastfeeding)

The evidence base for current UK infant feeding recommendations

Current UK recommendations are that infants should be exclusively breastfed for around 6 months before introducing solid foods alongside breastfeeding, which should continue ideally for up to 2 years. Mothers who formula-feed are also advised to introduce solid foods from around 6 months. The scientific evidence behind both of these recommendations needs to be understood, particularly the limitations discussed above. The health effects of breastfeeding *per se* also need to be distinguished from the effects of *exclusive* breastfeeding (EBF) for a particular duration, as these are often confused.

Overview of the scientific evidence supporting breastfeeding

Question 13.1

Breastfeeding

Which of the following is most strongly associated with breastfeeding? Select ONE answer only.

A. Increased later IQ

B. Reduced incidence of eczema under the age of five

C. Reduced risk of leukaemia

D. Reduction in hospital admissions for gastroenteritis

E. Reduction in the incidence of asthma

Answer 13.1

D. Reduction in hospital admissions for gastroenteritis. Answers to the other stems are considered below.

The strongest scientific data on the health effects of breastfeeding for infants in developed countries, with consensus from recent systematic reviews and meta-analyses, are for a reduced risk of infection – particularly gastroenteritis and otitis media, but with weaker evidence for a reduced risk of severe lower respiratory tract infection (LRTI) requiring hospitalization. This effect is biologically plausible given the many anti-infective substances in breast milk, although it is also possible that higher infection rates in those not breast-fed could reflect exposure to contaminated milk or solid foods. Data from the UK Millennium Cohort Study suggested that 53% of hospital admissions for gastroenteritis and 27% of admissions for LRTI could be prevented each month by EBF, with figures of 31% and 25% for partial breastfeeding. In both cases, the protective effect of breastfeeding was lost soon after cessation.

The scientific data for other short-term health effects of breastfeeding are less robust, with less agreement between expert groups. With respect to eczema, one RCT testing a breastfeeding promotion intervention found significantly reduced risk of eczema in the intervention group with more prolonged and more exclusive breastfeeding. Observational data also suggest that breastfeeding for at least 3 months may be protective in infants with a positive family history. However, two studies have also reported a higher risk of asthma in association with breastfeeding; it is of note that this is the only suggestion of a significant *negative* effect of breastfeeding.

The data supporting beneficial effects of breastfeeding on later 'cardiovascular' health outcomes, such as plasma lipid profile, blood pressure and risk of obesity, are reasonably strong. Although there is undoubtedly the possibility of residual confounding in observational studies, effects on blood pressure and plasma cholesterol are supported by data from a RCT in preterm infants. The reported effect size for the reduction in cholesterol in both observational studies and the preterm RCT is similar and has been estimated to be larger than the effect of lifestyle interventions such as diet in adult life. The observed effect size for blood pressure in observational studies, whilst significant, is smaller than the effect of non-pharmacological interventions in adult life, although the larger effect size seen in the preterm RCT during adolescence would be of greater public health significance. The estimated effect size for obesity risk at around 20% is likely to compare favourably with interventions in adult life. It is worth considering that if the underlying mechanism for a beneficial effect of breast milk on later cardiovascular outcomes relates to a slower early growth pattern – a hypothesis increasingly supported by both animal and human studies; this could perhaps explain some of the variation in findings between studies in which the exposure of infants to breast milk, in terms of duration and exclusivity, may have varied considerably.

Data on the effect of breastfeeding on later cognitive outcome remain controversial. Observational studies that include the most complete statistical adjustment for confounders – for example, including maternal IQ – suggest that there is no significant effect. However, data from a RCT of a breastfeeding promotion intervention suggest there is a small positive effect. Although a difference in IQ of 2–3 points would be unimportant for an individual, this magnitude of shift in a population would be highly relevant.

Overview of the scientific evidence on complementary feeding

Complementary foods are defined by the World Health Organization (WHO) as any food or liquid other than breast milk. This definition means that infant formulas and follow-on formulas (human milk substitutes; HMS) are regarded as complementary foods, which can be confusing, since many infants receive them from the first weeks of life. Other authorities have suggested that the term 'complementary food' should be applied to foods and liquids *other than* breast milk or infant formulas.

Complementary foods are needed during the second part of the first year of life for both nutritional and developmental reasons, and to enable the transition from milk feeding to family foods. The ability of breast milk to meet nutritional requirements becomes limited, infants develop the ability to chew and start to show an interest in foods other than milk.

Current WHO recommendations on the age at which complementary foods should be introduced are based on consideration of the optimal duration of exclusive breastfeeding. Since infant formulas are defined by WHO as a complementary food, this recommendation does not apply to formula-fed infants. Following a systematic review and expert consulation in 2001, the WHO recommended that infants should be exclusively breastfed for 6 months, with breastfeeding continued alongside complementary foods until 2 years. (See Further reading for WHO papers on infant feeding). However, in many countries, complementary foods are commonly introduced starting from 3–4 months.

The scientific basis for any recommendation on the duration of exclusive breastfeeding or the introduction of solid foods is fairly weak. Gastrointestinal and renal functions are likely to be sufficiently mature by around 4 months of age to enable infants to process some complementary foods, and most infants attain the necessary motor skills within the 4–6 month period. There is general agreement that complementary foods should not be given before 17 weeks of age, as this may be associated with increased later fatness, respiratory symptoms and eczema (see Further reading for the European Food Safety Authority (EFSA) report). The WHO recommendation was initially based on data from 16 studies, only 2 of which were randomized trials, both conducted in a developing country; hence, the evidence base is limited, and non-existent when it comes to the issue of introducing solid foods to formula-fed infants. The strongest and most consistent benefit for more prolonged EBF is a reduced risk of infection. Interestingly, one UK study reported that infection risk was higher if formula was introduced to breastfed infants but not if solids were introduced. Whilst there is agreement that exclusive breastfeeding for 6 months is desirable in situations where there is a lack of clean drinking water or safe nutritious complementary foods, there is less consensus for infants in higher income settings and the balance of positive and negative effects need to be considered for different outcomes in different settings (Table 13.5).

Although many countries (including the UK) have adopted the WHO recommendation, other countries still recommend the introduction of complementary foods at 4–6 months. From a practical perspective, it is most important to emphasize that *any* breastfeeding is beneficial for the infant and mother, and to support mothers in their choice of feeding.

Table 13.5 Benefits and risks of exclusive breastfeeding for 6 months versus 3–4 months

Benefits	Risks
Protects against gastrointestinal and respiratory infection, and hospitalization for such infections, in infants living in higher-income settings as well as those from low-income settings	May not be nutritionally optimal for all infants, particularly for iron and zinc; available data on nutritional adequacy come from the small group of highly selected mothers and infants who EBF for 6 months – generalizability to the rest of the population is uncertain
Delayed return of menses (advantageous for mothers without access to alternative birth control methods)	Delayed introduction of certain allergenic foods, especially at the point where breastfeeding has decreased or ceased, may be associated with increased risk of allergy
More rapid postpartum weight loss in mother	

Nutritional considerations in specific groups of infants and children

Preterm infants

Nutrient requirements

Nutrient requirements for preterm or low-birth-weight (LBW) infants are not provided by the DRVs, which focus on healthy subjects. However, recommendations have been provided by international expert groups, who have comprehensively reviewed the available literature for individual nutrients. Data from a variety of sources were used to derive recommendations for the intake of specific macro- and micronutrients for both enteral and parenteral feeding. Sources of data included:

- Relating nutrient intake to growth. Historically, weight gain has been the main parameter considered, although it is increasingly recognized that promoting gain in lean tissue rather than fat mass may be a more optimal goal. However, currently there are few data relating nutrition to body composition in this population
- A factorial approach, combining data on body composition and tissue accretion with balance studies
- Assessment of under- and over-nutrition using biochemical markers or clinical symptoms
- Studies examining short- and long-term clinical outcome.

The evidence base for nutritional recommendations for preterm infants, especially in relation to health outcomes, is in some ways stronger than that for term infants or older children, as a larger number of randomized trials have been conducted in this population.

When considering nutritional requirements for preterm infants, many of whom are also growth restricted, it is important to consider fetal nutritional physiology; several nutrients are acquired predominantly during the last trimester, so that preterm infants are at particular risk of deficiency (Table 13.6). Recent recommendations take into account not only the nutrients required for growth, but also the need to provide additional nutrients for compensatory growth, since many infants experience a period of relative growth failure in the postnatal period. There is also increasing recognition that a 'one size fits all' approach is not sensible, and that extremely-low-birth-weight (ELBW) infants have different nutrient requirements to more mature preterm infants. For example, recent international expert groups have

Table 13.6 Examples of the clinical importance of fetal physiology in the preterm infant

Nutrient	Clinical relevance
Calcium, phosphorus	90% acquired during the third trimester Extremely difficult to match *in utero* accretion rates *ex utero* Inadequate supply results in metabolic bone disease of prematurity
Iron	Maximal accretion in last 6 weeks Risk of iron deficiency and iron deficiency anaemia, especially combined with frequent blood sampling
Fat	Accretion during second half of gestation (3.5% body weight at 28 weeks, 7.8% at 34 weeks, 15% at term) Has implications for ability to withstand starvation
Carbohydrate	Total body carbohydrate estimated to be 9 g at 33 weeks and 34 g at term; liver glycogen stores very low with implications for the ability to withstand starvation
Enzyme maturation	Key enzymes in gluconeogenic pathways (e.g. phosphoenolpyruvate carboxykinase) may not develop until near or even just after term delivery; combined with low liver glycogen stores, this renders preterm infant vulnerable to hypoglycaemia
Fetal intestine	Structurally mature by 25 weeks Digestive capability matures rapidly with onset of enteral feeds Motility matures more slowly with implications for feed tolerance

recommended different protein intakes for infants weighing less or more than 1 kg.

Feeding the preterm infant

A range of options are available for feeding preterm infants, including the following:

- Parenteral nutrition:
  - partial
  - total
- Human milk:
  - mother's own 'preterm milk'
  - banked donor milk
  - fortified human milk
  - human milk formulas (separated and reconstituted human milk)
- Special 'preterm' infant formulas.

Parenteral nutrition

Parenteral nutrition is an essential part of the care of many preterm or sick infants, when adequate enteral feeding is not possible. Although enteral feeding, even in very small non-nutritional amounts has beneficial effects on the gut mucosa, if there is a delay in establishing full enteral feeds, it is important to support nutrition using the intravenous route. ELBW infants have a very limited ability to withstand starvation due to their low fat and carbohydrate stores; inadequate nutrition in the early postnatal period may adversely affect survival or have adverse effects on outcome, including cognitive development. Preterm infants will lose approximately 1% of their protein stores each day if fed on glucose alone, so it is extremely important to start amino acids within the first 24 hours; 1.5 g/kg/day will prevent catabolism but is insufficient to support growth. Recommended parenteral protein intakes are 3.5–4 g/kg/day for ELBW infants and 3.2–3.8 g/kg/day for very-low-birth-weight (VLBW) infants. Traditionally, protein intake was increased gradually over a period of days, but recent studies initiating intravenous feeding with high infusion rates have shown better nitrogen retention without any adverse short-term effects. In order to utilize amino acids efficiently and prevent their use as an energy supply, the infant also needs sufficient non-protein energy in the form of carbohydrate or fat.

Carbohydrate is required to maintain a normal blood glucose level (above 2.6 mmol/L) and to promote growth. Glucose infusions should be commenced at 4 mg/kg/minute and increased as tolerated. The risks of hyperglycaemia increase with decreasing gestation and birth weight.

Lipid is required to prevent fatty acid deficiency, facilitate the provision of fat-soluble vitamins and promote optimal growth. Essential fatty acid deficiency can be prevented by as little as 0.5 g/kg/day of lipid emulsion. RCTs have established the benefits and safety of starting parenteral fat on the first day of life. It is recommended that a 20% lipid emulsion should be started at 1 g/kg/day, increasing by 1 g/kg/day to 3 g/kg/day as tolerated. For many years, the available lipid emulsions were based on soybean oil. These emulsions contained high concentrations of linoleic and α-linolenic acid and very low concentrations of α-tocopherol, which could result in low blood concentrations of the long-chain polyunsaturated fatty acids and increased oxidative stress. More recently, lipid emulsions containing olive oil or fish oil have become available. A recent systematic review and meta-analysis concluded that these newer emulsions might be associated with a significantly lower risk of sepsis in preterm infants compared to soybean emulsions.

Trace elements, vitamins and minerals should also be provided in parenteral nutrition. As discussed above, preterm infants have very high requirements for calcium and phosphorus in order to match *in utero* accretion rates; inorganic glycerophosphate salts can

reduce solubility issues and allow larger amounts of mineral to be provided.

Human milk

Human milk has an important place in neonatal intensive care. Gastrointestinal tolerance of human milk is greater than that of formulas. Human milk passes through the stomach faster than formula in preterm infants, and intestinal lactase activity (a marker of intestinal maturity) is greater in infants fed human milk compared to formula and greater in those fed early in life. It often takes substantially longer to establish full enteral feeding in infants fed formulas, leading to a greater requirement for parenteral nutrition. The use of breast milk is associated with a reduction in the incidence of necrotizing enterocolitis (NEC) and systemic infection, and it is associated with improved cognitive outcome, lower blood pressure, more favourable plasma lipid profile and higher bone mass during childhood and adolescence. In addition, the slower initial growth rates seen in infants receiving human milk may be beneficial for later insulin resistance and arterial distensibility. However, in the preterm population, the risks and benefits of promoting growth must be balanced; poor early growth may have adverse consequences for short-term survival and for later cognitive development and bone health, whereas promoting growth (particularly during very early postnatal life) may be bad for later cardiovascular risk. On balance, in this group of infants current data clearly support the promotion of growth, since the later cardiovascular outcome of infants who grow well is no worse than that of infants born at term.

The composition of breast milk depends on its source (mother or donor), how it is collected and on the postnatal and postconceptional age of the donor; it can be further modified by subsequent treatment such as pasteurization and freezing.

Unmodified human milk may not always meet the theoretical requirements of LBW infants for several nutrients, including:

- Protein
- Energy
- Sodium
- Calcium, phosphorus and magnesium
- Trace elements, e.g. iron, zinc and copper
- Certain vitamins (e.g. B_2, B_6, folic acid, C, D, E and K).

However, human milk does have theoretical nutritional advantages compared with formulas, including the composition and easier absorption of its fats, and the bioavailability of certain trace metals. Human milk may be given raw to the mother's own infant, in which case antimicrobial components will remain intact. Neither microbiological examination nor pasteurization is necessary in this situation, provided that the collected milk is refrigerated adequately and fed to the infant within 48 hours, or at most 72 hours, or if it is frozen.

Many mothers who plan to provide milk for their own infants either totally or partially fail to do so in practice. Factors contributing to lack of success in producing sufficient breast milk include physical separation of mother and child, inadequate support, the inherent difficulty of maintaining the milk supply by manual or mechanical expression, lack of motivation, and – not least – poor advice. The difficulties faced by mothers trying to provide milk for their preterm infant must not be underestimated. They may need to express milk for a period of weeks or months in the absence of significant suckling stimulus and in the presence of a great deal of stress, a potent inhibitor of the milk ejection reflex. Simple measures have been shown to improve milk volume. These include increasing the frequency of expression (around six to eight times a day as a minimum), kangaroo care or skin-to-skin contact, relaxation tapes, and avoidance of smoking. There is strong evidence that short periods of kangaroo skin-to-skin contact increase the duration of any breastfeeding for 1 month after discharge and for more than 6 weeks among clinically stable infants in industrialized settings. The type of breast pump and mode of expression may also be important. Clinical trials have shown that the amount of milk expressed can be increased by the use of breast massage prior to pumping, simultaneous (double) pumping, and the design of more physiological breast pumps – that is, using alternative strategies to simple suction, which is inherently unphysiological in human lactation. Pharmacological interventions have also been investigated. Some data suggest that use of dopamine antagonists to increase prolactin concentrations may improve milk production of preterm mothers experiencing lactation failure at or beyond 3 weeks post-partum, without substantially altering the nutrient composition. Oxytocin can theoretically enhance let-down reflex, although a recent RCT did not show significant advantages over placebo in final milk production in preterm mothers when used early in the postnatal period.

Expressed donor milk

Expressed donor milk (DBM) can be foremilk or hindmilk, obtained either before or after the donor's own infant has fed from the breast; these two types of milk will have, respectively, lower or higher fat and energy content than milk received by the breastfed infant. Meta-analysis of data from 5 trials comparing the use of DBM versus formula suggested that preterm infants fed DBM had a significantly reduced risk of developing NEC (typical relative risk 2.5), although feeding DBM was also associated with slower neonatal growth. Most of these studies were 20–30 years old and from an era

when DBM was fed without fortification or mineral supplements, often as the sole diet. It is not clear whether similar effects would be seen when DBM is used in a more 'modern' context – that is, as a supplement to mother's breast milk (MBM) and supplemented with minerals and/or fortifiers. Only one trial compared nutrient-fortified donor breast milk vs preterm formula (PTF) as supplement to mother's breast milk. The study was unable to establish any short-term benefit for DBM over PTF.

Human milk fortifiers

One solution to overcome the nutrient deficits in human milk for the preterm infant is to add a fortifier containing protein, energy, macrominerals, trace minerals and a range of vitamins. However, the addition of nutrients to a complex biological medium such as milk poses theoretical problems. In particular, breast milk varies greatly in composition, and the addition of a fixed supplement may result in some infants exceeding the upper recommended limit for certain nutrients while others remain below desirable intake levels. Fortification may also influence nutrient availability or alter the biological properties of human milk. A systematic review concluded that the use of multinutrient fortifiers is associated with short-term improvements in weight gain, linear growth, head growth, nitrogen retention and blood urea levels but that there is currently no evidence of long-term benefit, and insufficient evidence to be reassured that there are no deleterious effects. More recently, a 'humanized' milk fortifier and infant formula, produced from pooled DBM processed to ensure the highest safety standards, has been developed. Clinical trials of the new products, which avoid any exposure to cows' milk, have shown a significantly reduced risk of NEC when compared to bovine fortifiers and formulas.

Preterm infant formulas

Preterm infant formulas are designed to meet the increased nutrient requirements of these infants. Clinical trials have shown that such formulas have a number of short-term advantages over unsupplemented human milk: they promote faster weight, length and head circumference gain, reduce hospital stay, and reduce the incidence of hyponatraemia, bone disease of prematurity, hypophosphataemia, hyperbilirubinaemia and some vitamin deficiencies. Nevertheless, they have some disadvantages, as discussed above, including reduced feed tolerance and increased risk of NEC.

Recommendations for feeding preterm infants

Human milk is regarded as the optimal form of enteral nutrition for these infants; preferably the mother's expressed milk. This needs to be supplemented with phosphorus as a minimum, especially for extremely preterm infants, and a human milk fortifier can be used to support adequate growth. Donor milk or preterm formula may be used in situations where the mother's own milk is not available or insufficient. Parenteral nutrition should be used if there is a delay in establishing enteral feeding.

> **How science has improved clinical practice – improved nutrition in preterm infants**
>
> Randomized trials of nutrition in preterm infants demonstrated beneficial effects of breast milk on short- and long-term health outcomes, but also the importance of avoiding growth failure for achieving good cognitive outcomes. These findings led to a greater emphasis on encouraging mothers to provide breast milk for their preterm infants, but also to the importance of supporting growth with parenteral nutrition, breast milk fortifiers or preterm formulas if required.

Term infants

During the first 4–6 months of life, the nutritional needs of a healthy term infant can be met by breast milk alone. The iron content of breast milk is low, but it is well-absorbed and the infant predominantly relies on iron stores obtained during fetal life and from placental transfusion after delivery. However, beyond 4–6 months, an additional source of iron is required to meet requirements for continuing rapid growth. It has been shown that delayed clamping of the umbilical cord improves iron status later in infancy without complications for infant or mother, including in a randomized trial in healthy Swedish infants who were at low risk for iron deficiency.

Vitamin D concentrations in breast milk are also low and most countries recommend that infants should receive a vitamin D supplement to prevent deficiency. In the UK, current recommendations suggest that breastfed infants should receive a supplement from 6 months if their mother has taken vitamin D supplements during pregnancy and lactation, and from 1 month if not. Infants from 'at risk' groups – those whose mothers have low vitamin D status, LBW infants, those with dark skin and those with limited sunlight exposure – should also receive supplements from birth. However, in many countries, supplements are recommended for all infants from birth, regardless of whether they are breastfed or formula-fed. Although infants who receive infant formula do not require a supplement since formula milks contain sufficient Vitamin D, the risk of toxicity from a supplement is considered to be very low and outweighed by having a single supplementation policy for all infants.

Infant formulas

The composition of infant formulas is regulated in the UK by a European Union directive, which sets out minimum and maximum levels for specific nutrients, micronutrients, vitamins and minerals. The directive also governs permitted protein sources; the majority of infant formulas used in the UK are based on cows' milk, but other permitted sources are goats' milk and soy protein. These protein sources require modifications to ensure the correct balance of amino acids, and an appropriate balance of whey and casein. Human milk is whey-predominant with a predominance of α-lactalbumin, whereas unmodified cows' milk contains a greater proportion of casein and β-lactoglobulin.

In recent years, many additional modifications have been made to infant formulas, generally adding substances found in human milk, such as preformed long-chain polyunsaturated fatty acids, and pre- and probiotics, in an attempt to render the formula 'closer' to the composition of breast milk. Many of these additions and modifications have been tested in RCTs and the main modifications and their effects are summarized in Table 13.7.

Infant formulas for special situations

Table 13.7 Common modifications to term infant formulas

Modification	Rationale	Clinical effect
Addition of preformed LCPUFA	LCPUFAs are present in breast milk. Essential for normal brain and visual development Suggested to mediate effects of breastfeeding on cognitive outcome.	Supplementation improves LCPUFA status. Inconsistent effects on development or visual outcomes in RCTs, possibly due to different LCPUFA sources and doses in different studies.
Prebiotics	Present in breast milk. Substrate for gut bacteria. Suggested to promote a healthier gut flora.	RCTs show inconclusive effects on health outcomes.*
Probiotics	Live bacteria (different strains) suggested to result in healthier gut flora.	RCTs show inconsistent results.* Cannot pool results from trials with different strains of bacteria.
Addition of β-palmitate	Breast milk contains a higher proportion of palmitate esterified in the sn-2 or beta position than cows' milk formulas. Increasing the proportion of β-palmitate in infant formula may improve absorption, reducing the formation of calcium soaps in the gut and producing softer stools.	Some RCT data suggests softer stools in infants fed formulas with higher β-palmitate (the same effect can be produced by reducing the amount of palmitate in the formula to levels lower than that in breast milk).
Altered protein (adding α-lactalbumin (ALA))	ALA is the predominant whey protein in human milk (28% of total protein compared to 3% in cows' milk) and is a rich source of essential amino acids. Adding ALA to formula might allow lower total protein whilst still supplying essential amino acids.	RCTs show ALA-supplemented formulas with lower total protein result in growth patterns and amino acid profiles more similar to those of breastfed infants.
Reduced protein	Higher protein may result in rapid weight gain and increased risk of obesity.	Two RCTs (one in term AGA, one term SGA infants) found slower growth and reduced BMI or fatness later in infancy/childhood.
Hydrolysis (partial and extensive)	Hydrolysed proteins may be less allergenic.	Inconsistent effects on the prevention of allergy in RCTs. Meta-analyses suggest that certain extensively hydrolysed casein and certain partially hydrolysed whey formulas may reduce the risk of allergy (especially atopic dermatitis) in infants at high risk when formula feeding is initiated.

*A recent systematic review by the ESPGHAN Committee on Nutrition concluded that although the addition of pre- and probiotics to infant formulas appears safe, there is currently insufficient evidence of benefit to recommend their routine use in infant formulas.

AGA, appropriate for gestational age; LPUFA, long-chain polyunsaturated fatty acid; RCT, randomized controlled trial; SGA, small for gestational age.

Answer 13.3

B. Extensively hydrolysed formula.

A number of formulas are available which have additional modifications for use in infants with particular conditions such as cows' milk protein intolerance, as in Question 13.3 (see Chapter 16, Allergy for further details). These include:

- *Partially and extensively hydrolysed formulas*, in which the proteins are hydrolysed to form smaller peptides, which are less allergenic. Extensively hydrolysed formulas are indicated for infants with allergy to cows' milk. They usually contain corn syrup and modified corn starch as the carbohydrate source, so they are also lactose and sucrose free. The main drawback of these products is the taste and smell, which may affect acceptance, especially if they are introduced after the first few weeks of life, although infants who

receive them from soon after birth appear to tolerate them well. It remains uncertain whether partially or extensively hydrolysed formulas should be recommended as an alternative to term formula in infants considered at risk of allergy who are not breastfed. There is some evidence that this strategy could reduce the risk of developing atopic dermatitis, but not all studies are in agreement.

- *Amino acid formulas* contain 100% amino acids and are used for infants who cannot tolerate even extensively hydrolysed products. The major problem with these products is their palatability, especially once an infant is accustomed to another type of milk.

- *Soya protein formulas* can be used in infants with intolerance of cows' milk, and by families who wish to avoid cows' milk. They are not recommended for infants with cows' milk protein allergy since there is cross-reactivity (10–15% of infants with IgE mediated and 50% of those with

non-IgE mediated allergy). Soya formulas contain plant oestrogens (phyto-oestrogens) and their use is generally not recommended in male infants, although there is no convincing evidence of any long-term impact of exposure to these formulas on subsequent health or reproductive outcomes.

Complementary foods

During the second six months of life, all infants require complementary foods since breast milk alone cannot meet the nutrient requirements for normal growth and development. Complementary foods should fill the gap in provision of nutrients between those provided by milk and the recommended total intake; and this shortfall will depend on the type of milk the infant is receiving. Thus, the diet should be considered on an individual basis. Most current guidelines for gradual introduction of different foods during complementary feeding are based on cultural factors and food availability rather than scientific evidence. Whilst in developing countries, the focus is still on providing adequate nutrients to support growth and development, in more affluent environments, achieving a better balance of nutrients and avoiding excess may be more important.

Question 13.4

Breastfeeding

Which of the following statements regarding the nutrient content of breast milk is true? Select ONE answer only.

A. During the first six months, breast milk contains enough iron for the infant's needs

B. During the second six months, breast milk contains insufficient iron for the infant's needs

C. During the second six months, breast milk contains sufficient vitamin D for the infant's needs

D. During the second six months, breast milk contains sufficient zinc for the infant's needs

E. The fat content of the diet should not exceed 25%

Answer 13.4

B. During the second six months, breast milk contains insufficient iron for the infant's needs.

Energy requirements remain high during the first year of life. The fat content of the diet is an important determinant of its energy density and should not be less than 25% of energy intake. A higher proportion

might be required if the appetite is poor, the infant has recurrent infections or is fed infrequently. Reduced-fat cows' milk reduces the energy density of the diet and consideration should be given to the rest of the infant's diet and to his growth when deciding when to introduce this. However, in countries with high rates of child obesity, it may be advantageous to accustom children to low-fat products from a fairly early age.

More than 90% of iron requirements during the complementary feeding period in a breastfed infant must be provided by complementary foods. Strategies for achieving adequate iron and zinc intakes include the use of fortified weaning foods, iron-fortified infant formulas, foods rich in bioavailable iron such as red meat, or supplements. The most suitable strategy depends on the circumstances. Cows' milk is a very poor source of iron, and it is generally recommended that it should not be used as the main drink before 12 months of age.

Other considerations regarding complementary feeding in infants are:

- High intakes of salt in infancy may be associated with later higher blood pressure. Furthermore, infants may become accustomed to a salty taste, which could affect subsequent food preferences. Hence, salt should not be added to complementary foods.
- Sugar is associated with the development of dental caries. Its use should be restricted, and good dental hygiene practices introduced early.
- For populations affected by coeliac disease, recent evidence from RCTs suggests that the timing of introduction of gluten after 4 months of age, or breastfeeding at the time of introduction of gluten do not influence the development of coeliac disease.
- Certain foods, including egg, fish, nuts and seafood, are potentially allergenic. However, the evidence that delaying the introduction of such foods reduces the risk of developing food allergy is not convincing. Allergy may be increased if solids are introduced before three to four months, but also by delayed introduction of certain allergens. Furthermore, the exclusion of fish and eggs from the diet could itself have undesirable nutritional consequences.
- Vegan diets are not generally recommended for infants, as avoidance of meat, fish, dairy and egg products renders the infant at risk of deficiencies of both macronutrients and micronutrients, especially vitamin D, calcium, iron, zinc and vitamin B_{12}. Particular care must be taken to provide adequate sources of these nutrients if an

infant is following a vegan diet, and vegan mothers must also receive advice on supplementation and diet during pregnancy and lactation.

- Children are predisposed to like high energy foods, to prefer sweet and salty tastes and to reject new foods, but these predispositions may be modified by early dietary experience and feeding practices. Parents play an important role in establishing good dietary habits. A feeding style typified by emotional warmth and responsiveness but high expectations for children's dietary adequacy and behaviour, accompanied by practices such as parents leading by example, making fruit and vegetables available within the home, moderately restricting unhealthy alternative snack foods, and encouraging children to try fruit and vegetables, is associated with better consumption in the childhood years.

Toddlers (1–3 years)

During the second year of life, energy requirements remain high and children continue to need energy-dense diets. By this stage, children should be eating a balanced, varied diet and an over-reliance on milk at this stage may be problematic, since it will tend to reduce appetite for other foods. The consumption of more than 500 mL of cows' milk per day is associated with an increased risk of iron deficiency and should be discouraged. Growing-up milks, which are fortified with iron and vitamin D, are not essential, although they may be helpful in achieving a healthy nutritional intake in certain infants, depending on the adequacy of the remainder of their diet.

Term, small-for-gestational-age infants

The optimal nutritional management of LBW or small-for-gestational-age term infants (generally defined as a birth weight below the 10th centile for gestational age and sex) has been controversial in recent years. Historically, management was aimed at promoting 'catch-up' growth, often using calorie-enriched formulas or supplements. However, data from randomized trials and observational studies suggest that more rapid catch-up growth, defined as upward centile crossing, may have adverse consequences for later risk of obesity and cardiovascular disease, without demonstrable benefits for cognitive outcome. Hence, for otherwise healthy LBW infants, the current recommendation is not to actively promote catch-up growth. Breastfeeding is regarded as the optimal form of nutrition and allows the infant to regulate his or her own intake; alternatively, a standard term infant formula

should be used. Catch-up growth should only be promoted if the infant is likely to suffer morbidity or mortality if he remains small; this might be the case in certain low-income settings, where the risk of morbidity or mortality associated with infection may be considered to be significant.

Nutrient requirements for sick children

Malnutrition is common in children with a wide range of illnesses, with figures typically between 20 and 40% depending on the population and type of hospital. It is associated with longer hospital stays and poorer clinical outcomes and with significant cost implications for health services. Of even greater concern, nutritional status frequently deteriorates during periods of hospitalization due to the effects of treatment or surgery. There is increasing emphasis on identifying children who are either malnourished on admission or who may become so whilst in hospital, and a number of malnutrition screening tools have been developed for this purpose. These tools (e.g. PYMS, STAMP, STRONGkids) typically combine simple anthropometric measures with other parameters, including subjective observations of 'wasting', underlying disease and the likely impact of planned treatments on nutritional status, in order to score and categorize children. Those most 'at risk' can then be targeted for additional dietetic or nutritional input. However, the existing tools have not so far been shown to improve patient outcome or reduce hospital stay in children.

Malnutrition in sick children can arise because of inadequate intake, increased requirements or excessive losses, or a combination of these factors. Each child must therefore be assessed individually in order to identify the main issues and plan the appropriate management. Currently, nutritional management is largely based on monitoring weight. However, this can be misleading since it is recognized that in children with a variety of chronic diseases, simply aiming to promote weight gain may result in increased fat mass rather than improving linear growth or lean mass, which might be clinically more favourable.

Overweight and obesity

Defining obesity

Although the adverse health effects of being overweight or obese are thought to result from excess adiposity rather than alterations in lean mass, in practice it is difficult to measure fatness accurately at an individual level. Thus, BMI or waist circumference are generally used as proxy measures for fatness (Fig. 13.3).
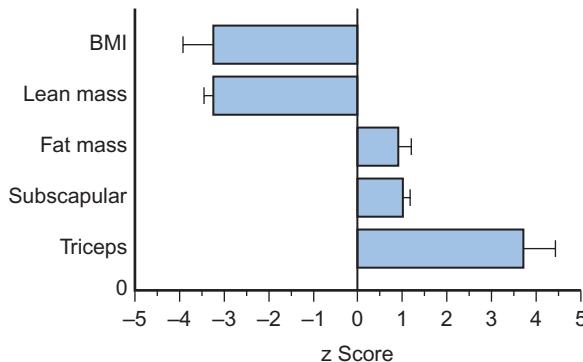
Fig. 13.3 Illustration of the limitations of BMI as a measure of 'fatness' in patients. Data from infant patients with congenital myasthenia. Despite extremely low BMI SDs, the patients have body fat levels higher than the average in healthy children. This paradox can be attributed to extremely low levels of lean mass. Though underweight, energy intake is not itself constraining their growth. *(Data from Arch Dis Child. 2006;91(7):612–17. doi: 10.1136/adc.2005.085522. Measuring body composition. Wells JCK, Fewtrell MS. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2082845/figure/fig1/)*

Ideally, the definition used for obesity would relate to one or more health outcomes. The adult cut-off points in widest use – a body mass index of 25 kg/m^2 for overweight and 30 kg/m^2 for obesity – are related to health risks such as the development of type 2 diabetes. Furthermore, lower cut-offs have been proposed for adults of south-east Asian origin, who may develop diabetes at a lower threshold. However, this is not the case for children, partly because they manifest fewer immediate health consequences. Hence, any cut-off is somewhat arbitrary. Two main approaches have been proposed. For clinical purposes, overweight and obesity are generally defined in terms of BMI centiles using local reference data – essentially aiming to identify extremes within the population. Thus, in the UK, obesity is defined as a BMI >98th centile on the UK 1990 reference chart for age and sex, and overweight as BMI >91st centile. The second approach, frequently used in research and when making comparisons between different countries, is to use the International Obesity Task Force BMI cut-offs. Using reference data from >190,000 children from six countries, age- and sex-specific cut-off points for BMI for overweight and obesity were defined between the ages of 2 and 18 years, using dataset-specific centiles linked to the adult BMI cut-off points.

Regardless of the definition used, overweight and obesity are an increasing problem worldwide, including in developing countries where under- and over-nutrition often coexist. Although at a simplistic level, excess weight gain results from an imbalance of energy intake and energy expenditure, preventing or managing the condition is extremely difficult in practice and cannot rely simply on improving nutrition, given the multifactorial nature of eating behaviour and lifestyle. It is widely recognized that the prevention and treatment of obesity requires multi-component interventions addressing nutrition, diet, activity, lifestyle and involving the whole family; a number of such programmes are available (e.g. MEND, HENRY, TrimTots). Most programmes work in the short term, but evidence for a sustained effect beyond the period of intervention is not convincing. Ultimately, these programmes do not address the availability of unhealthy food or the increasingly obesogenic environment found in countries such as the UK; such factors require intervention at a population level involving all stakeholders, and are complex and sometimes controversial. Based on a review of the effects of sugar on both weight gain/obesity and on dental caries, the SACN (Scientific Advisory Commission on Nutrition) in the UK recently recommended that the average population intake of free sugar should not exceed 5% of dietary energy from the age of 2 years, and that the consumption of sugar-sweetened beverages should be minimized in children.

Undernutrition and growth faltering

Undernutrition in low-income countries is covered in Chapter 33, Global child health. The definition of growth faltering or malnutrition used in high-income settings is inconsistent and depends on the context. Growth faltering generally refers to infants who are not growing as expected; it should be diagnosed in terms of the pattern of growth rather than on a single measurement. For example, mild growth faltering is often described as a fall in weight across two centile lines and severe growth faltering as a fall across three centile lines. As discussed above in the context of defining obesity, such definitions are aimed at detecting infants at the extreme of the population, since between 6 weeks and 1 year of age, only 5% of children will cross two lines, and only 1% will cross three. The growth reference used needs to be taken into account as the pattern of growth may appear different on different growth charts.

Undernutrition in older children is generally described in terms of BMI or weight-for-height; different cut-offs have been proposed, but again the aim is to identify children at the extremes of the population.

Infants and children with poor growth, however defined, must be managed individually, taking into account parental, socio-economic and psychological factors as well as nutritional intake, feeding patterns and symptoms or signs suggesting an underlying organic cause.

Further reading

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Huw Jenkins, Lisa Whyte
With contributions by
Toni Williams

CHAPTER

14

Gastroenterology

Embryology and anatomy

An understanding of the embryology is helpful in understanding why particular problems arise. The human gastrointestinal tract first appears at 4 weeks' gestation and is complete by 12 weeks' gestation. At the 4th week of gestation, the embryo consists of three parts: the endoderm, the ectoderm and the mesoderm. Eventually all three layers form important constituents of the gut: the endoderm gives rise to the epithelial lining of the gastrointestinal tract; the mesoderm, the smooth muscle; and the ectoderm will develop into the enteric nervous system.

Embryonic folding results in a tubular structure with a craniocaudal distribution. Further folding results in the cranial and caudal sections forming into blind-ending tubes which later become the foregut and hindgut, respectively, separated by a section which is still attached to the yolk sac – this later becomes the midgut. As the embryo further develops, the yolk sac becomes smaller and the midgut becomes a separate structure that is still attached to the yolk sac by the vitelline duct. The gastrointestinal tract now has three different structures (Fig. 14.1):

- Foregut – forming the pharynx, oesophagus, stomach, proximal duodenum
- Midgut – forming the distal duodenum, small bowel and distal colon
- Hindgut – forming the distal colon and rectum

The intestine undergoes a number of changes in position (Fig. 14.2):

- By week 5, the intestine elongates and begins to form a loop, which protrudes into the umbilical cord.
- By week 6, the stomach and duodenum have rotated 90° clockwise.
- At week 8, the duodenum and jejunum herniate further from the abdominal cavity and rotate around the axis of the superior mesenteric artery (counterclockwise) by 90° and take up a position behind the superior mesenteric artery.
- At week 11, the intestine retracts into the abdomen, although the control mechanism for
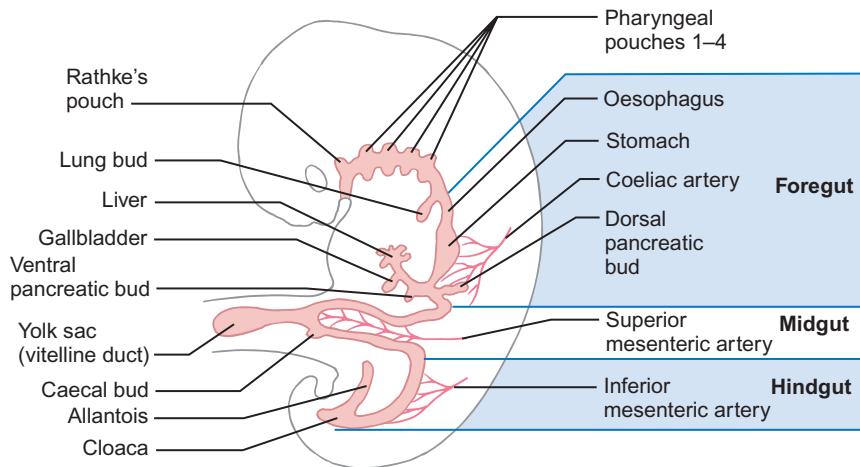
Fig. 14.1 Schematic representation demonstrating the early development of the gut.
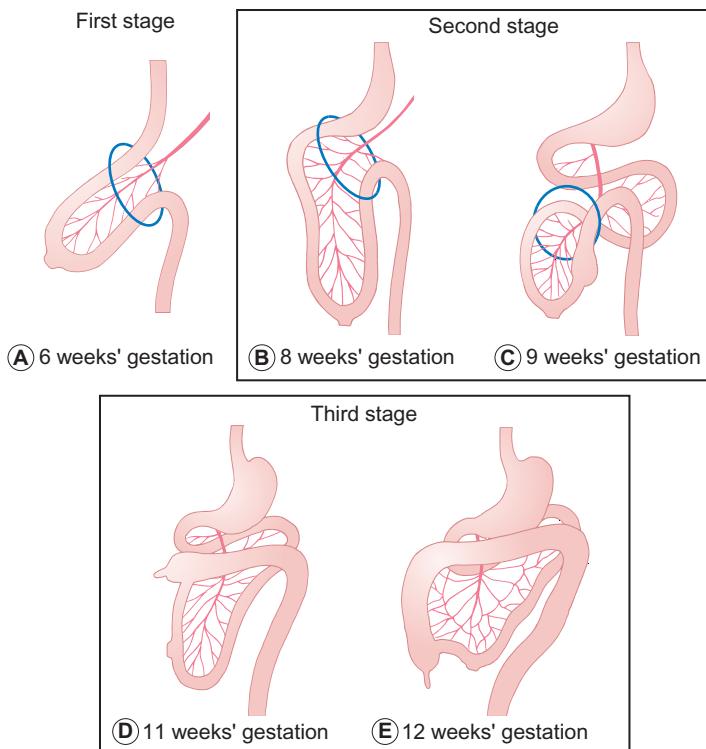
Fig. 14.2 Normal elongation and rotation of the midgut. This process is complex and can easily go wrong (see below). Failure of correct rotation leads to malrotation and failure of contents to return to the abdominal cavity results in exomphalos.

this is not understood. The jejunum returns first (to the left half of abdomen) followed by the ileum (to the right half) and then the rest of the small intestine and the colon last. By the end of week 11, the caecum has moved downwards and the intestines have reached their final adult position.

During this period of movement of the gut, the intestinal endoderm is uniform and it only starts to differentiate after the final positions are reached.

Abnormalities arising from abnormal embryological development

Duodenal atresia or stenosis

Atresias can occur at any point along the gastrointestinal tract, and may be singular or multiple, complete or incomplete. The duodenum is one of the most

common sites of atresia; the incidence is 1 in 10,000–30,000 live births. Most occur at the ampulla of Vater, either due to a complete mucosal membrane or a blind-ending proximal loop, probably due to failure of canalization of the duodenum after the 7th week of life due to ischaemia. Associated anomalies occur in about 50% of cases, including Down's and Prader–Willi syndromes. Presentation may be antenatal with polyhydramnios, or a 'double bubble' on ultrasound scan. Bilious vomiting is a presenting feature, usually immediately after the first feed.

Exomphalos

With an incidence of 1 in 3000, this is a midline defect of the anterior abdominal wall, where some of the organs lie outside the abdominal cavity. The organs are encased in a membranous sac derived from the amniotic membrane. The organs that are contained within the sac vary but can include stomach, intestine, liver and spleen. The defect is classified according to size (major being >4 cm abdominal wall defect and minor <4 cm). Exomphalos is associated frequently with other congenital abnormalities, including trisomy 13, 18 and 21, and 75% of cases also have other associated structural problems such as cardiac anomalies. It is usually identified on antenatal scanning. Surgical closure is required but, depending on the size of the defect and whether the sac remains intact, this is generally not an emergency providing the intra-abdominal structures are well perfused.

Gastroschisis

The incidence is 4 per 10,000 births and risk factors include low maternal age, drug misuse, low socio-economic status, smoking and ethnic origin. The abdominal muscles are normal but the stomach and intestines herniate through the anterior abdominal wall on the right-hand side of the umbilicus. Associated atresias are found in up to 10% of cases (due to ischaemic events) but other congenital anomalies are not usually present.

The cause is spontaneous herniation of the intra-abdominal wall *in utero* (possibly at the site of the right omphalomesenteric artery) or from incomplete reduction of the abdominal contents following rotation during the first weeks of fetal life. The abdominal contents are not covered by a membrane and therefore are exposed to amniotic fluid. This results in serositis with matting together of the intestines, which may need resection after birth.

There is a high risk of intrauterine death (15%) due to ischaemia and thus serial antenatal ultrasound scans are recommended. Delivery can be either vaginal or operative, but should take place in a specialist paediatric surgical centre. A protective membrane is placed over the eviscerated abdominal contents to prevent them drying out and urgent surgery is usually required to close the defect. The surgery may be a primary closure, or secondary if the defect is too large to replace all the contents in one stage without causing respiratory compromise from splinting of the diaphragm. In this case, a silo may be used to preserve the intestinal contents while complete closure is awaited.

It often takes time for feeding to be established due to poor intestinal motility. A prolonged course of parenteral nutrition may be necessary. Overall survival is 90%.

Meckel's diverticulum

This is common (2–4% of newborn infants) and occurs when the remnant of the omphalomesenteric duct does not fully regress and remains attached to the ileal mucosa (Fig. 14.3). The diverticulum contains gastric mucosa, which produces acid. It can often be detected using a technetium-99m scan (the sensitivity of this is 85% in children with a specificity of 95%).

A Meckel's diverticulum may present with lower gastrointestinal bleeding, intussusception, small bowel volvulus or it may never cause any problems, depending on the size of the sac. If problems occur, surgical resection is necessary.

Rarely, failure of the omphalomesenteric duct to regress results in an intestinal fistula that may present

Fig. 14.3 A surgical specimen of Meckel's diverticulum. This is a 'true' diverticulum having its own blood supply and containing all four layers of the bowel wall, including the mucosa, submucosa, muscularis externa and serosa. *(From Gleason CA, Devaskar SU. Avery's diseases of the newborn. Saunders 2012.)*

with an umbilical discharge. It may appear similar to an umbilical granuloma, but it is possible for a catheter to be inserted. Surgical resection is required.

Midgut malrotation

This occurs when the intestine lies in an abnormal position within the peritoneal cavity. It is subsequently at risk of torsion (volvulus) around the superior mesenteric artery axis (Fig. 14.4). Malrotation is due to incomplete rotation of the gut contents during the first 11 weeks of embryogenesis. The most common defect results in the duodenum lying to the right of the vertebral column instead of the left, with the caecum lying in the upper abdomen to the left of the duodenum (Pattern A in Fig. 14.4). Bands of peritoneum (Ladd's bands) pass from the caecum, across the duodenum, to the posterior abdominal wall. This may cause extrinsic obstruction of the duodenum, resulting in bilious vomiting, usually in infancy. As a result, the midgut has a short attachment to the base of the superior mesenteric artery and so may twist clockwise around this pedicle, resulting in potentially fatal midgut ischaemia. Midgut volvulus should be suspected in any child with bilious vomiting, as the ischaemia can be potentially reversed if the Ladd's bands are divided and the pressure from the arterial supply to the midgut is relieved. Children may also present with subacute symptoms of intermittent abdominal pain and vomiting. A barium meal is then the investigation of choice as it can show the position of the duodenal–jejunal flexure. The true incidence is not known, as there are probably individuals with undiagnosed malrotation who never have any problems if the pedicle is long enough.

Fig. 14.4 Pathophysiology of midgut volvulus with malrotation. A narrow mesenteric attachment may cause midgut volvulus. *(From Filston HC, Kirks DR. Malrotation – the ubiquitous anomaly. J Pediatr Surg 1981;16(4 Suppl 1):614–20, with permission. © Elsevier.)*

Question 14.1

Malrotation

A thriving 3-year-old boy had intermittent vomiting from birth. Gastro-oesophageal reflux was diagnosed, but intermittent vomiting continued, with occasional bilious vomiting. A barium study was requested as an outpatient and was planned for a month later, but he was admitted in shock and was taken to theatre, where malrotation with infarction was diagnosed. He needed major gut resection and the child was maintained on long-term parenteral nutrition for 4 years.

Which segment of gut is most likely to have received the ischaemic insult? Select ONE correct answer only.

A. Distal gastric body, duodenum, small intestine and proximal colon, as these originate from the midgut and are supplied by the superior mesenteric artery

B. Distal small intestine and proximal colon, as these originate from the midgut and are supplied by the inferior mesenteric artery

C. Duodenum, small intestine and proximal colon, as these originate from the midgut and are supplied by the superior mesenteric artery

D. Duodenum, small intestine and colon, as these originate from the hindgut and are supplied by both the inferior and superior mesenteric artery

E. None of the above

Answer 14.1

C. Duodenum, small intestine and proximal colon, as these originate from the midgut and are supplied by the superior mesenteric artery.

Any child with intermittent bilious vomiting must have an urgent contrast study to diagnose an anatomical abnormality such as malrotation.

Meconium ileus

In cases of pancreatic insufficiency, the distal ileum becomes impacted with thick, viscous meconium. This is associated with cystic fibrosis in most cases, with 20% of newly diagnosed children developing meconium ileus.

Duplication cysts

Duplication cysts are congenital cysts attached to the gastrointestinal tract anywhere between the mouth and anus, but are found most commonly in the ileocaecal region. The histological nature of the cyst is related to the adjoining structure. Presentation may be with an abdominal mass, or obstruction. When problems occur, surgical excision is required.

Hirschsprung's disease

In Hirschsprung's disease, there is an absence of ganglion cells in a variable segment of bowel (aganglionosis). The incidence is 1 in 5000 live births, and is more common in boys. The sigmoid and rectum are the most commonly affected sites, although the whole colon and, very rarely, the entire large and small bowel can be affected. The lack of ganglion cells causes an inability of the bowel to relax, resulting in a functional bowel obstruction.

It should be suspected in infants who have not passed meconium in the first 48 hours of life or in infants who present with bowel obstruction. Dramatic decompression occurs on digital examination of the rectum, with so-called 'explosive diarrhoea'. Digital examination should be performed by a senior doctor, and limited to only one examination, where possible.

Diagnosis is confirmed by rectal suction biopsy to confirm the absence of ganglion cells (in older children, a strip rectal biopsy). Surgery is needed to remove the aganglionic section of bowel. Enterocolitis is one of the major complications after surgery, when children can present with malaise, fever, diarrhoea and generalized sepsis. The pathophysiology of this is incompletely understood, but is thought to be due to gastrointestinal stasis, altered gut flora and impaired mucosal immunity.

Anorectal anomalies

These occur in 1 in 2500 births. The pathophysiology is poorly understood, but it is thought to be due to failure of the breakdown of tissue at the caudal end of the gastrointestinal tract in week 3 of gestation. Most often identified on routine post natal check, 60% have other congenital malformations of the gastrointestinal tract and/or genitourinary tract; in boys there may be a fistula to the urethra, in girls to the vestibule adjacent to the vagina. Other anomalies (e.g. VACTERL) should be considered.

Intussusception

Intussusception is not classically considered as an embryological abnormality and can occur in the presence of a structurally normal gut. However, even minor gut abnormalities, such as a polyp or Meckel's diverticulum, may predispose a child to this condition. It occurs when one section of the intestine invaginates into another section and can result in obstruction. The most common site is at the ileocaecal junction, but it can occur at other sites if there is a lead point such as a polyp or a Meckel's diverticulum. Patients usually present with acute onset abdominal pain, drawing up of the legs and pallor. They may have 'redcurrant jelly' stool, but this is a late sign. Diagnosis is by ultrasound scan, which shows a target-shaped mass. Treatment aim is to reduce the intussusceptions with an air enema, but surgical reduction may be necessary.

Normal gut function

The primary functions of the gut are to maintain fluid homeostasis and to facilitate absorption of dietary nutrients. There are complex mechanisms of secretion, digestion, absorption and motility that take place throughout the gastrointestinal tract to allow these functions to take place.

Secretions

The digestive juices that are secreted throughout the GI tract are a mixture of water, electrolytes, enzymes, bile salts and mucins, which aid digestion. When there is excess secretion or a failure to reabsorb enough of these secretions, either vomiting or diarrhoea results.

Digestion

This is the process by which complex food particles are broken down to smaller units that can be absorbed across the gut mucosa. Enzymes aid this breakdown.

- Carbohydrates must be broken down to monosaccharides before absorption. The starch, glycogen and cellulose, the main sources of dietary carbohydrates, must be broken down to fructose, glucose and galactose to allow absorption.
- Proteins are broken down to their constituent amino acids.
- Fats (mainly triglycerides) are broken down to monoglycerides and fatty acids.

Absorption

Most absorption takes place in the small intestine (see the later section on small intestine for details).

Motility

Motility is the function of the gastrointestinal tract that allows movement of the contents of the intestine in a craniocaudal direction. It is the food contents themselves that stimulate the contraction of the muscles above the food bolus and relaxation of the muscles below the bolus to produce craniocaudal progression.

Functions of the components of the GI system

Mouth

The smell, thought and presence of food stimulates production of saliva from the sublingual, submandibular, parotid and buccal glands. Saliva contains mainly water, but also contains small quantities of the salivary enzymes amylase (which converts polysaccharides to maltose), mucus (to allow lubrication) and lysozyme (that lyses certain bacteria). Chewing of food particles is the first stage of breakdown of food and allows easier passage into the oesophagus. Whilst some drugs can be absorbed through the buccal mucosa (e.g. midazolam), no absorption of nutrients takes place here.

Oesophagus

When a food bolus is moved to the back of the pharynx, the swallowing centre in the cerebral medulla is activated. This results in closure of the vocal cords and epiglottis, and facilitates safe passage of the bolus into the oesophagus. Sphincters at the lower and upper end of the oesophagus prevent food particles from refluxing back to the mouth.

The upper oesophageal sphincter remains tonically contracted and only relaxes to allow food particles through. It is under the control of cranial nerves V, IX and X. Peristalsis within the oesophagus is stimulated by swallowing of a food bolus. Inhibitory neurons induce lower oesophageal sphincter relaxation and coordinate proximal-to-distal peristaltic contraction. When the lower oesophageal sphincter fails to relax, achalasia results, and usually needs surgery to divide the muscles at the lower oesophageal sphincter to allow the passage of food into the stomach. Achalasia is a rare condition in children, but can still occur. No further digestion or absorption of food takes place here.

Stomach

The stomach has a number of functions including storage of food, secretion of the digestive juices and mixing up the contents of the stomach into chyme.

Gastric motility (Fig. 14.5)

The smooth muscle of the stomach wall has the unique property of 'plasticity'. In fully grown children and young adults, this allows the stomach to hold between 50 mL and 1000 mL of stomach contents whilst the pressure or tone exerted on the contents remains the same. The folds of stomach mucosa, or 'rugae', stretch out as the stomach becomes fuller. Once the stomach has become fully distended, the individual will experience discomfort and usually this will prompt them to stop eating.

The cells in the fundus generate slow-wave potentials that move down the length of the stomach towards the pylorus at a rate of 3 per minute. This contraction occurs rhythmically and does not cause contraction of the circular muscles. The muscle layers in the fundus of the stomach are significantly thinner than the antrum, so the strength of these contractions is lower at the proximal end.

Fundus
Accommodation
Fundus emptying
Pacemaker region
Body
Corpus-antral filling/mixing
Mixing of food with gastric contents
Antral peristalsis-emptying (3/min)
Antroduodenal coordination
Pyloric resistance
Pylorus
Duodenal resistance
Antrum
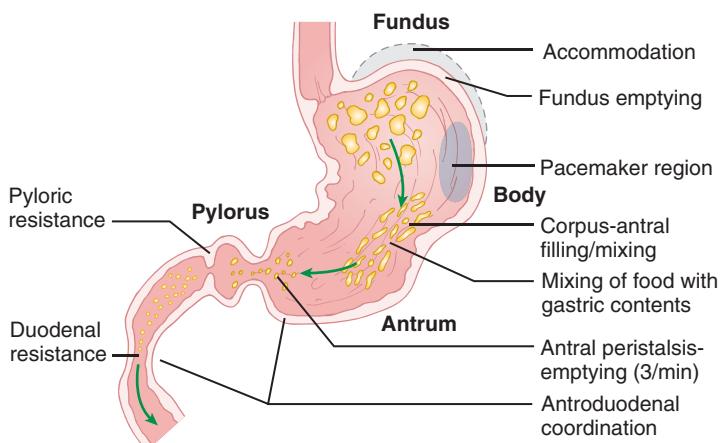
Fig. 14.5 Schematic representation of the stomach. The stomach acts as a storage area for mixing of food with gastric secretions. The narrow diameter of the pylorus allows only watery chyme to enter the first part of the duodenum.

The antral peristaltic contractions are responsible for the mixing of food. The pylorus will only open enough to allow the very watery chyme through; the thicker chyme is not able to pass through, so as the peristaltic wave meets the pylorus, the majority of the contents of the antrum are actually propelled backwards against the pylorus and back into the antrum for further mixing.

Gastric secretions

In a well-hydrated typical child, the stomach produces between 10 and 20 mL/kg of gastric fluid per day. This includes water and a combination of secretions which arise from the gastric pits.

Mucous neck cells secrete bicarbonate and mucus. The latter provides a protective barrier against damage from mechanical trauma from peristalsis, autodigestion and acid.

Chief cells produce pepsinogen. Pepsinogen is actually a precursor of pepsin, and must be converted to pepsin in order to allow protein digestion to amino acids.

Parietal cells produce hydrochloric acid and intrinsic factor. Hydrochloric acid activates pepsinogen to its active form, pepsin, and helps break down connective tissue fibres within food contents whilst destroying microorganisms within the food. Intrinsic factor is important for the absorption of vitamin B_{12} in the terminal ileum.

G cells are found in the pyloric area and secrete the hormone gastrin, which is integral in stimulation of the parietal and chief cells to produce their enzymes.

Enterochromaffin-like cells produce histamine, which in turn stimulates gastric acid secretion by the parietal cells. *D cells* produce somatostatin, whose functions include the inhibition of acid secretion.

At birth, gastric pH is in the neutral range (between 6 and 8), owing to the presence of alkaline amniotic fluids within the stomach. Within a day, the pH generally falls to between 1 and 3. However, gastric acidity is poorly maintained in neonates and is increased towards neutral following a milk feed. Only by age 3 years does the production of acidity reach adult capacity.

The stomach absorbs relatively few products of digestion but can absorb glucose, simple sugars, amino acids and some fat-soluble substances (notably ethanol). The gastric pH determines absorption for some drugs. For instance, at a low pH aspirin is absorbed from the stomach almost as rapidly as water, but, as the pH of the stomach rises, aspirin is absorbed more slowly. Water moves freely from the gastric contents across the gastric mucosa into the blood. The net absorption of water from the stomach is small, however, because water moves just as easily from the blood across the gastric mucosa to the lumen of the stomach. The absorption of water and alcohol can be slowed if the stomach contains foodstuffs and especially fats, probably because gastric emptying is delayed by fats, and most water in any situation is absorbed from the small intestine.

The rate of emptying of the stomach depends upon the physical and chemical composition of the meal. Fluids empty more rapidly than solids, carbohydrates more rapidly than proteins, and proteins more rapidly than fats.

Question 14.2

An infant with projectile vomiting

A 6-week-old boy presents to the emergency department with a one week history of vomiting. The parents report that the vomiting has got much worse over the last two days and the child is now very hungry and unsettled. His older sister, who is now 5 years old, had pyloric stenosis as an infant, but neither parent had the condition themselves. A 10-year-old brother is unaffected. On examination, he has visible peristalsis (a slow muscular contracture, 3/minute) of the stomach visible in the upper part of the abdomen and ultrasound scan confirms pyloric stenosis.

Concerning the heritability of pyloric stenosis and assuming random mating in the future, which family member is MOST likely to conceive a child with pyloric stenosis in future pregnancies? Select ONE answer only.

A. The infant

B. The infant's father

C. The infant's mother

D. The older brother

E. The older sister

Answer 14.2

E. The older sister.

Pyloric stenosis is a classic example of a polygenic disease. There is an unequal sex distribution, with boys being more likely to be affected than girls. The explanation for this is thought to be that an affected female is more likely to have an affected child than an affected male. It is believed that the biological threshold for expression of pyloric stenosis is higher in females. It follows that an affected female must have a greater genetic predisposition than an affected male. Therefore, an affected female is more likely than any other member of this family to conceive a child with pyloric stenosis. This is a helpful example to consider in other polygenic diseases where there is an unequal sex distribution (and is called the Carter effect).

Pancreas, gall bladder and liver

Pancreas

As the contents of the stomach pass into the duodenum, they are mixed with secretions from the exocrine pancreas and the liver. The acinar cells of the exocrine pancreas produce the proenzymes trypsinogen, chymotrypsinogen and procarboxypeptidase and also sodium bicarbonate, which is required to neutralize the hydrochloric acid from the stomach, and provide the correct pH environment for pancreatic enzymes to work. These enzymes are secreted as precursors to reduce the risk of autodigestion of the pancreas. Trypsinogen is activated by enterokinase in the brush border of the small intestine to the active form, trypsin. Pancreatic amylase is also produced to further aid carbohydrate digestion.

Pancreatic lipase is the only enzyme throughout the GI tract that can break down fats, and, when there is pancreatic insufficiency, for example in cystic fibrosis, the pancreatic lipase must be supplemented to prevent fat malabsorption. Pancreatic insufficiency often presents as steatorrhoea.

Pancreatic exocrine secretions are controlled by the hormones secretin and cholecystokinin. Secretin is produced in response to the presence of acidic chyme in the duodenum. Cholecystokinin is produced when fat is present in the duodenum.

Liver

The liver has many functions, but with regard to the GI system, it is involved in the metabolic processing of all major categories of our diet following their absorption from the intestine. The venous drainage of the stomach and small intestine is via the portal vein to take the nutrients to the liver for processing and storage. The other major role of the liver in the GI system is to make and secrete bile salts via the gall bladder.

Intestinal absorption and secretion

Large volumes of fluid are secreted into and reabsorbed by the intestine. In adults, the daily fluid exchange is:

Input into small intestine: 9 L/day (diet: 1.8 L; endogenous secretions: 7.2 L)
Input into colon: 1.5–2.0 L/day
Output of fluid in faeces: 100–200 mL/day

Small intestine

The intestinal mucosa is a complex epithelium in which absorption and secretion occur simultaneously, with the majority of total water and electrolyte absorption occurring in the small intestine. The mucosa of the intestine acts as a semi-permeable membrane with pores in the membrane at intercellular junctions. Water movement is entirely passive, the majority passing paracellularly in response to osmotic gradients created by the transcellular absorption of solutes, particularly sodium.

Mechanism of carbohydrate, fat and vitamin absorption in the small intestine

The jejunum is the most permeable area of the small intestine and consequently there are rapid changes in luminal osmolality as food is digested and products absorbed. The most important absorptive mechanisms are those of sodium coupled cotransport of organic substrates such as glucose, galactose, amino acids and tripeptides.

The ileum is less permeable to water, though there is absorption of the same sodium and organic substrates as in the jejunum, but also with specific electrolyte absorptive mechanisms (sodium/chloride transport) becoming more significant.

Fat absorption is not as straightforward as monosaccharide and amino acid absorption, as the fat that

Question 14.3

Acute gastroenteritis

A 2-year-old boy was admitted to his local children's assessment unit with a 48-hour history of vomiting and diarrhoea. Several other members of his nursery had similar symptoms. He had been unable to tolerate oral fluids and diet at home and had not had a wet nappy for 14 hours. On examination, he was clinically dehydrated but his abdomen was soft and non-tender. He was able to tolerate small but frequent amounts of oral rehydration solution (ORS) and was discharged 6 hours later.

Which of the following mechanisms BEST describes the known physiology of oral rehydration solution? Select ONE answer only.

A. Glucose is rapidly absorbed across the duodenum and this pulls a water molecule across the epithelial surface

B. Glucose is absorbed passively and sodium is absorbed actively in the small intestine

C. ORS is hypotonic and therefore water enters the GI tract through osmosis, ensuring rapid rehydration

D. Sodium and glucose are absorbed passively in the jejunum

E. Water is absorbed rapidly from the stomach providing that glucose and sodium are present within the mixture

Answer 14.3

B. Glucose is absorbed passively and sodium is absorbed actively in the small intestine.

enters the duodenum is not soluble. Fat that enters the duodenum is in the form of triglyceride droplets, which must be emulsified by the addition of bile salts from the gall bladder. Biliary components facilitate absorption of the fats by the formation of micelles. The bile acids are then reabsorbed in the terminal ileum via the enterohepatic circulation. Once the micelles cross the brush border of the intestine, they are re-assimilated into triglycerides and form fat globules once again, known as chylomicrons. These enter the central lacteals and are absorbed via the lymphatic system.

Vitamin absorption is facilitated by the absorption of water for water-soluble vitamins and micelles for fat-soluble vitamins (vitamins A, D, E and K).

Mechanism of water and solute absorption in the small intestine

Overall, water absorption is dependent on the movement of electrolytes, especially sodium. The primary mechanism of sodium absorption is by the glucose-sodium transporter 1. This promotes the active absorption of sodium, allied to the absorption of glucose, with water moving down the electrochemical gradient that is created as jejunal contents are broken down. This is the scientific basis for the use of oral rehydration solutions used in the management of gastroenteritis (Fig. 14.6).

In gastroenteritis, giving oral saline solution is not helpful because normal sodium absorption is impaired in the diarrhoeal state and if the sodium is not absorbed, neither is water. In fact, excess sodium in the lumen of the intestine causes increased secretion of water and the diarrhoea worsens. If glucose is added to a saline solution then glucose molecules are absorbed through the intestinal wall. This is unaffected by the diarrhoeal disease state. In conjunction, sodium is carried through by a cotransport coupling mechanism. This occurs in a 1 : 1 ratio, one molecule of glucose cotransporting one sodium ion. Glucose does not cotransport water – rather, it is the relative increase in concentration of sodium ions across the intestinal wall which pulls water through after it. Several other molecules apart from glucose have a similar capacity to cotransport Na^+ including:

- Amino acids (e.g. glycine)
- Dipeptides
- Tripeptides
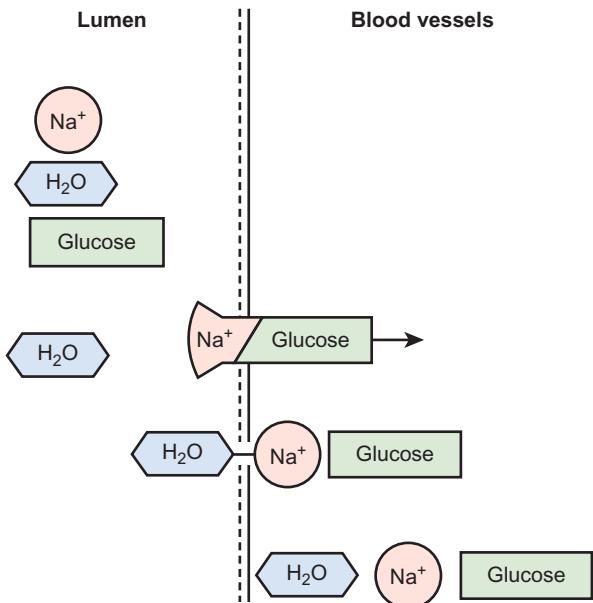
Fig. 14.6 **Mechanism of action of sodium-glucose cotransport in facilitating enhanced absorption of fluid from the gut with oral rehydration solution.**

The absorption of these molecules may occur independently of each other at different sites – thus, their effect can be additive. Research is currently being carried out to utilize these additive effects to develop a multi-component 'super ORS'.

The movement of sodium provides energy for the active transport of amino acids, glucose and galactose across the membrane. Di- and tripeptide amino acid transport over the brush border is coupled with hydrogen ion reabsorption, and so helps to create the electropotential across the brush border, which again aids the transport of sodium.

The ATPase sodium/potassium pump is located in the basolateral membrane of the intestinal crypt and villus tip cells. The epithelial cells at the tips of the villi are active in net absorption, whereas the cells in the crypts of Lieberkühn function as net secretors of electrolytes and water via the ATPase sodium/potassium pump. In these crypts, there is also a luminal bidirectional sodium/chloride channel, which is opened when there are higher levels of cyclic AMP and calcium ions. When these channels are open, there is a net movement of sodium, chloride and water into the lumen. Consequently, if there is a slight change in the flow across this channel, then secretion dramatically increases. Cholera toxin and *E.coli* cause an increase in the levels of cAMP, so driving chloride flow across the brush border into the lumen, and hence the net movement of water with it. This results in watery, secretory diarrhoea.

Colon

Whilst the majority of water and electrolyte absorption takes place in the small intestine, the colon is also important for the adequate reabsorption of fluid. It is often the adequacy of colonic function that determines whether or not the patient experiences diarrhoea. The maximal absorptive capacity of the adult large bowel is 2–3 L/day and, if the amount of fluid secreted from the small bowel exceeds this, then diarrhoea results.

The motility of the colon is produced via the haustrations, but these usually contract very slowly and 30 minutes can elapse between haustral contractions in adults.

Histopathology and cellular function

The gastrointestinal tract from the mouth to the anus is a tubular structure with four main layers:

1. Mucosa – epithelium, connective tissue and thin smooth muscle
2. Submucosa – connective and supporting tissue
3. Muscularis externa – two thick layers of smooth muscle
4. Serosa – thin outer layer of connective and supporting tissue

The oesophagus consists of non-keratinized stratified squamous epithelium. Peristaltic contractions of the muscularis externa propel the food boluses forward into the stomach.

The mucosa of the stomach is made of columnar epithelium with mucus-secreting cells that invaginate down, forming gastric pits. The gastric pits become deeper from the fundus to the pylorus. The gastric mucosa is populated with many immune cells, including plasma cells and lymphocytes.

The small intestine shares similar histological elements, including an inner lining formed of transverse ridges (*plicae circularis*), tall finger-like projections of mucosa (villi) between which are the crypts of Lieberkühn and the mucosal epithelium is columnar. Microvilli greatly increase the surface area of the small intestine, to approximately 250 m^2 in adults. The duodenum can be clearly distinguished by the presence of Brunner's cells. Brunner's cells are found at the hepatopancreatic sphincter (sphincter of Oddi) and produce an alkaline substance to aid digestion. The jejunum has the tallest villi, which extend from the permanent circular fold of the mucosa and submucosa. The ileum is identified by the presence of aggregated lymphoid follicles, known as Peyer's patches, which are found in the submucosa.

Throughout the gastrointestinal tract there are many immune cells, but predominantly lymphocytes in the surface epithelium and in the lymphoid follicles. Collectively, these make up the gut-associated lymphoid tissue (GALT). Other immune-mediating cells are found in the small intestine, called Paneth cells, which are located in the crypts and contain granular material important in the lysis of microorganisms.

The colon appears smooth when viewed macroscopically, but has a number of microscopic crypts that extend down to the muscularis mucosa. Many goblet cells, whose main function is the production of mucus, are found here.

Abnormalities diagnosed by histopathology

Coeliac disease

Coeliac disease (CD) is a multisystem disease, including a small intestinal enteropathy secondary to exposure to gluten. The classic histological findings of coeliac disease include:

- Flattened duodenal mucosa with loss of crypt architecture
- Intraepithelial lymphocytosis
- Glandular hyperplasia

These histological findings are completely reversible on a gluten exclusion diet.

Inflammatory bowel disease

Crohn's disease and ulcerative colitis both show typical histological findings.

Crohn's disease can demonstrate changes anywhere from mouth to anus. It typically shows areas of chronic inflammation, comprising increased lamina propria plasma cells and lymphocytes. So-called 'skip lesions' including patchy erosions or ulcers, vertical fissures, and fistulas are typical. Transmural inflammation with multiple lymphoid aggregates and granulomas are pathognomonic.

Ulcerative colitis affects only the large bowel with alteration of crypt architecture including cryptitis and crypt abscesses and increased chronic inflammatory cells in the lamina propria including lymphocytes and plasma cells.

Eosinophilic diseases

Eosinophils are normally found throughout the GI tract. The normal number of eosinophils per high-powered microscopic field remains uncertain. However, in eosinophilic disease of the GI tract there is a markedly increased eosinophilic infiltrate in the mucosa. The symptoms associated with eosinophilic

disease vary according to the site of the disease. For example, eosinophilic oesophagitis often presents with dysphagia and retrosternal chest pain or bolus dysphagia (food boluses lodged in the oesophagus), whereas eosinophilic intestinal disease may present with recurrent abdominal (often epigastric) pain, vomiting, dysphagia or diarrhoea. Data pertaining to eosinophilic oesophagitis is the most researched and better understood, with an accepted diagnostic range of 15 eosinophils per high-powered field. The disorder is described in more detail in Chapter 16, Allergy.

Oesophagitis, gastritis and gastro-oesophageal reflux

Inflammation of the oesophagus and stomach can occur when there is excess secretion of gastric acid and if the contents of the stomach reflux back into the oesophagus, causing oesophagitis. Gastro-oesophageal reflux is common in infants due to immaturity of the lower oesophageal sphincter, but is seldom associated with the formation of dysplastic cells, such as those seen in Barrett's oesophagus in adults.

Other causes of oesophageal and gastric inflammation include ingestion of caustic materials, the presence of *Helicobacter pylori* and general severe systemic illness such as sepsis, which can result in secondary gastritis.

Genetic and environmental factors in the aetiology of gut disease

The GI tract is exposed to multiple antigens and under normal circumstances can distinguish between dangerous antigens that are pathogens and antigens from components of our diet and harmless microbiome. This section will focus on a number of conditions seen commonly in children, where disease results from a breakdown of this control system.

Gut microbiome

The GI tract is home to >10^{14} bacteria comprising more than 1000 different species. Of these, 90% belong to two different phyla: Gram-negative bacteria (Bacteroides) and Gram-positive bacteria (Firmicutes). The remainder are made up of phyla such as Proteobacteria (*E. coli*, *H. pylori*) and Actinobacteria.

These microorganisms are important in regulation of the innate and adaptive immune system:

- Innate immune system
  - *Bacteroides thetaiotaomicron* regulates antimicrobial peptide (e.g. angiogenin) in the intestinal epithelium through direct activation

of Toll-like receptors (TLR) on Paneth cells. Paneth cells are cells found in the crypts of Lieberkühn that secrete defensins, lysozyme, phospholipid A2 and anti-tumour necrosis factor, all of which are involved in intestinal antimicrobial activity.
- Adaptive immune functions – determined by specific bacteria
  - Related to intraepithelial lymphocytes
  - T regulatory cells (Tregs)
  - Th17 cells

Examples of the genetic/environmental interaction in specific diseases

Inflammatory bowel disease

Inflammatory bowel disease exhibits an element of genetic susceptibility, with higher rates in other family members. However, the incomplete concordance seen between monozygotic twins (44–58% concordance) and a higher incidence in immigrants who move to high prevalence countries suggests that the environment also plays a significant role.

In 2001, the *NOD2/CARD15* gene was identified as a susceptibility gene and has been found to have a central role in the regulation of the innate immune system. Subsequently, a genome-wide association study (by the International Inflammatory Bowel Disease Genetic Consortium) has identified over 160 loci, with 110 of these loci shared between ulcerative colitis and Crohn's disease. There is significant overlap with loci associated with other diseases, such as psoriasis, type 1 diabetes mellitus, ankylosing spondylitis and primary immune deficiencies.

The study of alteration in intestinal microbiome has shown differences between healthy individuals and those with inflammatory bowel disease, both at diagnosis and subsequently. It is not clear yet how this plays a role in the development and progression of inflammatory bowel disease, but preliminary studies using faecal transplants (the transplantation of faeces from a healthy control to a patient with inflammatory bowel disease) have shown a reduction in symptoms in some individuals.

Coeliac disease

Coeliac disease is prevalent in 1% of the UK population. Although classically a disease of childhood presenting with gastrointestinal symptoms, poor growth and malnutrition, an increasing number of children are being diagnosed following presentation without gastrointestinal symptoms, or following screening for those in high risk groups. It is now also recognized

that it can develop at any time throughout childhood or adulthood, and the term 'coeliac iceberg' is often used to emphasize that there are many undiagnosed, relatively asymptomatic people with coeliac disease.

It is thought to be multifactorial in origin. There is a definite genetic preponderance, with 95% of all patients with coeliac disease being either HLA-DQ2 or DQ8 positive. Absence of these HLA types has a negative predictive value close to 100%. However, approximately 40% of the population also have these haplotypes, though clearly not all of them go on to develop the disease. The risk of coeliac disease is increased in those in high-risk groups, namely a first degree family member affected, patients with type 1 diabetes mellitus, thyroid disease, autoimmune liver disease, Down's or Turner's syndrome; in these groups, the incidence is as high as 10%. Therefore, it is suspected that there must be environmental factors that contribute to its onset. This is supported by the absence of complete concordance in monozygotic twins (70–85%). Environmental factors associated with coeliac disease include low birth weight, neonatal infection, artificial feeding in infancy, and high socio-economic status.

The role of the gut in homeostasis and its dysfunction

The role of the gut is to maintain fluid homeostasis by both absorption and secretion and to allow absorption of dietary nutrients to allow growth, repair and maintain normal function of the body.

When fluid homeostasis is not maintained, diarrhoea results and when the homeostasis of nutrient absorption is not maintained, malabsorption and deficiency results. The gut will always absorb nutrients to its maximal ability, and hence if calorie intake exceeds energy expenditure, obesity results.

Diarrhoea

Diarrhoea (from the Greek word 'to flow through') is defined as the rapid transit of gastric contents through the bowel. The frequency of defecation is variable in childhood, but the median is one bowel movement per day, with the World Health Organization describing diarrhoea as three or more loose or watery stools per day. The absorption and secretion of water and electrolytes into the gut is a finely balanced, dynamic process and, when there is loss of this balance, diarrhoea results.

Diarrhoea in childhood remains a major cause of morbidity and mortality throughout the world and a common cause of death worldwide in children under the age of 5 years, currently accounting for 0.6 million deaths per year. This problem is not confined only to the developing world, but is also a significant cause of morbidity in the developed world, particularly in the first year of life. If diarrhoea becomes protracted, then severe malnutrition may develop and result in prolonged impairment of physical and intellectual development. This is particularly the case when there is restriction in growth at a vulnerable period of brain development. Episodes of acute diarrhoea occur most commonly in the first year of life, at a time when not only brain development is incomplete, but also when the wide variety of intestinal transport mechanisms which are concerned with the absorption and secretion of fluid and electrolytes are poorly developed. Therefore, clinicians who regularly see children with acute and chronic episodes of diarrhoea must have a good understanding of the pathophysiology, and different treatment and management options, in order to reduce morbidity and mortality.

In general, diarrhoea can be considered to be either osmotic or secretory (Table 14.1).

Osmotic diarrhoea

When excessive numbers of osmotically active particles are present in the lumen, more fluid passively moves into the bowel lumen down the osmotic gradient, which may exceed the absorptive capacity of the gut and hence diarrhoea occurs. Osmotic diarrhoea therefore will stop when the child is not fed.

Excessive numbers of osmotically active particles can be present for a number of reasons, including:

- Ingestion of solutes that cannot be absorbed, e.g. osmotic laxatives such as lactulose
- Malabsorption of specific solutes, e.g. disaccharide deficiency, glucose-galactose malabsorption
- Damage to the absorptive area of the mucosa resulting in less fluid absorption, e.g. acute gastroenteritis, cows' milk protein allergy, coeliac disease and Crohn's disease

Table 14.1 Differences between osmotic and secretory diarrhoea

Osmotic diarrhoea	Secretory diarrhoea
Excess osmotically active particles in the gut lumen	Bowel mucosa secretes excess water into the lumen
Stops when the child is fasted	Continues when the child is fasted
Underlying causes: - Osmotic laxatives - Excessive carbohydrate solutes within the lumen from malabsorption - Damage to the mucosa - Motility disorders	Underlying causes: - Cholera toxin - Other infective causes - Specific electrolyte transport defects, e.g. congenital chloride-losing diarrhoea

- Motility disorders, such as those seen in gastroschisis, irritable bowel syndrome, and hyperthyroidism which result in reduced contact with the bowel lumen and consequently a higher concentration of solutes within the lumen.

Secretory diarrhoea

This occurs when the bowel mucosa secretes excessive amounts of fluid, either due to activation of a specific pathway by a toxin (such as cholera toxin), or inherent abnormalities in the enterocytes, (e.g. congenital microvillous atrophy). Often absorptive mechanisms, although present, are overwhelmed, resulting in diarrhoea. In the case of secretory diarrhoea, this does not stop if the child's enteral feeds are withheld.

In some instances, both osmotic and secretory diarrhoea can occur together, in acute or chronic disease, depending on the underlying cause.

Aetiology

Acute diarrhoea can be caused in a number of ways, the commonest being infective, when the diarrhoea may be a beneficial physiological response to harmful material within the bowel, by expelling the harmful bacteria and toxins from the body.

Infective causes of acute diarrhoea - gastroenteritis

This results from either:

- Damage to the mucosa (e.g. in rotavirus)
- Toxins produced by the infective organism itself (e.g. in cholera)

Most cases are due to viruses, with rotavirus being most common. Infections occur all year round, with peaks in winter and spring due to rotavirus. Rotavirus vaccine was introduced in the UK in July 2013 and may result in a change in epidemiology. Bacterial infections are less common and are mostly due to *Campylobacter*. Other causes are listed in Table 14.2.

Pathophysiology

Most enteric viruses are transmitted between people by the faeco-oral route. Noroviruses can also spread through contaminated food and water and via droplet spread from vomitus. Viruses infect mature

Table 14.2 Causative pathogens of gastroenteritis

Viruses	Bacteria	Parasites
Rotavirus	*Campylobacter jejuni*	Cryptosporidium
Norwalk virus	*Salmonella*	*Giardia lamblia*
Norovirus	*Escherichia coli*	
Calicivirus	*Shigella*	
	Yersinia enterocolitica	
	Clostridium difficile	

enterocytes of the small intestine, causing cell destruction and villous atrophy. Rotavirus also causes opening of calcium channels resulting in efflux of sodium and water into the intestinal lumen. Fluid loss decreases between day 2 and day 5 and villous structure is restored by days 6–10. Bacterial enterocolitis results from mucosal invasion by bacteria and/or production of cytotoxins.

Haemolytic-uraemic syndrome can occur following infection, with bacteria producing Shiga-like toxin (also known as verotoxin) and has traditionally been most closely linked to *E. coli* 0157:H7 strains. This is discussed in detail in Chapter 19, Nephrology.

Assessment

The clinical assessment of dehydration is described in Chapter 6, Paediatric emergencies and critical care.

Management

The most important complications of viral gastroenteritis are dehydration and electrolyte abnormalities. Management is largely supportive.

Oral rehydration

The use of specific oral rehydration solution (ORS) for acute gastroenteritis is one of the most significant advances in the reduction in childhood mortality of the 20th century. Indeed, since its introduction, the childhood mortality rates from acute infective diarrhoea in children under five years old have reduced from some 5 million per year to 0.6 million in 2012.

In 1966, it was discovered that the sodium-glucose transporter is not necessarily affected by microbes and when sodium and glucose are present in the lumen the cotransporter will continue to work, even when the chloride channels continue to cause secretion. Therefore, when a solution is taken containing both sodium and glucose, in the correct proportions, the absorption of sodium is increased with a consequent increase in passive water absorption. This transporter works effectively even in the presence of inflammation of the gut and is the reason why ORS is effective in diarrhoeal illness. The ORS does not actually 'stop' the diarrhoea, which often continues, but the absorption of water and solutes will exceed the secretion and will ensure the child remains hydrated until the infective organism is eradicated. The ORS recommended by the WHO contains 75 mmol/L sodium, 75 mmol/L glucose, and has a total osmolarity of 245 mOsm/L. Of note, other traditional rehydration solutions, such as Coca-Cola and apple juice, have a significantly lower content of sodium and a very high osmolarity and are unsuitable as oral rehydration solutions.

ORS has been shown to be effective in both developing and developed countries for the rehydration of

children. Studies have shown that less that 5% of children with acute diarrhoea, regardless of the underlying cause, fail to improve with oral therapy and that intravenous rehydration, with its consequent risks, is rarely needed. The management of severe diarrhoea leading to shock is described in Chapter 6, Paediatric emergencies and critical care.

Refeeding following gastroenteritis

Breastfed infants should continue to be breastfed during an episode of acute diarrhea, as it promotes faster recovery and rehydration. Artificially-fed infants may return to normal feeding after a 6 hour period of oral rehydration solution if they recover well. The long-held myth that lactose-free diets should be adhered to after diarrhoea is not evidence-based and the 3% of children that develop reducing substances in their stools following diarrhoea will recover within 5 days (NICE guidance on the management of acute gastroenteritis).

Antibiotics or probiotics for gastroenteritis

Antibiotics are rarely indicated. Even for proven or suspected bacterial infections, antibiotics are reserved for those with an unusually protracted course or in immunocompromised hosts. Some studies suggest that antibiotics may prolong symptoms. The efficacy of probiotics in the treatment and/or recovery from diarrhoea remains unclear and currently these are not recommended.

Non-infective causes of acute diarrhoea

Non-infective causes of acute diarrhea are as follows:

- Inflammatory processes within the bowel cause a reduction in the absorptive surface of the bowel as the villi are damaged, e.g. coeliac disease, cows' milk protein allergy, and surgical conditions such as acute appendicitis and intussusception
- Drug induced – antibiotics or laxatives may cause increased motility of the bowel, allowing less time for absorption.

Chronic diarrhoea

Chronic diarrhoea is defined as diarrhoea that lasts for more than three weeks. As with the acute diarrhoea, the pathophysiology of chronic diarrhoea can be either secretory or osmotic, or indeed a combination of the two.

Infective causes

Infective causes of chronic diarrhea include the following:

- *Giardia lamblia* – giardiasis: This flagellate protozoan causes acute watery diarrhoea,

abdominal pain, intermittent diarrhoea, abdominal distension, weight loss and chronic diarrhoea. It is diagnosed on a stool smear, but sensitivity of this test is only 75–95%, so an empirical trail of metronidazole for 3–5 days may be of benefit.

- *Cryptosporidium parvum* – cryptosporidiosis: This protozoan organism can cause chronic diarrhoea. Diagnosis is made by specific antigen testing. Although usually self-limiting, it may be treated with nitazoxanide for 3 days.
- Viruses: In immunosuppressed children, viruses such as cytomegalovirus can cause chronic diarrhoea.

Question 14.4

Diarrhoea

A 10-day-old baby born at term, birth weight 2.7 kg, presented with a history of diarrhoea, which began on day 2 of life. Parents report that she had profuse watery stools at least 10 times per day. She had lost 16% of her birth weight despite bottle feeding well. On examination, she had clinical features of shock and was malnourished. She was admitted to the ward and given fluid resuscitation. Despite bowel rest, her diarrhoea continued with further weight loss and a drop in serum albumin. Stool culture was repeatedly negative and stool electrolyte analysis confirmed secretory diarrhoea. Her capillary blood gas remained normal throughout.

What is the most likely cause of her diarrhoea? Select ONE answer only.

A. Coeliac disease
B. Congenital chloride-losing diarrhoea
C. Congenital microvillus inclusion disease
D. Fructose intolerance
E. Giardiasis

Answer 14.4

C. Congenital microvillus inclusion disease.

It is relatively easy to discount coeliac disease (the child has no gluten in the diet), fructose intolerance (also no fructose) and giardiasis (stool culture is repeatedly negative). A child with congenital chloride-losing diarrhoea would have a metabolic alkalosis (see below).

Non-infective causes

Secondary to damage to the mucosa: In coeliac disease or inflammatory bowel disease, inflammatory mediators act locally within the intestinal mucosa to stimulate secretion and inhibit reabsorption of electrolytes. They also act on enteric neurons to increase motility.

Specific and rare abnormalities of enterocytes or the brush border membrane: Presentation is often with chronic diarrhoea from early infancy. Examples include congenital microvillus inclusion disease, where there is a net reduction in the surface area of the bowel and massive excretion of electrolytes in the stools. Another rare cause is autoimmune enteropathy, where anti-enterocyte antibodies damage the bowel mucosa.

Specific and rare electrolyte transport defects:

- Carbohydrate malabsorption: Primary (very rare in the newborn) or secondary lactose intolerance, sucrose-isomaltase deficiency, congenital glucose-galactose malabsorption cause osmotic diarrhoea due to high osmolality of luminal contents. Fructose intolerance is known to cause osmotic diarrhoea in children and should be considered as a differential diagnosis in chronic diarrhoea.
- Chloride malabsorption: Congenital chloride-losing diarrhoea in which the chloride/bicarbonate transporter does not function, results in high luminal chloride levels and secretion of fluid. In this situation, the Na/ H$^+$ exchangers continue to operate, so hydrogen is secreted in the faeces without bicarbonate to neutralize it, resulting in a metabolic alkalosis.
- Pancreatic and biliary disorders: Cystic fibrosis may lead to pancreatic insufficiency and protein and fat malabsorption. The contents of the intestinal lumen are therefore of a higher osmolality, resulting in osmotic diarrhoea. The liver disease, cholestasis, may cause reduced bile salts and insufficient fat malabsorption, thereby causing diarrhoea secondary to highly osmolar luminal contents.
- Disorders of intestinal motility: These disorders may cause rapid transport through the gut resulting in less overall absorption of electrolytes and water.

Irritable bowel syndrome variant of childhood: 'Chronic non-specific diarrhoea of childhood' or irritable bowel variant of childhood are terms for what used to be called toddler diarrhoea. This diagnosis is one of exclusion, but can be useful as many parents have heard of it and there is often a positive family history.

Case history

Chronic diarrhoea with blood in an older child

A 13-year-old boy presented with a 4-month history of loose motions occurring up to 6 times per day. There has been associated abdominal pain (which was relieved by opening his bowels), reduced appetite and weight loss of approximately 2 kg. On questioning, there had been blood in his motions and on wiping for the past 2 months and perianal soreness. Examination revealed a pale, thin boy with multiple oral aphthous ulcers. There was tenderness to palpation in the left iliac fossa. Blood tests revealed a microcytic anaemia with an ESR 32 mm/h, CRP 45 mg/dL and hypoalbuminaemia. A white cell scan and barium meal with follow through identified multiple areas of likely inflammation within the ileum and large bowel. He underwent endoscopy, which confirmed the diagnosis of Crohn's disease in the colon and terminal ileum with multiple areas of transmural inflammation and non-caseating granulomas seen on biopsy.

Vomiting

Vomiting is a common symptom of childhood. In some children it occurs without a GI pathology and one must not forget that there is a powerful central component to the vomiting reflex. There are many causes, as listed in Table 14.3.

Table 14.3 Causes of vomiting in childhood

Anatomical anomalies	Atresias
	Pyloric stenosis
	Strictures secondary to inflammatory processes
	Achalasia
	Dysmotility
Infection	Acute gastroenteritis
	Other infections, e.g. meningitis
Gastro-oesophageal reflux disease	
Central nervous system	Raised intracranial pressure
	CNS trauma (i.e. head injury)
	Drugs e.g. chemotherapeutic agents
Psychological	Regurgitation
Renal	Renal failure
	Urinary tract obstruction

Investigations of the gastrointestinal tract

Breath tests (Fig. 14.7)

The urea breath test is a non-invasive method to detect the presence of *Helicobacter pylori*, although it is less reliable in younger than older children. Urea, labelled with ^{13}C isotope, is ingested, usually with a test meal to delay gastric emptying. Urea rapidly moves down its concentration gradient into the epithelial blood supply and appears in the breath within minutes.
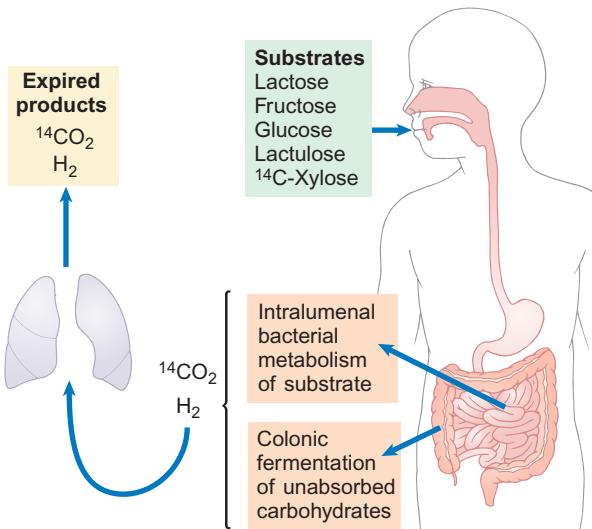
Fig. 14.7 Schematic drawing showing the principles behind breath tests. *(From Simren M, Stotzer P-O. Gut 2006;55(3):297–303, with permission.)*

Breath samples are collected at variable times post ingestion and then analysed using mass spectrometry. Values which exceed a fixed cut-off value suggest *H. pylori* infection. The basis of the breath test is the high urease activity of *H. pylori*, which hydrolyses urea to carbon dioxide and ammonia. In the presence of *H. pylori*, the carbon dioxide expired is labelled with the ^{13}C isotope, which is measured in the expired breath.

Hydrogen breath tests are based on the fact that there is no source for hydrogen gas in humans other than bacterial metabolism of carbohydrates. For these tests, different carbohydrates are administered orally and the concentration of hydrogen is measured in expired air. When defective sugar absorption is present, unabsorbed sugars are available in the colon for bacterial fermentation. When exposed to bacteria in the bowel, the substrate will be metabolized to hydrogen, which is quickly absorbed, expired, and possible to measure in expired air.

Stool tests

Stool tests that may be performed are:

- Stool microscopy and culture (including for *C. difficile* and *C. difficile* toxin presence).
- Faecal calprotectin – this is an abundant neutrophil protein found in both plasma and stool that is markedly elevated in infectious and inflammatory conditions, including inflammatory bowel disease. It is therefore useful as a non-invasive measure of inflammation in the bowel and is proving to be a useful

Table 14.4 Stool tests and their implications

Test	Normal values	Implications
Alpha-1 antitrypsin levels	Low	Alpha-1 antitrypsin deficiency
Steatocrit	Low (>2 years)	Fat malabsorption
Faecal reducing substances	Absent	Carbohydrate malabsorption
Faecal elastase	Raised	Pancreas function
Chymotrypsin	Raised	Pancreas function
Faecal calprotectin	Low	Inflammation of the gut

Case history

Diagnosis of coeliac disease

A 3-year-old boy was seen with a 6-month history of diarrhoea and weight loss, with a family history of thyroid disease and type 1 diabetes. An anti-TTG antibody was greater than 10 times normal with a positive endomysial antibody and positive HLA-DQ2 haplotype. Thus, a diagnosis of coeliac disease was made using the 2013 ESPGHAN criteria, without the need for endoscopic biopsy.

non-invasive screening test for inflammatory bowel disease.

- Faecal elastase is a marker of exocrine pancreatic function as elastase is produced by the pancreas, but remains undegraded during intestinal transit. It is used as a non-invasive measure of pancreatic function and has largely replaced formal pancreatic function testing.
- In some centres, the measurement of *H. pylori* antigen in the faeces is available. This test is useful as a non-invasive marker of *H. pylori*. However, its use tends to be restricted to diagnoses of treatment failure, or reinfection after initial eradication therapy.
- Stool electrolytes are used to assess whether chronic diarrhoea in an infant is secretory or osmotic.
- Other stool assessments are shown in Table 14.4.

Coeliac disease diagnostic blood tests – HLA typing and antibody tests

As described above, in coeliac disease, 95% are either HLA-DQ2 or DQ8 positive. Absence of these HLA types has a negative predictive value close to 100%. However, approximately 40% of the population also have these haplotypes, though clearly not all of them go on to develop coeliac disease.

Over the last 10 years, the identification and accurate assaying of anti-endomysial antibodies (EMA) and anti-tissue transglutaminase antibodies (anti-TTGa) has developed. These, in the presence of a normal IgA level, are highly specific for coeliac disease. They have markedly increased the number of positive diagnoses at small bowel endoscopy, and recent guidelines (European Society of Paediatric Gastroenterology, Hepatology and Nutrition, ESPGHAN 2012) suggest that in symptomatic children with positive anti-TTG and EMA and who are HLA-DQ2 or DQ8 positive, a small bowel biopsy is not always necessary for diagnosis.

Recent scientific advances that have changed clinical practice

New diagnostic blood tests for coeliac disease means that in some cases endoscopy is no longer necessary.

Motility studies

pH monitoring

24-hour monitoring of the pH in the lower oesophagus can be useful in the assessment of acid gastro-oesophageal reflux in infants and children. The test evaluates episodes of reflux of acidic stomach contents into the distal oesophagus using the detection of gastric acid (via pH measurement) and recording the duration and frequency of these episodes. Oesophageal pH monitoring does not provide information on the presence of aspiration, oesophagitis or hiatus hernia and will only detect acid rather than alkaline reflux. The relationship of reflux episodes with position, feeding and sleeping/symptoms may be of benefit, particularly in the relationship of respiratory symptoms to episodes of acid reflux. A pH study is not required in the majority of children who have a typical clinical diagnosis of gastro-oesophageal reflux, but is most useful in those children where the medical management of gastro-oesophageal reflux has failed, where there are unexplained respiratory symptoms or when fundoplication is being considered.

Multi-channel intraluminal impedance

Newer techniques combine the measurement of pH and intraluminal electrical impedance. Multi-channel intraluminal impedance (MII) allows the detection of all types of reflux, both acidic and non-acidic, and can determine the duration and proximal extent of reflux episodes. This technique involves the measurement of impedance at multiple sites in the lumen of the oesophagus in order to detect the retrograde movement of gastric contents. It detects changes in

resistance to current flow when a bolus crosses a pair of electrodes. This technique can distinguish between liquid and gas boluses since liquid has low impedance whereas gas has high impedance. When combined with a pH probe, the reflux episodes can then be classified as acidic or non-acidic. A combined probe is inserted intranasally in a similar way to conventional pH probes. Having impedance sensors at multiple sites along the length of the oesophagus also allows the proximal extent of reflux episodes to be identified.

Oesophageal manometry

Oesophageal manometry is used in the evaluation of motility disorders of the oesophagus. A catheter is placed into the stomach intranasally. The catheter is gradually withdrawn, recording the pressure at different parts of the oesophagus. It provides information on pressure and coordination of muscle contraction in the oesophagus. Oesophageal manometry may be performed in patients with symptoms of oesophageal dysfunction such as dysphagia, chest pain, food impaction and odynophagia (pain in the mouth or oropharynx on swallowing). It can also aid in the diagnosis of oesophageal dysmotility disorders such as achalasia, intestinal pseudo-obstruction and systemic conditions such as scleroderma if the oesophagus is affected.

Manometric studies of the intestine, colon and anorectum

Anorectal manometry is used in some centres to assess anorectal function. A balloon inserted into the rectum causes distention, with sensors measuring the pressure at the internal anal sphincter. It is possible to measure anal resting pressure, squeeze pressure and anal canal length, as well as rectal sensation in the presence of the rectoanal inhibitory reflex. In normal children, when the rectum is distended with the balloon, there is relaxation of the internal anal sphincter, but in Hirschsprung's disease, the internal anal sphincter fails to relax. Manometric investigation of both the colon and small intestine is undertaken in some specialized tertiary centres in order to diagnose the very rare conditions of intestinal dysmotility.

Investigation in constipation

Most children with constipation do not require extensive evaluation. Further investigation should be considered in those children who fail to respond to sufficient medical therapy. These investigations include thyroid function tests, coeliac disease screening and referral to a tertiary gastroenterologist, where rarer diagnoses of Hirschsprung's disease and dysmotility can be considered.

Radiological investigations
Contrast studies

Barium contrast studies can be useful in the investigation of both congenital and acquired gastrointestinal conditions. For assessment of the upper GI tract, barium is ingested and a series of films are taken over time as the barium moves through the gut. It can be used to identify anatomic abnormalities including achalasia, malrotation, tracheo-oesophageal fistula and hiatus hernias. The investigation can be used to identify the site of intestinal atresias and to aid diagnosis in suspected obstruction.

An upper GI series with small bowel follow through is used in the assessment of suspected inflammatory bowel disease, providing information of the parts of the GI tract which cannot be accessed by endoscopy. It can be used to assess the bowel lumen and identify fistulas and strictures.

Barium can also be given via enema for assessment of the large bowel, but is rarely indicated as it has largely been superseded by colonoscopy.

Ultrasound scan

Ultrasound scanning in the hands of a skilled radiographer/radiologist is useful in assessment of solid organs, particularly of the size and nature of the liver and spleen, and the blood flow to these organs. In the hollow viscera, assessment is more difficult. The gall bladder can be assessed for stones, sludge and size when the patient is starved. The appendix can be seen occasionally when inflamed, particularly if there is a fluid collection or cyst surrounding it. It is difficult to comment on bowel wall thickness, but identification of a fluid collection or abscess adjacent to the bowel is helpful. The pancreas is difficult to see due to overlying gas, though a pseudocyst may be seen. The pylorus may be seen if hypertrophied in pyloric stenosis.

MRI

MRI is a more recently used modality for the investigation of the bowel in inflammatory bowel disease, particularly for the assessment of perianal disease. It has the advantage of no radiation exposure. The patient is required to drink oral contrast media such as a mixture of barium and sorbitol or a polyethylene glycol-electrolyte compound for distension of the bowel as well as intravenous contrast (gadolinium-based), which allows inflammatory lesions within the bowel to be detected.

Indium-111 white blood cell scans

The 'white cell scan' is a nuclear medicine investigation which can be used to identify sites of acute inflammation or infection within the body. In

inflammatory bowel disease, this investigation can identify affected sites and the extent of inflammatory bowel disease. Blood is taken from the patient, labelled with the isotope Indium-111 and reinjected intravenously. The labelled white cells will move to sites of inflammation.

Colonic transit studies

Marker studies can be used in the evaluation of children with severe constipation, refractory to standard therapy. The patient swallows capsules containing non-digestible radio-opaque markers (usually daily for 3 days) with an abdominal X-ray taken on day 5. The X-ray is examined for the presence of the markers. Their number and position provide information regarding colonic transit time and whether the patient has slow transit constipation.

Endoscopy

Upper gastrointestinal endoscopy and colonoscopy allow direct visualization of the mucosa of the bowel, identifying areas of inflammation and mucosal abnormalities. It is vital in the diagnosis and monitoring of conditions such as coeliac disease, inflammatory bowel disease and polyposis syndromes. Endoscopy can also be used therapeutically to remove ingested foreign bodies (coins, batteries, etc.) and resection of polyps. In children and young people, endoscopy can be performed under general anaesthetic or intravenous sedation depending on their age and compliance and the nature of the procedure. Colonoscopy requires adequate preparation of the large bowel prior to the procedure with a low-residue diet and laxatives. Although the entire length of the GI tract cannot be accessed by endoscopy, an upper endoscopy allows visualization from the oesophagus, into the stomach and as far as the second part of the duodenum. The colonoscopy allows examination of the entire large bowel from the rectum and aims to intubate the ileocaecal valve to allow examination of the terminal ileum. Biopsies can be taken from all areas, allowing histological examination. Complications of this procedure include bleeding and perforation and particular care is taken if the tissue appears friable or inflamed. Endoscopy should only be performed in centres with particular expertise in paediatric endoscopy supported by surgical specialities.

Capsule endoscopy is performed in some centres, with an endoscopic capsule swallowed (or placed in the intestine in smaller children via endoscopy) and images are recorded of the mucosa of the intestine as the capsule passes through the gastrointestinal tract. These can then be analysed to look for signs of mucosal inflammation, particularly in the small bowel, which is not accessible by conventional endoscopy. The disadvantage is that it is not possible to take mucosal biopsies using this technique.

Capsule endoscopy, where a capsule was passed into the duodenum to obtain a specimen of mucosa, was used until the mid-1990s to diagnose coeliac disease in symptomatic children by identifying flattened duodenal mucosa, which, on repeat capsule endoscopy after a gluten-free diet, had become normal. As upper gastrointestinal endoscopy was developed, the gold standard for diagnosis became a duodenal biopsy taken at endoscopy, showing typical, and often patchy, features. As outlined above, the use of endoscopy to demonstrate flattened duodenal mucosa is no longer essential if symptomatic, HLA-DQ2 or DQ8 positive, anti-endomysial antibodies (EMA) and anti-tissue transglutaminase antibodies (anti-TTGa) positive with normal IgA.

Pharmacology of the gastrointestinal tract

Gastro-oesophageal reflux disease

Feed thickeners

Feed thickeners such as Carobel may be of benefit in mild cases of gastro-oesophageal reflux. Gaviscon is a compound alginate preparation which may be effective in older children, with its mechanism of action being the formation of a viscous raft over the stomach contents, therefore reducing reflux. When used in infants, Gaviscon works as a feed thickener but a cheaper, safer alternative, such as Carobel, is preferable.

Acid-reducing medications

H_2-receptor antagonists: ranitidine

H_2-receptor antagonists, such as ranitidine, reduce gastric acid secretion through blocking the histamine H_2 receptors. Indications include dyspepsia, gastro-oesophageal reflux disease and in the healing of duodenal and gastric ulcers. Side effects include diarrhoea, headache and dizziness. Ranitidine is available in liquid formulation which makes it a preferable alternative to proton pump inhibitors in many infants.

Proton pump inhibitors

Proton pump inhibitors (PPIs) act by blocking the proton pump of the gastric parietal cell, thereby inhibiting gastric acid secretion. They are used in the management of gastro-oesophageal reflux disease, for erosive, stricturing or ulcerative oesophagitis and as part of the regimen for eradication of *H. pylori*. Commonly used PPIs are omeprazole (available in tablet

form or as a dispersible tablet) and lansoprazole (available as a tablet or orodispersible tablet). Side effects include gastrointestinal disturbance, headache and dry mouth.

Prokinetic agents

Domperidone is used as a prokinetic agent to increase gastric emptying and increase the lower oesophageal sphincter pressure. There is no convincing evidence of its efficacy and its safety profile has not been fully studied. Currently not recommended for the treatment of gastro-oesophageal reflux disease.

Agents affecting motility

Anti-spasmodic agents – mebeverine, peppermint oil, antimuscarinics

These agents may reduce intestinal motility and may be used in the irritable bowel syndrome variant of childhood to reduce smooth muscle spasm, although evidence for their efficacy is poor.

Motility stimulants – domperidone and metoclopramide

Dopamine receptor antagonists act as prokinetic agents by stimulating gastric emptying and small intestinal transit. Metoclopramide, and to a lesser extent domperidone, can cause a dystonic reaction and should be used with caution. The antibiotic erythromycin, at a low dose, can also be used as a prokinetic for the treatment of gastrointestinal stasis.

Anti-diarrhoeal medications

Anti-diarrhoeal medications (e.g. loperamide) may reduce diarrhoea but should be used with caution in children and are not indicated as a first-line treatment. They have no place in acute diarrhoea (gastroenteritis) where fluid and electrolyte management using oral rehydration solutions is the most important treatment. However, medications such as loperamide and codeine phosphate may help in the symptomatic relief of chronic diarrhoea once children have been investigated and anatomical abnormalities excluded.

Medications used in management of constipation

NICE guidance on chronic constipation in childhood provides an excellent overview of medications indicated.

Osmotic laxatives
Movicol
Movicol is a polyethylene glycol (PEG) compound which is non-absorbable and not digested by intestinal bacteria. It acts by retaining water within the bowel and therefore makes stools softer and bulkier. The medication comes in sachet form, which is mixed with water to form a solution. It is effective for both faecal impaction and maintenance treatment. Movicol is well tolerated and side effects are rare.

Lactulose
Lactulose is a non-absorbable disaccharide which acts to draw fluid into the bowel and soften stool. It can take up to 48 hours to have effect and the dose can be adjusted according to response. Side effects include flatulence, cramps and abdominal discomfort; polyethylene glycol solutions such as Movicol are the preferred choice.

Stimulant laxatives

Stimulant laxatives such as sodium picosulphate, docusate and senna may increase intestinal motility and can be useful in the treatment of childhood constipation. Their use may be limited by abdominal cramps and they should not be used in bowel obstruction. If stools are hard, they should first be softened by increasing fluid intake or with the use of Movicol or lactulose.

Drugs used in the management of inflammatory bowel disease

Children with inflammatory bowel disease should be managed by a specialist paediatric gastroenterologist with specialist nutritional, pharmacy and surgical support.

Aminosalicylates

Sulfasalazine consists of 5-aminosalicylic acid (5-SA) and sulfapyridine, linked by an azo bond. It is an oral medication, which is partially absorbed in the jejunum and passes into the colon where it is reduced to sulfapyridine and 5-SA. Sulfapyridine is responsible for the majority of the side effects seen with sulfasalazine and for this reason newer 5-SA medications such as mesalazine are better tolerated whilst having similar efficacy. Precisely how these medications work is unknown, but they have anti-inflammatory properties. Suggested possible mechanisms of action include inhibition of the synthesis of cytokines, prostaglandins and leukotrienes, free radical scavenging, impairment of white cell adhesion and function and immunosuppression. Mesalazine and sulfasalazine are licensed in children for the treatment of mild Crohn's disease and maintenance of remission in ulcerative colitis. Side effects are reported in up to 30% of cases, with headache and nausea being the commonest reported symptoms and diarrhoea reported in

around 8%. Approximately 3% of patients experience a paradoxical worsening of their colitis on sulfasalazine and 5-SA derivatives. These medications should be used with caution in children with renal impairment, and renal function must be checked 3 months after commencement and annually thereafter. Mesalazine can be given topically for left-sided colitis and proctitis.

Dietary therapy

Modulen (a polymeric liquid feed) or an elemental feed are effective in reducing intestinal inflammation in Crohn's disease (and occasionally in ulcerative colitis) although their precise mode of action is unknown. They are as effective as corticosteroids, but their use is limited by their unpalatability.

Corticosteroids

Corticosteroids are used as first-line therapy in the induction of remission in children with Crohn's disease and ulcerative colitis. This is usually in the form of prednisolone for 2–4 weeks until remission is achieved, with the dose tapered over the next 4–8 weeks. In those with severe disease, intravenous hydrocortisone may be used. Budesonide has fewer side effects than prednisolone but is generally less effective. Young people and their parents should be warned of the importance of gradual withdrawal of steroids and not stopping the medication abruptly. Long-term corticosteroids are not recommended as maintenance treatment due to the effects on growth and bones.

Azathioprine and 6-mercaptopurine

Azathioprine is the commonest used second-line medication in the management of inflammatory bowel disease. 6-Mercaptopurine is its metabolite and is more commonly used in the US, although azathioprine is favoured in the UK. It is a powerful immunosuppressive agent with the potential for bone marrow suppression. Children started on the medication must have regular full blood counts.

Methotrexate

Methotrexate is used as a third-line management of inflammatory bowel disease, but the evidence in children is less compelling than that for azathioprine.

Monoclonal antibodies

Monoclonal antibodies, such as infliximab and adalimumab, are used with increasing frequency in Crohn's disease (and with less efficacy in ulcerative colitis). They are powerful medications which should only be used in tertiary centres where the therapeutic benefit and potential side effects can be monitored.

> **Recent scientific advances that have changed clinical practice**
>
> The use of biological therapies (monoclonal antibodies such as infliximab and adalimumab) in inflammatory bowel disease has altered disease progression, and led to fewer surgical resections.

Other system disorders and their impact on the GI tract

Immune system

The GI tract has the largest surface area of the body and is exposed to the largest number of foreign antigens. Normally, the immune system develops tolerance to these 'normal antigens' and does not mount an immune response to them. When the immune system becomes dysregulated, these normal food and microbial antigens are identified as being foreign, and therefore a threat, and stimulate inflammation and system immune responses which may lead to allergy and inflammatory processes within the GI tract and beyond.

Primary immunodeficiency

See Chapter 15, Infection and immunity, for further details.

Selective IgA deficiency

Secretory IgA forms an integral part of the innate immune system within the lining of the GI tract. When deficiency occurs, children are at higher risk of dental caries, recurrent giardiasis and coeliac disease.

X-linked agammaglobulinaemia

Children with this condition are at higher risk of chronic gastroenteritis with pathogens such as *Campylobacter*, *Cryptosporidium*, *Salmonella*, *Giardia* and rotavirus. The findings at endoscopy are similar to those seen in Crohn's disease, although granulomas are not seen. Treatment is with IgG replacement.

Severe combined immunodeficiency

As a result of the abnormal T and B cell differentiation, individuals with this condition are highly susceptible to infection. Severe forms of gastroenteritis can result in small intestinal villous atrophy. Autoimmune manifestation can result in enteropathy. Infections of the GI tract with organisms such as rotavirus, candida, CMV and EBV cause significant morbidity and mortality.

Chronic granulomatous disease

In this condition, neutrophils are unable to produce superoxide and hydrogen peroxide, which are

necessary for the protection against infections from *Staph. aureus*, *Serratia*, *Aspergillus*, and *Candida*.

Presentation with this condition may be with gastric antral obstruction due to narrowing caused by infection and granulomatous inflammation. Small bowel involvement is similar to Crohn's disease.

Wiskott–Aldrich syndrome

This may present with GI bleeding from thrombocytopenia. Infectious diarrhoea is also common. Inflammatory bowel disease can also be triggered in early infancy. There is an increased risk of gut-associated lymphomas.

IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked)

This usually presents within a few months of birth with diabetes mellitus, protracted diarrhoea of infancy, faltering growth, eczema and anaemia. Thrombocytopenia and hypothyroidism may also occur. Mutations in the *FOXP3* gene (associated with T cell function) are the cause of this condition. Severe villous atrophy is found at endoscopy and the presence of anti-enterocyte antibodies also suggests this diagnosis.

Secondary immunodeficiency

The main causes of secondary immunodeficiency are HIV and the use of immunosuppressive therapies for either inflammatory or malignant conditions. These diseases leave the individual open to infection within the gut from infections that would not normally cause problems, such as CMV, HSV and EBV.

Graft-versus-host disease

Allogeneic bone marrow transplant and solid organ transplants are increasingly performed to treat a number of malignant and metabolic conditions, and organ failure. Graft-versus-host disease (GvHD) is a complication, in which the immune cells from the grafted tissue recognize the recipient (the host) as 'foreign'. The transplanted immune cells then attack the host's body cells. The sites that are commonly affected are the skin, intestine and liver. Gut manifestations include an enteropathy with diarrhoea and faltering growth, or a gastropathy with haematemesis and excessive vomiting. Steroids and immunosuppressive therapy are the mainstay of treatment.

Respiratory system

Cystic fibrosis

Gastrointestinal manifestations are:

- *Pancreatic disease*: Due to increased viscosity of secretions from the pancreatic duct, there is autodigestion of the pancreas from enzymes that are normally secreted into the gastrointestinal tract. Consequently, islet cells may be damaged leading to type 1 diabetes mellitus. Due to reduced pancreatic enzymes within the intestinal lumen, malabsorption of fat occurs, which clinically manifests as steatorrhoea and faltering growth. Treatment with enzyme replacement therapy (e.g. Creon) is necessary to allow the child to thrive.
- *Intestinal disease*: The chloride cotransporter (CFTR) within the small bowel that is involved in secretion of water into the gut is ineffective and may result in meconium ileus at birth (15% of children with cystic fibrosis present with intestinal obstruction within the neonatal period) or distal intestinal obstruction syndrome (DIOS) in childhood and adolescence. In DIOS there is ineffective secretion of water and chloride into the small intestine, which results in obstruction around the area of the terminal ileum, caecum and ascending colon. Gastrografin or intestinal lavage is necessary in some cases; however, severe cases require surgery and stoma formation.

Endocrine disorders

Hyperthyroidism can result in diarrhoea due to increased motility of the bowel (rapid gastric emptying and intestinal motility) due to the higher levels of circulating T3. Due to rapid passage, the intestinal contents have high osmolality, which also results in higher secretory activity of the intestine. Conversely, hypothyroidism results in constipation for the opposite reasons.

Hypocalcaemia/hypomagnesaemia can result in diarrhoea. Hypercalcaemia can result in constipation.

Acute illness/trauma

Severe acute illness, particularly requiring high-dependency or intensive care, can have a detrimental effect on the GI tract and may require a period of rehabilitation before the GI tract is fully functional again. GI manifestations include:

- *Stress gastropathy*: Usually within 24 hours of an acute event, presents with upper GI haemorrhage. Lesions are usually found in the gastric fundus and proximal body initially. There is a risk of perforation. GI rest and conservative treatment with antacids and anti-acid drugs (e.g. PPIs) are the mainstay of treatment.
- *Traumatic gastropathy*: Occurs after forceful retching or vomiting, which causes the proximal stomach to get stuck in the distal oesophagus. This results in vascular congestion and subepithelial haemorrhages in the fundus and

body. Nasogastric tubes and gastrostomies are associated with this.

- *Traumatic perforation*: May occur after blunt trauma to the abdomen (always consider in a handlebar injury) – will require surgical input for both conservative and surgical intervention.

Further reading

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Christine E Jones, Manish Sadarangani, Graham Davies
With contributions by
**Mike Sharland, Omendra Narayan, Daniel Langer, Christian Harkensee,
Chris Barton, Kirsty Le Doare, Aubrey Cunnington**

CHAPTER

15

Infection and immunity

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Know the classification and essential features of infectious agents
- Understand the pharmacology and rational use of antimicrobials
- Understand host defence mechanisms and their pattern of development
- Know the causes and common presentations of vulnerability to infection, including primary/secondary immunodeficiency
- Understand the pathophysiology of fever and some infections of childhood such as meningitis
- Understand the scientific basis of immunization

The classification and essential features of infectious agents

Viruses

Viruses are the commonest cause of human infection. They are small (20–300 nm) and cannot be visualized with a light microscope. They are unable to synthesize their own energy or proteins and so are dependent on the host cell to replicate. However, once a virus particle (virion) infects a cell, it can replicate within hours to produce hundreds of virions, allowing the virus to rapidly spread from cell to cell.

Structure (Fig. 15.1)

Viruses consist of a core of nucleic acid surrounded by a protective protein coating known as the capsid. The capsid mediates the attachment of the virus to specific host cell receptors and defines the species and organ specificity of the virus. The capsid may induce host immune responses. In some viruses, the capsid is covered by a lipoprotein envelope, which confers instability to the virus. Enveloped viruses, such as RSV, dry out rapidly in the environment and are easily inactivated by detergent and alcohol. Viruses without an envelope, such as rotavirus or Norwalk virus, are less easily eradicated in the environment. The classification of viruses is based on the viral nucleic acid (DNA or RNA), capsid (size, symmetry) and presence of envelope.

Pathogenesis

Viral infection of a host cell may result in a number of consequences:

- Cell death due to inhibition of host cell protein synthesis while allowing ongoing viral protein synthesis. This may be visualized with light microscopy as the cytopathic effect (CPE) in cell cultures, aiding diagnosis.
- Fusion of host cells to form multinucleated giant cells, which can be visualized in cell cultures. For example, fusion protein of RSV results in syncytia through this mechanism.
- Malignant transformation by causing unrestrained growth, prolonged survival and morphological changes of the cell, for example, human papillomavirus.
- Viral replication without killing of the host cell can result in chronic carriage, for example hepatitis B. Disease may result from the host inflammatory response against viral antigens expressed on the host cell surface rather than from direct damage by the virus itself.
- The virus may remain within the cell but not replicate and latent infection ensues – a feature of
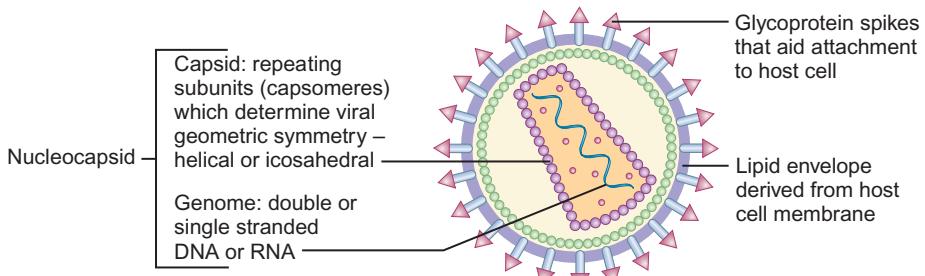
Fig. 15.1 General structure of a virus.
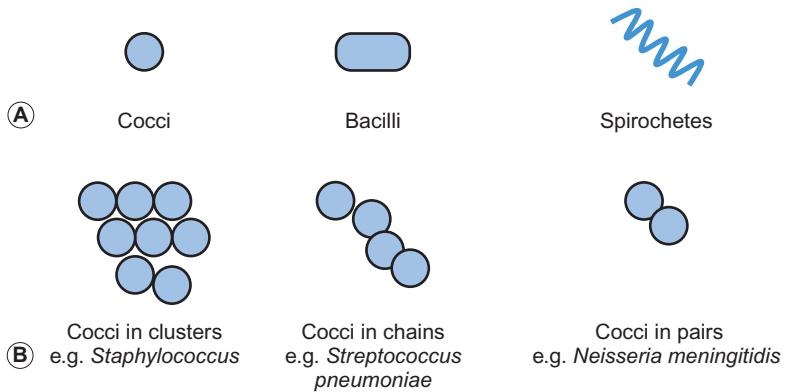
Fig. 15.2 Bacterial morphology. A. Three basic shapes of bacteria. B. Cocci can take up particular arrangements, which assist in identification of bacteria.

all herpesviruses. Varicella zoster virus (VZV) enters a latent phase following primary infection and later causes shingles when reactivated.

Bacteria

Bacteria vary in size; the smallest bacteria are similar in size to the largest viruses and the largest bacteria are the size of red blood cells. They are round (cocci), rod-like (bacilli) or spiral (spirochetes) in shape and tend to take up specific arrangements (Fig. 15.2).

Most bacteria are capable of independent metabolic existence and growth, with the exception of obligate intracellular pathogens such as *Chlamydia* and *Rickettsia*. They multiply by binary fission, each cell dividing into two daughter cells, and this allows exponential growth of bacterial colonies from a single bacterium to one million organisms within hours.

Classification

Bacterial classification is based on four features: Gram reaction, bacterial shape (see Fig. 15.2), growth requirement and the presence of spores (Table 15.1). Most bacteria grow in the presence of oxygen (aerobes), some require it (obligate aerobes) whilst others can still generate energy in the absence of sufficient oxygen

(facultative aerobes). A number of bacteria will only grow in an atmosphere containing less than 20% oxygen (anaerobic). Some bacteria produce spores in adverse conditions, allowing the organism to survive when exposed to chemicals and heat (i.e. *Clostridium* species).

A number of important pathogenic bacteria do not fit neatly into this classification as they do not take up the Gram stain: *Mycoplasma* (no cell wall), *Chlamydia* and *Rickettsia* (intracellular bacteria) and *Mycobacteria* (acid fast staining only).

Structure

Bacterial cells consist of cytoplasm surrounded by a cell wall. The DNA is free within the cytoplasm as a single chromosome of circular DNA and within plasmids, along with ribosomes and all elements required for growth and pathogenesis.

The cell wall is essential for survival and is a key target for antibiotics; differences in the components of the cell wall between Gram-negative and Gram-positive bacteria (Fig. 15.3) are therefore clinically important (see antimicrobial section). Gram-positive bacteria have a thick peptidoglycan layer with no outer membrane, whereas Gram-negative bacteria have a thin peptidoglycan layer surrounded by an outer lipid membrane. The periplasmic space of Gram-negative

Table 15.1 Classification of common bacteria

Gram reaction	Shape	Growth requirement	Spores	Examples
Gram-positive	Cocci	Aerobic	No	*Staphylococci*
				Streptococci
				Enterococci
	Bacilli	Aerobic	No	*Listeria*
			Yes	*Bacillus*
		Anaerobic	Yes	*Clostridium*
Gram-negative	Cocci	Aerobic	No	*Neisseria*
	Bacilli	Facultative aerobic	No	*E. coli*
				Klebsiella
				Salmonella
				Shigella
				Haemophilus
		Aerobic	No	*Pseudomonas*
		Anaerobic	No	*Bacteroides*
	Spirochete	Anaerobic	No	*Borrelia*

Gram positive bacterial cell wall

Flagellum
Pilus
Surface protein
Teichoic acid
Capsule
Thick peptidoglycan
Inner membrane (cytoplasmic membrane)
Membrane protein

Gram negative bacterial cell wall

Flagellum
Pilus
LPS
Capsule
Outer membrane
Surface protein
Thin peptidoglycan
Periplasmic space
Inner membrane (plasma membrane)
Membrane protein
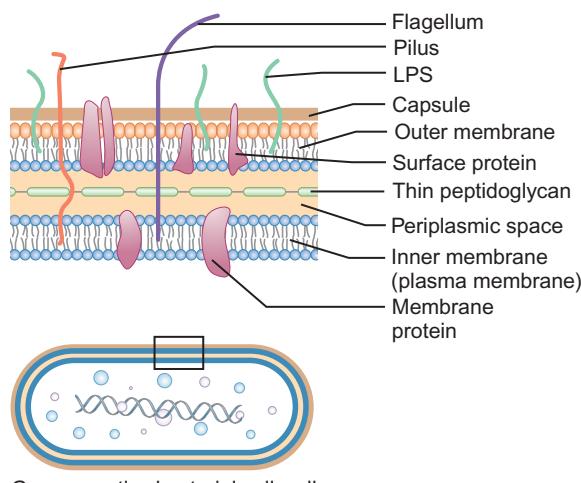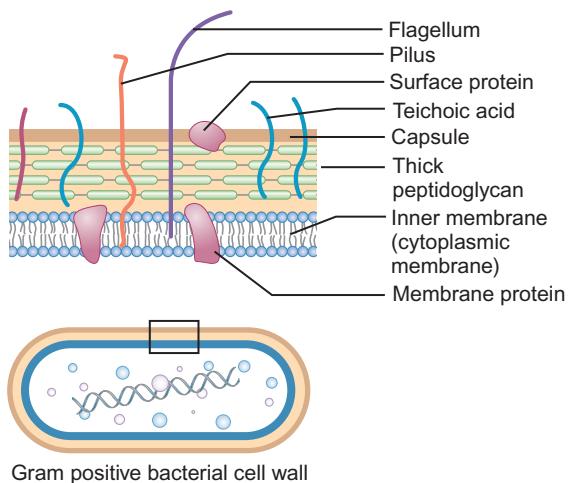
Fig. 15.3 Structure of the cell wall in Gram-negative and Gram-positive bacteria. Gram-positive bacteria appear blue/purple on a Gram stain due to retention of crystal violet dye in the thick cell wall and Gram-negative bacteria appear red/pink.

bacteria may contain β-lactamase, which degrades antibiotics such as penicillin.

The cell surface may contain different components. Gram-negative bacteria have endotoxin (lipopolysaccharide, LPS) in their outer membrane, which can induce septic shock. Teichoic acid is only found in Gram-positive bacteria and this can also induce septic shock. Numerous pili, hair-like structures, facilitate adhesion and acquisition of external DNA. Flagella are important in locomotion and may help with bacterial identification. Other proteins act as sensors, receptors and adhesins.

Bacteria such as *Streptococcus pneumoniae, Neisseria meningitidis, Klebsiella pneumoniae* and *Escherichia coli* are surrounded by a polysaccharide capsule, which enables them to evade phagocytosis. The spleen forms an important role in clearing these bacteria, therefore individuals who are hyposplenic, such as children with sickle cell, are more susceptible to these organisms.

Some bacteria produce slime in addition to the capsule and this helps with the formation of biofilms. This tough protective matrix is very difficult for antibiotics to penetrate and may form on foreign material.

Pathogenesis

Bacteria may be transmitted via the respiratory, gastrointestinal, urogenital or cutaneous route. Once transmitted, bacteria adhere to mucosal sites, facilitated by pili and surface proteins. Once a stable population of bacteria has been established, the host is colonized. In some instances, invasion occurs and the bacteria penetrate host cells and tissues. Not all strains of bacteria are equally pathogenic, for example, there are six serotypes of *Haemophilus influenzae*, but type b (Hib) causes the most serious disease. Moreover, different strains with differing virulence determinants

cause distinct patterns of infection; for example, *E. coli* may cause disease in the gastrointestinal tract, meningitis, sepsis or a UTI.

Eukaryotes

Protozoa, fungi and helminths are eukaryotic organisms, in contrast to viruses and bacteria. The DNA of eukaryotes is contained within a nucleus.

Protozoa

Protozoa are unicellular organisms that can exist in a vast range of environments. The cytoplasm is surrounded by a plasma membrane, which may have external structures such as a cell wall to enable the organism to survive outside the host (*Giardia intestinalis*) or flagella (*Leishmania*) to propel the protozoa.

They can be divided into three main groups that cause disease in humans:

1. Spore-forming (sporozoa): *Plasmodium*, *Toxoplasma gondii*
2. Flagellates: *Giardia intestinalis* and *Trichomonas*
3. Amoeboid: *Entamoeba histolytica* (causes amoebic dysentery or liver abscess)

They reproduce sexually and/or by binary fission. Their life cycle may involve vectors; for example, *Plasmodium* parasites are transmitted by mosquitoes (vector) and cause malaria in humans. Other protozoa are waterborne and only involve humans (*Entamoeba histolytica*).

Fungi

Fungi are widespread in the environment and can survive in hostile environments. They are saprophytes, living off dead matter in soil and water. Their cell wall contains chitin polysaccharide and not peptidoglycan. As a result, fungi are not sensitive to antibiotics that inhibit peptidoglycan synthesis. The cell wall also contains the polysaccharide β-glucan and ergosterol, which are targeted by various antifungal drugs (see antimicrobial section).

Fungi can be classified into yeasts, moulds and dimorphic fungi.

Yeasts are simple unicellular organisms that reproduce by asexual budding, *Candida albicans* is responsible for most disease caused by yeasts in humans.

Moulds grow as long filaments. Their branching filamentous hyphae assist with reproduction and acquisition of nutrients. They produce germinative spores, which enable them to colonize new environments. Airborne spores of *Aspergillus fumigatus* may be inhaled and cause infection in immunocompromised hosts.

Dimorphic fungi take the form of moulds at room temperature, but transform into yeasts at body temperature. *Histoplasma capsulatum* is a dimorphic fungus that may cause disease in individuals with HIV infection.

Fungal infections (mycoses) mainly cause superficial infections that are localized to epidermis (tinea corporis if it affects the body, tinea pedis if it affects the feet), hair (tinea capitis) and nails (tinea unguium). All forms of tinea that affect the skin may be referred to as ringworm; these are typically caused by dermatophytes. Dermatophytes belong to one of three fungal groups: *Trichophyton*, *Microsporum* and *Epidermophyton*. Systemic infections are most commonly due to opportunistic fungi in immunocompromised hosts.

Helminths

Helminths are complex multicellular parasitic worms that range in size from microscopic filarial parasites to tapeworms several metres in length. They reproduce sexually and have complex lifecycles. Helminths typically cause chronic rather than acute diseases.

They can be classified into nematodes (round worms) and platyhelminths (flatworms), which include cestodes (tapeworms) and trematodes (flukes).

Nematodes appear worm-like and cause infection in the intestine (*Enterobius vermicularis,* causing pruritus ani in children), blood (*Filaria,* such as *Wuchereria bancrofti* causing lymphatic filariasis) and tissues (*Onchocerca volvulus,* causing river blindness).

Cestodes (e.g. *Taenia solium, T. saginata*) are ribbon-like worms and can grow up to 10 m in length. The excreted eggs are ingested by an intermediate host, such as a cow or pig; humans become infected by eating meat from this animal.

Trematodes are flat, leaf-like organisms. Humans are the definitive host and freshwater snails are the intermediate host. *Schistosoma* species are a medically important example of trematodes.

Pharmacology and the rational use of antibiotics

Key concepts in antimicrobial pharmacology

An understanding of the pharmacology of antimicrobial agents is important to ensure adequate concentrations at the site of infection and therefore efficacy of the drug.

An understanding of pharmacokinetic–pharmacodynamic profiles guides dosage and dose frequency (Box 15.1). For example, antibiotics with a short half-life, such as penicillins, need to be given more frequently. Azithromycin has a very long half-life and is administered once daily. Another factor that guides

decisions related to dose frequency is the mechanism of action of an antibiotic. The activity may be related to the time that the concentration exceeds the minimum inhibitory concentration (MIC), e.g. penicillin. The activity of other antibiotics, such as gentamicin, is related to the peak antibiotic concentration reached. The therapeutic index describes how likely the drug is to cause toxicity to the host. It is the maximal tolerated dose that can be tolerated by the patient divided by the minimum effective dose (i.e. the lowest dose that will give the required MIC at the site of infection). The higher the therapeutic index, the less likely the drug is to cause toxicity, e.g. β-lactam agents have a high therapeutic index. Where the therapeutic index is low, serum level monitoring and dose adjustment is required (e.g. aminoglycosides). Therapeutic index can be seen as the balance between safety and efficacy.

Key points – antibiotic therapy

Antibiotics can be classified into the following major groups:
- **β-Lactam agents**:
  - penicillins, e.g. penicillin, flucloxacillin, amoxicillin, piperacillin
  - cephalosporins, e.g. ceftriaxone, cefuroxime
  - carbapenems, e.g. meropenem, imipenem
- **Macrolides**, e.g. erythromycin, azithromycin, clarithromycin
- **Tetracylines**, e.g. doxycycline
- **Aminoglycosides**, e.g. gentamicin, amikacin
- **Glycopeptides**, e.g. vancomycin, teicoplanin
- **Fluoroquinolones**, e.g. ciprofloxacin

Antibiotics exert their antimicrobial effect in four major ways:

i) Disruption of bacterial cell wall

β-Lactam and glycopeptide agents prevent cross-linkage of peptidoglycan, a key component of the bacterial cell wall. The bacterium is then killed by osmotic lysis. β-Lactams such as penicillin are predominantly used to treat Gram-positive infections caused by *Streptococci*. Third-generation cephalosporins such as ceftriaxone are active against a much broader spectrum of bacteria, including Gram-positive and Gram-negative organisms; however, ceftriaxone has poor action against *Pseudomonas* and *Enterococci*. Glycopeptide activity is limited to Gram-positive bacteria, as the large molecules are not able to penetrate the outer membrane of Gram-negative bacteria.

ii) Inhibition of protein synthesis

Protein synthesis is inhibited by macrolides, tetracylines, aminoglycosides and clindamycin at the level of the ribosome. As a group, these antibiotics are active against a wide range of bacteria. Macrolides have a similar spectrum of activity as penicillin but *Mycoplasma*, Mycobacteria and *Chlamydia* are also sensitive to macrolides. Aminoglycosides have excellent Gram-negative activity.

iii) Inhibition of DNA replication

Fluroquinolones inhibit enzymes involved in the coiling and uncoiling of DNA, thereby inhibiting DNA replication. Fluroquinolones have good activity against Gram-negative organisms, but poor activity against Gram-positive organisms, such as *Streptococci* and *Staphylococci*.

iv) Interruption of microbial chemical pathways

Bacteria produce folate for the synthesis of DNA as they cannot absorb folate from the host. Trimethoprim inhibits the conversion of dihydrofolate to tetrahydrofolate, thereby preventing purine and pyrimidine metabolism and DNA formation. It is active against Gram-negative and Gram-positive organsims and is most commonly used to treat urinary infections due to its excretion and high concentrations in the urine compared to blood.

Antibiotics may be considered as narrow or broad spectrum according to the range of bacteria they are active against. Broad-spectrum antibiotics should be reserved for when a wide range of bacteria could be responsible for an infection or when polymicrobial infection may be present. Antibiotics such as β-lactams and aminoglycosides are bactericidal and kill the bacteria they are effective against; these should be selected for serious infections or immunosuppressed patients.

Bacteriostatic antibiotics, such as tetracyclines or trimethoprim, inhibit bacterial growth but do not kill them, and therefore rely on the immune system to erradicate the organism.

Box 15.2 Antimicrobiobial stewardship principles

Start smart:
- Only use antibiotics where there is clinical evidence of bacterial infection
- Use local guidelines to select appropriate antibiotic
- Obtain cultures before initiation
- Document route, indication, dose and duration

Then focus:
- Review clinical diagnosis and need for antibiotics daily
- Decide whether to stop, switch routes, change antibiotics, continue or use outpatient parenteral antibiotic therapy

Resistance

A bacterium is considered resistant when its growth cannot be inhibited by a concentration of drug that is achievable in the blood. Resistance may be innate; for example, *Pseudomonas* is innately resistant to penicillin. Alternatively, resistance may be acquired as a result of genetic change. If genetic change results in a survival advantage, then the population of resistant bacteria may outgrow the sensitive population. Antibiotics exert a considerable selection pressure on bacterial populations, favouring populations that are able to withstand them. Inappropriate and overuse of antibiotics is the main driver for the emergence of resistant bacteria and given the shortage of new antibiotics, it is essential to maintain the efficacy of current drugs. The principles of selection of antibiotics (see Key points) and of antimicrobial stewardship (Box 15.2) should be followed to ensure reduction in the inappropriate use of antibiotics.

Antiviral therapy

Viral replication depends on host cellular processes, therefore drug antiviral selectivity is harder to achieve than with antibacterial drugs and fewer antiviral agents are available. Another limitation of antiviral therapy is that viruses replicate rapidly and infection is often widespread before clinical symptoms are apparent and treatment is initiated. Antiviral drugs target different stages in virus-specific replication, from entry into the cell, transcription, nucleic acid and protein synthesis to the final stages of package and release of virions. Agents are considered here according to the virus they are most commonly used to treat. Most antivirals in clinical use are nucleoside analogues, i.e. they look like the basic nucleosides (e.g. guanosine or thymidine) but have been chemically altered to stop viral replication.

Herpesviruses

Aciclovir is able to induce selective toxicity against viruses because it is a pro-drug which requires a viral enzyme to help convert it to the active form by phosphorylation. In clinical practice, it is used for herpes simplex virus (HSV) and VZV. Valaciclovir is absorbed orally and becomes hydrolysed to aciclovir in the blood. Ganciclovir is active against cytomegalovirus (CMV) and also requires phosphorylation using an enzyme present in CMV. It is more toxic than aciclovir, as host cells can also add the phosphate group. Valganciclovir is better absorbed orally than ganciclovir.

Influenza

Oseltamivir inhibits newly formed influenza virions from being released from host cells by inhibiting viral neuraminidase (surface proteins).

HIV-1

There are five main classes of antiretroviral drugs: nucleoside analogue reverse transcriptase inhibitors (NRTIs, e.g. AZT) and non-nucleoside analogue reverse transcriptase inhibitors (NNRTI, e.g. nevirapine), protease inhibitors (PI, e.g. ritonavir), fusion inhibitors (FI, e.g. maraviroc) and integrase inhibitors (e.g. raltegravir). Side effects can limit their tolerability, e.g. on glucose and lipid metabolism, as seen with the protease inhibitors. Mutations in the virus can lead to drug resistance, thus the need for combination treatment and good adherence.

Antifungal therapy

A growing number of antifungal agents exist, however some are limited to topical application due to their toxicity.

Polyenes (e.g. nystatin, amphotericin B)

Polyenes bind to ergosterol in the fungal cell wall, causing lysis of the cell membrane and cell death. Some polyenes are toxic only to fungi, whilst others also cause toxicity in the host. For example,

amphotericin also binds to cholesterol in the kidneys causing nephrotoxicity, however this effect is reduced in the lipid preparations. They have a broad spectrum of antifungal activity.

Azoles (e.g. fluconazole, itraconazole, voriconazole)

Azoles block the synthesis of ergosterol, leading to fungal cell wall dysfunction. Fluconazole is often used to treat *Candida* infections, but where activity against *Aspergillus* is required, voriconazole is the treatment of choice.

Echinocandins (e.g. caspofungin, micafungin)

Echinocandins inhibit an enzyme responsible for β-glucan synthesis and prevent fungal cell wall synthesis leading to cell death. They are active against *Candida* and *Aspergillus*.

Antifungal agents may exert a fungostatic or fungicidal effect on fungi and this effect varies between different fungi; for example, voriconazole is fungicidal against *Aspergillus* sp., but fungostatic against *Candida* sp.

Antihelminth agents

Effective agents with antihelminth activity are limited. Intestinal nematodes are treated with mebendazole, a poorly absorbed agent that is active locally, causing parasite immobilization and death. Albenazole is better absorbed and therefore is active against blood and tissue nematodes. The treatment of cestodes and trematodes are limited to praziquantel.

Anti-protozoal agents

A number of antimalarial agents are available, however geographic resistance limits their use. Knowledge of malaria species and travel destination are essential for appropriate prescribing. Options for intestinal protozoa are more limited.

Question 15.1

Antibiotic principles of practice

Which of the following antibiotics disrupts the bacterial cell wall by inhibiting the cross-linkage of peptidoglycan? Select ONE answer only.

A. Amoxicillin
B. Ciprofloxacin
C. Erythromycin
D. Gentamicin
E. Trimethoprim

Answer 15.1

A. Amoxicillin

Peptidoglycan chains form a major structural component of the bacterial cell wall. These chains are cross-linked by an amide bond. β-Lactams (such as amoxicillin) inhibit the cross-linkage of peptidoglycan chains, weakening the integrity of the bacterial cell wall, and bacteria are killed by osmotic lysis.

Fluroquinolones (such as ciprofloxacin) prevent supercoiling of DNA in the bacterial cell.

Trimethoprim acts by interrupting synthesis of folate and thereby prevents DNA formation.

Erythromycin is a macrolide antibiotic and gentamicin is an aminoglycoside; they inhibit bacterial protein synthesis.

Host defence mechanisms and their pattern of development

The structure of the immune system

Robust mechanical, biochemical and microbiological barriers (such as skin, bile acid and host flora) fend off many microorganisms before they come in contact with the immune system. The lymphoreticular system represents the main anatomical structure of the immune system. This includes the bone marrow from which all cells of the immune system are produced, the thymus (where T cells mature), lymph nodes, tonsils, Peyer's patches, appendix and spleen. The immune system can be considered as the innate and adaptive immune system (Fig. 15.4).

The role of the innate immune response

The innate immune system includes antigen non-specific immune cells, receptors and soluble effector molecules, such as cytokines and complement. It provides a rapid response to a broad range of pathogens. However, it may not completely eliminate them, particularly intracellular ones.

Macrophages and dendritic cells recognize invading pathogens using receptors called pattern recognition receptors (PRRs). These receptors detect classes of molecules common to groups of pathogens called pathogen-associated molecular patterns (PAMPs); Table 15.2 lists some examples. Macrophages and dendritic cells become activated and take up the pathogen by phagocytosis. Activated macrophages initiate an acute inflammatory response to attract
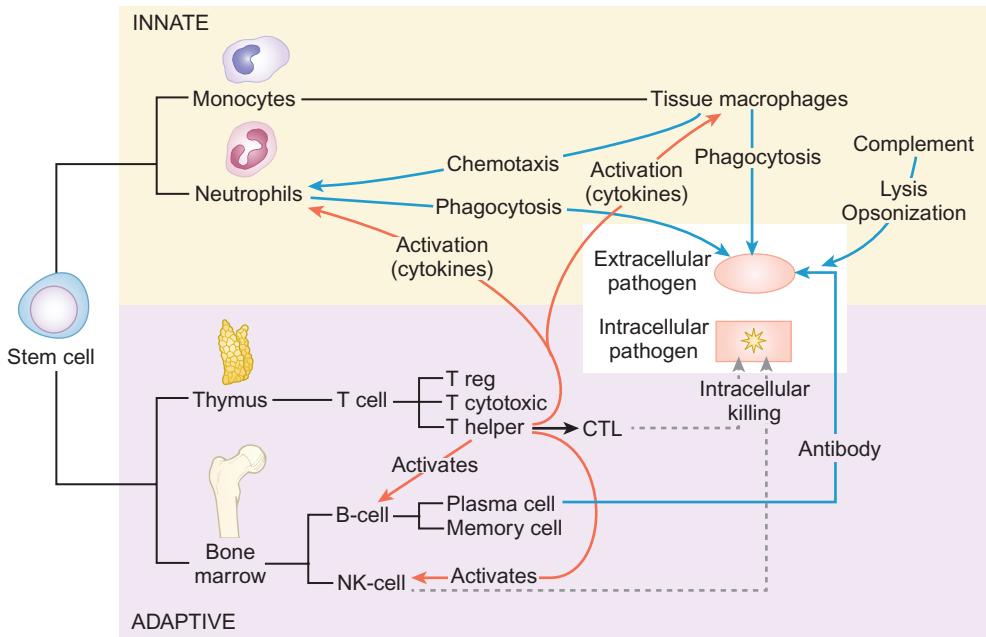
Fig. 15.4 Overview of the structure and function of the immune system.

Table 15.2 Selected examples of pathogen-associated molecular patterns of the host inflammatory response

Pathogen type	PAMP	PRR
Gram-negative bacteria	Lipopolysaccharide	TLR4
Gram-positive bacteria	Peptidoglycan cell wall	TLR2
Viruses	Double-stranded RNA	TLR3
Intracellular pathogens	Pathogen RNA	NLRP3
Fungi	β-glucan	Dectin-1

NLRP3, nucleotide-binding oligomerization domain (NOD)-like receptor pyrin domain containing 3; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; TLR, Toll-like receptor.

neutrophils and specific antigen-presenting cells. This inflammatory cascade consists of pro-inflammatory cytokines (e.g. IL-1β, IL-6, TNF-α), chemokines (e.g. IL-8), lipids (e.g. prostaglandins, leukotrienes) and complement. Complement can lyse pathogens directly, or opsonize them to assist phagocytosis by macrophages and neutrophils.

The role of the adaptive immune system

The adaptive system consists of T and B cells, which provide cell-mediated and antibody-mediated immunity. T cells can be divided into subpopulations of T-helper cells and T-cytotoxic cells.

Antigen-presenting cells carry antigens to regional lymph nodes, where they present antigen on major histocompatibility complex (MHC) class II receptors to T-cell receptors, leading to activation and proliferation of T-helper cells. Activated T-helper cells secrete cytokines that activate T-cytotoxic cells, which

recognize and kill altered host cells, such as virus-infected cells. Cytokines from activated T-helper cells also help activate B cells. B cells encounter antigen, clonally expand and terminally differentiate into plasma cells, which produce antibody.

Activated T-helper cells develop into different types of T-helper cells. T-helper 1 type cells produce pro-inflammatory cytokines (such as IL-2 and IFN-γ) and are responsible for activating T-cytotoxic cells, macrophages and B cells, which produce opsonizing antibody (IgG). T-helper 2 cells produce anti-inflammatory cytokines (such as IL-4, IL-13) and favour a humoral response with IgM, IgA and IgE. Th17 (producing IL-17 and IL-22) cells are important players in tissue inflammation and mucosal/epithelial defences against fungal and bacterial infections. T-regulatory cells (Tregs) have an important role in shutting down immune responses in an antigen-specific manner, as well as preventing autoimmunity by inducing apoptosis of T-effector cells.

The adaptive immune system is highly specific. This ability to distinguish between antigens is achieved by the enormous diversity of T- and B-cell receptors. These are generated by random association of the genes for the constant parts of the receptor chains with one of a large number of variable, diversity and joining (VDJ) region genes. As many as 10^{14}–10^{18} unique antigen receptors are produced through this process.

T-cell receptors have a sustained high antigen-specific affinity. B-cell receptors and antibodies have to undergo affinity maturation through the selection of cells bearing the receptors with the greatest avidity. IgM has low antigen affinity and avidity but high

binding capacity, and is produced early in the immune response with later switching to IgG or IgE with higher affinity and avidity or to IgA.

Effector phase of the immune response

T-helper cells secrete cytokines that orchestrate local (e.g. recruitment and activation of macrophages) and systemic (e.g. fever) immune responses. Cytotoxic T-cells and NK cells target intracellular organisms by inducing apoptosis through the perforin–granzyme system. T-helper cells have a key role in amplifying and shutting down the immune response. Whilst a pro-inflammatory response (Th1) predominates in the early phase of the immune response, innate and adaptive responses are shut down as the specificity of the humoral and cytotoxic response increases, shifting to a Th2-type response involving T-regulatory cells. A proportion of T and B cells form long-lived memory cells capable of mounting a faster and more efficient secondary response.

Immune system development and maturation

Cells of the adaptive and innate immune systems develop early in fetal life. Due to the high tolerance required for maternal antigens *in utero*, the fetus is in an overall immunosuppressed state with a Th2 bias and a predominance of T-regulatory cells. Fetuses are capable of foreign antigen recognition and can mount adaptive responses but these may be ineffective in clearing infections so congenital infection may result, for example CMV or rubella. Fortunately, the fetus is largely protected by the placental barrier. Materno-fetal IgG transfer begins from around 17 weeks' gestation, reaches half of the maternal level by 30 weeks and full maternal level close to term. Infants born prematurely are therefore highly susceptible to infection.

After birth, transferred maternal IgG declines and virtually disappears by 6 months of age. Although the infant's own IgG increases, there is a nadir around 3–6 months. As the infant is immunologically naïve, symptomatic infections are more frequent and severe in the early years than at older ages.

The onset of sex hormone secretion in early adolescence has a temporary immunosuppressive impact on immune function.

Primary immunodeficiency disorders

Primary immunodeficiency disorders (PIDs) range from common minor and often asymptomatic disorders, such as mannan-binding lectin deficiency (with an incidence of 1 in 20) or selective IgA deficiency (1 in 500), to more severe, rare disorders such as severe combined immunodeficiency (SCID; 1 in 35,000) or chronic granulomatous disease (1 in 200,000). The incidence of PID severe enough to require haematopoietic stem cell transplantation (HSCT) is about 1 in 30,000–50,000.

Classification of primary immunodeficiency disorders

Primary immunodeficiency not only encompasses an increased susceptibility to infection, but also to autoimmunity, immunodysregulation and malignancy. Primary immune deficiency can be categorized into defects in innate or adaptive immunity (Tables 15.3–15.6). Other approaches to categorization rely on clinical presentation, age of onset or spectrum of encountered pathogens.

In principle, the more severe the immune defect, the earlier the child presents with features of opportunistic infections or immune dysregulation. In the early newborn period, even those infants with severe immune defects may appear well due to protection from maternal antibodies and from breastfeeding, but this effect is short-lived. Severe combined immunodeficiency, the most severe PID where infants have no adaptive immunity, is an immunological emergency with a very high risk of life-threatening infection, particularly with viruses and *Pneumocystis jirovecii*.

Approach to the child with suspected primary immune deficiency

Frequent symptomatic infections are common in early childhood. Distinguishing healthy children from those with an immunodeficiency is crucial to ensure early diagnosis and treatment. Warning signs of primary immune deficiency include:

- Four or more new ear infections within 12 months
- Two or more serious sinus infections or episodes of pneumonia within 1 year
- Infections that present atypically or with unusual severity
- Failure of an infant to gain weight or grow normally
- Prolonged/recurrent diarrhoea
- Recurrent deep skin or organ abscess
- Severe or long-lasting warts or molluscum
- Persistent mucocutaneous candidiasis after 1 year of age
- Episode of infection with an opportunistic pathogen
- Complication after live vaccination (disseminated BCG, varicella, paralytic polio, rotavirus)

Table 15.3 Common immunodeficiency disorders: antibody deficiencies

Condition	Description	Laboratory features
Antibody deficiencies Increased susceptibility to bacterial infections such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Mycoplasma*. Also increased susceptibility to enteroviruses and *Giardia lamblia*		
X-linked agammaglobulinaemia (Bruton's disease)	• B-cell development blocked. • Typical presentation 6 months to 5 years with recurrent bacterial infections.	• IgG, IgM, IgA ↓ • Absent B cells • Absent isohaemagglutinins • *BTK* gene mutation
Combined variable immunodeficiency (CVID)	• Lack of IgG antibody production. • Typical age presentation 2nd–4th decade of life with recurrent bacterial, viral, fungal and parasitic infections. • Lack of IgG antibody production. Increased risk of autoimmune disease and malignancy.	• IgG↓, occasionally IgM/IgA↓ • Occasionally low/dysfunctional T or B cells. Abnormal patterns of B-cell phenotype, e.g. absence of switched memory B cells • Decreased vaccine responses • One of a number of genetic defects identified in 10%
IgA deficiency	• Recurrent upper respiratory tract infections at age >4 years. • Increased frequency of allergies and autoimmunity. • May be asymptomatic.	• IgA absent, normal IgG, IgM • Normal vaccine responses
Ataxia telangiectasia	• Recurrent respiratory infections in 2nd year of life. • Associated with ocular or facial telangiectasia, progressive cerebellar ataxia, increased risk of leukaemia and lymphoma.	• IgA↓ • Increased radiation-induced chromosomal breakage in cultured cells • α-fetoprotein↑ • Mutations in *ATM* gene

- Need for intravenous antibiotics to clear infection
- Two or more invasive infections (meningitis, osteomyelitis, pneumonia, sepsis)
- Unexplained autoimmune disease
- Positive family history suggestive of primary immunodeficiency (relatives with infections or immunodeficiency, infant deaths to infection or unexplained, consanguinity)

A detailed history and clinical examination is essential. Family history is particularly important as primary immune deficiencies have a genetic basis. Examination should specifically focus on the assessment of growth and nutrition, skin, nails, teeth and hair, ENT and respiratory systems, lymphoid tissue, organomegaly and dysmorphism and neurodevelopment. Initial laboratory investigations should be tailored to the clinical presentation and differential diagnosis based on the spectrum of infections suffered. A small number of simple tests (e.g. a full blood count, immunoglobulins, lymphocyte subsets and vaccine antibody responses) may confirm or rule out many forms of PID, but if there is a strong clinical suspicion, assessment by a paediatric immunologist is required.

Management aspects of primary immune deficiency

Specific management strategies depend on the underlying syndrome. Prophylactic measures include avoidance of exposure to infection, prophylactic antimicrobials and intravenous or subcutaneous immunoglobulin to maintain normal levels of IgG. Immunization may be helpful in the less severe immunodeficiencies, remembering that live vaccines will be contraindicated in some conditions. Infections in patients with primary immune deficiencies need to be treated promptly and aggressively. Immunodysregulatory problems resulting in autoimmune disease or lymphoproliferation may require immunomodulatory treatments including monoclonal antibodies or immunosuppressive drugs. For severe primary immune deficiencies, a curative approach using haemopoietic stem cell transplantation is used with increasing success rates. Recently, gene therapy has been used with promising results.

Secondary immunodeficiency

Secondary immunodeficiencies are acquired by a range of mechanisms, including immunosuppressive drugs, hyposplenism and chronic illness. For many such patients, general advice on preventing exposure to infection is sufficient. Optimizing management of the underlying disorder can significantly reduce the risk of infection. In the more severely immunocompromised patients, prophylactic antimicrobials, judicious use of vaccines and immunoglobulin therapy may be indicated. In situations when immunosuppression can be anticipated, such as elective splenectomy, planned vaccination can be administered prior to immunosuppression.

Table 15.4 Common immunodeficiency disorders: combined immunodeficiencies

Condition	Description	Laboratory features
Combined immunodeficiencies Increased susceptibility to: Bacteria: *Streptococcus pneumoniae, Haemophilus influenzae,* Gram-negative *Enterobacteriaceae* and intracellular pathogens such as *Salmonella, Mycobacteria, Cryptosporidium, Pneumocystis* Viruses: Respiratory (e.g. parainfluenza, RSV), enteric (e.g. rotavirus), systemic (e.g. CMV, EBV) Fungi: *Candida* species		
Severe combined immunodeficiency (SCID)	• Development of lymphocytes blocked by genetic defects. • Presents within the first 6 months of life with faltering growth, persistent diarrhoea and recurrent mucocutaneous candidiasis or with severe pneumonitis (viral or PJP). Commonly fatal if not recognized and managed early.	• Lymphopenia, hypogammaglobulinaemia • Abnormal lymphocyte subsets (absent T cells, +/–B, +/–NK cells – depending on type of SCID) • Various genetic defects (mutations in GAMMA C, *JAK3, RAG1, RAG2, IL7-RA,* ADA, MHC class II genes)
Omenn SCID	• SCID (any molecular type) complicated by expansion of a few clones of T cells producing severe inflammation of skin (generalized erythroderma) and gut with lymphadenopathy and hepatosplenomegaly	• T cells present but oligoclonal. B/NK present or absent depending on SCID type • Proliferation of T cells usually impaired
DiGeorge syndrome	• Absent/hypoplastic thymus with variable T-cell immunodeficiency from SCID-like (complete DiGeorge) to normal via a partial deficiency. • Presents any time from neonatal with viral and fungal infections. • Conotruncal cardiac defect, hypocalcaemia (>3 weeks, requiring therapy). • Facial dysmorphic features.	• Lymphopenia (<1500/mm^3) • Lymphocyte subsets and proliferation variable • Associated with chromosome 22q11.2 deletion or with CHARGE syndrome
Wiskott–Aldrich syndrome	• Presents in early infancy, usually with bleeding/bruising, recurrent respiratory infections, HSV and EBV infections. • Associated with bloody diarrhoea, eczema in early infancy, autoimmune manifestations (vasculitis, haemolytic anaemia), malignancy (leukaemia, lymphoma, EBV-driven brain tumours)	• Thrombocytopenia with small platelets • Abnormal polysaccharide vaccine responses • IgE↑, IgA↑, IgM↓ • T-cell number and function progressively declining • Mutation in *WASP* gene
X-linked hyper-IgM syndrome (CD40 ligand deficiency)	• Presents in infancy with recurrent bacterial infections, *Pneumocystis jirovecii* pneumonia, *Cryptosporidium* diarrhoea, sclerosing cholangitis, parvovirus-induced anaemia, faltering growth, oral ulcers.	• IgG↓, IgM normal or ↑ • Lymphocyte subsets and proliferation normal • No CD40 ligand expression on activated T cells • CD40 ligand gene mutation
X-linked lymphoproliferative syndrome	• XLP1 – Classically overwhelming EBV infection (often fatal) but many other triggers resulting in haemophagocytic lymphohistiocytosis (HLH). • Occasionally other presentations such as hypogammaglobulinaemia or aplastic anaemia. • XLP2 – Classic presentation like XLP1 or may manifest with enteropathy, arthritis or other immune dysregulatory features.	• Immunological function tests variable. Usually low NK-cell function and often hypogammaglobulinaemia • XLP1 – Mutation in *SH2D1* coding for SAP protein • XLP2 – Mutation in *XIAP* (X-linked inactivator of apoptosis) gene.

Human immunodeficiency virus infection

The number of people living with human immunodeficiency virus (HIV) is approximately 40 million and continues to increase, due to ongoing transmission and the improving survival with increasing access to antiretroviral drugs. In the UK, there are around 900 children living with HIV and 50–60 new cases are identified annually, with few deaths since 2010. This reflects the success of universal HIV screening in pregnancy and prevention of mother-to-child transmission. Most children with HIV in the UK are now in their adolescence, and emphasis on care is now focusing on adherence, complex resistance, long-term drug toxicity, sexual and mental health and transition to adult services.

Table 15.5 Common immunodeficiency disorders: neutrophil defects

Condition	Description	Laboratory features
Neutrophil defects Increased susceptibility to: Bacteria: *Staphylococcus*, *Pseudomonas* and other Gram-negative *Enterobacteriaceae*. Fungi: *Candida*, *Aspergillus* species.		
Chronic granulomatous disease (CGD)	• Defect of pathogen killing within macrophage. • Presents usually before 5 years of age with recurrent, deep-seated infections (liver, perirectal or lung abscess, adenitis, osteomyelitis). • Diffuse granulomata in respiratory/gastrointestinal/ urogenital tract, failure to thrive, hepatosplenomegaly, lymphadenopathy.	• Neutrophil oxidative burst absent • Nitro blue-tetrazolium test negative • Molecular defect is X-linked in two thirds and autosomal recessive in one third
Leukocyte adhesion deficiency type 1	• Leukocytes unable to attach to vascular endothelium and leave circulation. • Typically presents in neonatal period with delayed umbilical cord separation and sepsis. • Recurrent/persistent bacterial or fungal infections with absence of pus, defective wound healing, periodontitis.	• Neutrophil counts persistently above normal range. • Leukocyte CD18 and CD15a expression <5% • Lack of β2 integrin expression
Severe congenital neutropenia	• Failure of neutrophil maturation. • Typically presents in neonatal period or early infancy. Recurrent superficial and invasive bacterial and fungal infections. May exhibit delayed umbilical cord separation or periodontitis	• Neutrophil counts persistently low • Bone marrow shows maturation arrest in myeloid series • Number of different genes include *ELANE* (autosomal dominant, codes for neutrophil elastase); *HAX1*, *GFI1*,*G6PC3*, and *WASP* (activating mutation)

Table 15.6 Common immunodeficiency disorders: innate immune defects

Condition	Description	Laboratory features
Innate immune defects Increased susceptibility according to specific defect		
Complement deficiency	• Severe bacterial infections with *Neisseria* species in alternative, lectin and early classical pathway deficiencies. For early classical deficiencies also increased susceptibility to encapsulated bacteria. • Lupus-like disease with classical pathway deficiencies. • Can present at any age. • Hereditary angioedema (HAE) with C1 esterase inhibitor deficiency. • HAE presents typically in mid-childhood (5–10 years).	• Complement function tests • Mannose-binding lectin (MBL) • C4 level invariably low in HAE. • C1 inhibitor protein and function tests confirm HAE.
Hyper-IgE syndrome – type 1 (Job syndrome)	• Usually presents before 5 years of age but may present later with mucocutaneous candidiasis in infancy, recurrent or persistent respiratory infections, pneumatocoele formation pathological fractures, scoliosis, increased malignancy risk.	• IgE↑ • Lymphocyte subsets and proliferations usually normal • Dominant mutations in gene encoding STAT3
Autosomal recessive hyper-IgE syndrome – DOCK8 deficiency	• Usually presents before 5 years of age but variable. • Eczema and severe superficial viral infections including papilloma virus, molluscum contagiosum and herpes simplex. Recurrent bacterial and opportunistic infections. • High risk of squamous cell cancer.	• IgE↑ • Lymphocyte studies show variably low T-cell numbers and proliferation • Recessive mutations in gene encoding DOCK8
Mendelian susceptibility to mycobacterial disease	• Usually presents before 5 years of age with severe disseminated infections with environmental mycobacteria or BCG and/or non-typhoidal *Salmonella* species.	• Defects of the interleukin 12/ interferon gamma pathway • Tests involve measuring cytokine production and response followed by genetic testing

Testing for HIV in infants born to an HIV-positive mother

As HIV IgG antibody is placentally transferred, a positive antibody test reflects the maternal status. HIV proviral polymerase chain reaction (PCR) at birth has a low sensitivity (due to low viral load) and does not rule out infection. By 3 months of age, sensitivity rises to >99%.

HIV infection is very unlikely if the infant has two negative PCRs, one after 3 months, or two negative antibody tests if <12 months, or one negative antibody test after 18 months.

HIV infection is considered further in Chapter 33, Global child health.

Question 15.2

Host defence mechanisms

The following (A–J) is a list of immunodeficiency disorders:

A. Chronic granulomatous disease
B. Common variable immunodeficiency
C. Complement deficiency
D. DiGeorge syndrome
E. Hyper IgE syndrome type 1 (Job syndrome)
F. IgA deficiency
G. Leukocyte adhesion deficiency type 1
H. Mendelian susceptibility to mycobacterial disease
I. Severe combined immunodeficiency
J. X-linked agammaglobulinaemia (Bruton's disease)

Select the most likely diagnosis for each of the following clinical scenarios. Each answer may be used once, more than once or not at all:

1. A 9-month-old boy requires incision and drainage of a perianal abscess. *Staphylococcus aureus* is isolated from the pus. When he was 4 months old, he had osteomyelitis of his left humerus and received a 6-week course of antibiotics.

2. A 2-month-old girl presents with tachypnoea, respiratory distress and hypoxia. A chest X-ray shows bilateral perihilar interstitial infiltrates. A bronchoalveolar lavage confirms *Pneumocystis jirovecii*. Her weight is on the 0.4th centile and she has mucocutaneous candidiasis.

3. A 5-year-old boy presents with an upper respiratory tract infection. He has a history of recurrent otitis media. He had grommets inserted last year but continues to have recurrent episodes of otitis media. He is allergic to peanuts, but is otherwise well and his growth is normal.

Answer 15.2

1. A. Chronic granulomatous disease
2. I. Severe combined immunodeficiency
3. F. IgA deficiency

1. In chronic granulomatous disease, there is inability of neutrophils to kill ingested pathogens due to a failure to produce reactive oxygen species – hydrogen peroxide or superoxide. This leads to an increased susceptibility to bacteria, such as *Staphylococcus aureus,* or fungal infections with *Candida* or *Aspergillus*. Children may present with deep-seated abscesses, unusual pneumonias and bone infections. Other neutrophil defects also present with recurrent or persistent bacterial infections, however other features may also be present. Leukocyte adhesion deficiency would typically present in early infancy with delayed separation of the umbilical cord and sepsis. Severe congenital neutropenia would also present earlier in infancy.

2. Features suggesting combined immunodeficiency are young age of the patient, presentation with an unusual infection not seen in the immunocompetent host, failure to thrive and candidiasis. DiGeorge syndrome is also likely to present in infancy, but the more prominent presentation would be severe viral and fungal infections in association with the classical facial features, cardiac defects and hypocalcaemia.

3. The 5-year-old boy with an upper respiratory tract infection on a background of recurrent otitis media and food allergy is most likely to have IgA deficiency, the most common immunodeficiency.

Infections of childhood

The most frequent organisms associated with a range of infections at different ages are shown in Table 15.7. The specific infections are considered further in the system-based chapters. Perinatal and neonatal infections are described in Chapter 10, Perinatal medicine and Chapter 11, Neonatal medicine.

Host response to infection

The innate immune system is the first line of defence against pathogens. However, this rapid and broad response comes at the price of collateral damage to host tissues. In most cases, this is localized and

Table 15.7 The most frequent organisms associated with different infections at different ages

Type of infection	<3 months	3 months–5 years	>5 years
Pneumonia	GBS *E. coli* Respiratory viruses* Enteroviruses *S. pneumoniae*	*S. pneumoniae* Respiratory viruses*	*M. pneumoniae* *S. pneumoniae* Respiratory viruses*
Gastroenteritis	(Uncommon)	Rotavirus Norovirus Sapovirus	Rotavirus Norovirus Sapovirus *Campylobacter* *Salmonella*
Urinary tract	*E. coli*	*E. coli*	*E. coli*
Skin and soft tissue	*S. aureus* GAS GBS	*S. aureus* GAS	*S. aureus* GAS
Bone and joint	GBS *S. aureus* *E. coli*	*S. aureus* *K. kingae*	*S. aureus*
Meningitis	Enteroviruses GBS *E. coli*	Enteroviruses *N. meningitidis* *S. pneumoniae*	Enteroviruses *N. meningitidis* *S. pneumoniae*
Encephalitis	HSV	HSV	HSV
Septicaemia	GBS *E. coli* *S. aureus*	*N. meningitidis* *S. pneumoniae* *S. aureus*	*N. meningitidis* *S. pneumoniae* *S. aureus*

*Including RSV, influenza, parainfluenza, coronaviruses.

GAS, group A *Streptococcus*; GBS, group B *Streptococcus*; HSV, herpes simplex virus.

repaired; the pathogen is eliminated when the host response shifts from pro- to anti-inflammatory, and homeostasis is restored. Sometimes the inflammatory response becomes so potent or widespread that it causes systemic physiological derangements in the host (sepsis).

Fever

A common presentation of infection in children is fever and is the second most common reason for acute hospital admissions in the UK.

Mechanisms of fever

Fever is one of the cardinal signs of infection, but hypothermia may also occur. Fever is usually defined by a core temperature greater than 38.0°C, and is caused by upregulation of the set-point for body temperature homeostasis. Pyrogenic mediators, the most important of which is prostaglandin E2 (PGE2), act on nuclei in the pre-optic area of the brain and trigger neuronal mechanisms to increase heat generation and reduce heat loss, such as brown fat thermogenesis, shivering and skin vasoconstriction. Fever is likely to be beneficial by inhibiting pathogen replication, but may also be harmful by increasing metabolic demand when essential tissues are suffering critical levels of hypoxia and ischaemia.

Management of fever

Since fever may have beneficial effects, it is not always necessary to reduce body temperature using antipyretics since there is no evidence that the use of these agents reduces the risk of febrile convulsions. Antipyretics should, however, be used with children who appear distressed, when the use of a single agent, paracetamol and ibuprofen may be alternated. Randomized controlled trials show that ibuprofen is associated with faster duration of action and an increased interval between fever than paracetamol. Children with fever should be offered regular fluids and signs of dehydration should be sought since transcutaneous fluid losses will be increased.

Infections of the central nervous system

Epidemiology and aetiology

The peak age of bacterial meningitis is children under 2 years. In countries with routine use of vaccines against *N. meningitidis*, *S. pneumoniae* and *H. influenzae* type b, there has been a dramatic decrease in bacterial meningitis and around 90% of meningitis is aseptic, with enteroviruses being the commonest pathogen. In neonates the most important organisms are Group B Streptococcus (GBS) and *E. coli*. Encephalitis is less

common, and is also usually caused by viruses, most commonly HSV.

Pathophysiology

In bacterial meningitis, infection usually starts in the nasopharynx, followed by bacteraemia and subsequent penetration of the blood–brain barrier. Bacteria continue to proliferate in the cerebrospinal fluid (CSF) stimulating a pro-inflammatory cascade, which may also occur in the blood to cause septicaemia. This leads to upregulation of specific adhesion molecules and recruitment of leukocytes into the CSF. CNS damage occurs directly by meningeal inflammation and indirectly due to circulatory collapse, with a high rate of neurological sequelae. Death can occur from cerebral oedema, which leads to raised intracranial pressure and cerebral or cerebellar herniation. The inflammatory response to viruses is much less severe. In cases of encephalitis, organisms can reach the brain via the blood to cause diffuse infection or via neuronal tracts resulting in localized disease. Immune-mediated encephalitis occurs when inflammatory lesions are caused by the host response to an infection or due to the presence of auto-antibodies.

Complications and outcomes

The CSF findings in meningitis are shown in Chapter 28, Neurology, and management in Chapter 6, Paediatric emergencies and critical care. Early complications of bacterial meningitis include seizures, SIADH, subdural effusions, focal neurological abnormalities, hydrocephalus, abscesses and venous sinus thrombosis. Long-term sequelae occur in 20–30% and include sensorineural hearing loss, epilepsy, motor and cognitive impairment, blindness and learning/behavioural problems. Case-fatality rates are 5–10% in developed countries. Full recovery is usual in uncomplicated viral meningitis, although neuropsychological sequelae can occur. The overall case-fatality rate from viral encephalitis is 3–4%, but this is up to 40–50% in neonatal disease.

> ### Case history
>
> **Meningitis**
>
> A 9-month-old girl has been unwell for 12 hours with a fever, poor feeding and lethargy. She looks unwell and is very irritable, with no focal abnormalities. She has a full septic screen and is started empirically on ceftriaxone. Initial CSF results: WBC 1237/µl, 83% neutrophils, glucose 0.9 mmol/L, protein 0.67 g/L, no organisms on Gram stain. Dexamethasone is started 2 hours after antibiotics were given. By 48 hours, she is improving and CSF and blood cultures confirm *S.*

pneumoniae. She completes 14 days of antibiotics and 4 days of steroids.

In the UK, corticosteroids are recommended in children over 3 months with suspected bacterial meningitis as soon as possible if there is any of the following: purulent CSF; CSF WBC >1000/µl; raised CSF WBC and protein >1 g/L; bacteria on Gram stain. This should ideally be started before/with the first dose of antibiotics, but may be beneficial if given up to 12 hours after antibiotics have been initiated. The rationale for the use of corticosteroids in bacterial meningitis is to reduce inflammation in the subarachnoid space. Their use is associated with a reduction in severe hearing loss and long-term neurological sequelae, however no effect on mortality has been shown. The benefit is most evident in children with Hib meningitis, now a rare cause of bacterial meningitis in the UK, but may extend to meningitis caused by other bacterial pathogens.

Healthcare-associated infections

Healthcare-associated infections (HCAIs) are generally considered to be those which occur >48 hours after hospital admission. The increased risk of infection in a healthcare setting is due to: close proximity of patients with transmissible infections; co-morbidities in hospitalized patients; surgery and other interventions (e.g. central lines); antibiotic use. Commonest types of HCAI are gastroenteritis (rotavirus, norovirus, *C. difficile*), urinary tract infections (UTIs), pneumonia (respiratory viruses) and surgical site infections (including MRSA). It should be noted that around one third of all bloodstream infection in children is now HCAI.

HCAIs can be acquired from/transmitted to other hospital patients, healthcare workers and the environment. The incidence depends on the patient population and is highest in intensive care (especially neonatal intensive care, where outbreaks of nosocomial infection are common), transplant recipients and burns patients. Infections may be endogenous (caused by a patient's own flora) or exogenous (caused by organisms acquired from the healthcare setting). Transmission can be reduced by effective infection control measures, which include hand hygiene, appropriate isolation of patients, good antimicrobial stewardship, careful use of indwelling medical devices and high quality surveillance.

Tuberculosis

It is estimated that one third of people globally are infected with TB, although the overall incidence of active disease and mortality is decreasing. It is considered further in Chapter 33, Global child health.

Malaria

Malaria remains an important cause of infectious childhood mortality, however successful implementation of simple interventions such as insecticide-impregnated bed nets have contributed to a reduction in global childhood mortality from malaria. Malaria is considered further in Chapter 33, Global child health.

General principles of immunization

Immunization can broadly be divided into active or passive. Active immunization involves administration of foreign antigen(s) into an individual to stimulate an immune response. Passive immunization is achieved by administering protective immune components themselves, usually specific antibodies.

Active immunization

Live, attenuated vaccines (e.g. MMR, rotavirus, BCG)

Live, attenuated vaccines contain modified organisms, which replicate but do not cause disease, and induce a protective immune response. The major advantage of live vaccines is exposure of the immune system to antigens in the normal conformation leading to an optimal immune response. Low amounts of antigen can be given (since replication occurs) and they may be administered via the same route as natural infection and therefore induce local mucosal as well as systemic immunity. In immunocompromised individuals, even these modified organisms may cause significant disease and therefore cannot be used.

Inactivated vaccines (e.g. inactivated polio, influenza vaccine)

Inactivated vaccines from whole organisms are obtained by chemical or heat treatment. All antigens from the organism can be presented to the immune system, but usually not in their natural conformation. More antigen is needed compared to live vaccines since no replication occurs and vaccines are generally given intramuscularly. These vaccines can usually be given to immunocompromised individuals, although they may induce a reduced immune response.

Subunit vaccines (e.g. diphtheria, pneumococcal, HPV, HBV)

Subunit vaccines only contain critical antigen(s) of the organism needed to induce an immune response. These vaccines usually require adjuvants to induce a sufficient immune response.

Passive immunization

Passive immunization involves administering protective immune components to individuals unable to mount their own immune response and/or when rapid protection is desired. Pathogen-specific antibody is given after a known exposure, however since no immune memory is generated, the individual soon becomes susceptible again. For example, varicella zoster immunoglobulin (VZIG) is given to non-immune, immunocompromised individuals after significant exposure to VZV. Protection lasts for 3–4 weeks and reduces the risk of developing chickenpox by approximately 50%. Since immunoglobulin is a pooled blood product, there are risks of hypersensitivity reactions and transmission of infective agents.

Vaccine design

The perfect vaccine would stimulate a protective, life-long immune response after a single dose against all strains of a pathogen with no adverse events. In reality, no such vaccine exists.

Historically, vaccines have been produced by laboratory modification and attenuation of the pathogen. Clinical trials then aim to demonstrate that the modified pathogen does not cause disease and a protective immune response occurs. Studies of the immune response in the blood from individuals after infection can help to identify which components of the pathogen may be protective. A new approach called 'reverse vaccinology' has been stimulated by the ability to perform sequencing of whole genomes. Pathogen genome sequences are used to predict immunogenic components and these sequences used to produce recombinant proteins *in vitro* as a vaccine. This approach was first successfully used to develop a new capsular group B meningococcal vaccine.

Polysaccharide antigens alone do not recruit T-cell help and so do not stimulate an immune response in children under 2 years of age. They do not lead to immunological memory and cannot be boosted. In contrast, when the polysaccharide antigen is linked to a carrier protein in conjugate vaccines, the immune system is tricked into processing the polysaccharide like a protein, engaging help from T cells, and overcoming these problems.

Adjuvants and multiple dosage schedules are strategies used to stimulate a protective and long-lasting immune response. Adjuvants either skew the immune response in one direction or another (e.g. increased humoral or cell-mediated immunity) and/or increase the amplitude of the response. Most current vaccines require multiple doses for persistent protection. The initial dose(s) prime the immune system and provide short-term protection for the most vulnerable, while

Table 15.8 Evolution of the routine UK childhood immunization schedule, 2002–2015.

Age	Oct 2002	Oct 2006	2015
2 months	DTwP/Hib OPV MenC	DTaP/IPV/Hib PCV7	DTaP/IPV/Hib PCV13 MenB Rotavirus (oral)
3 months	DTwP/Hib OPV MenC	DTaP/IPV/Hib MenC	DTaP/IPV/Hib MenC Rotavirus (oral)
4 months	DTwP/Hib OPV MenC	DTaP/IPV/Hib PCV7 MenC	DTaP/IPV/Hib PCV13 MenB
12 months	MMR	Hib/MenC	Hib/MenC booster MMR PCV13 booster MenB booster
13 months		MMR PCV7	
2–6 years			Influenza (annual, nasal spray)
3 years 4 months	MMR DTaP OPV	MMR DTaP/IPV	MMR DTaP/IPV
12–13 years			HPV [girls only] (2 doses 6–12 months apart)
14 years	Td OPV	Td/IPV	Td/IPV MenACWY

DT(w/a)P, diphtheria, tetanus, (whole cell/acellular) pertussis; Hib, *Haemophilus influenzae* type b; HPV, human papillomavirus; IPV, inactivated polio virus; MenC, meningococcal capsular group C; MMR, measles, mumps, rubella; OPV, oral polio vaccine; PCV7/13, 7/13-valent pneumococcal conjugate vaccine; Td, tetanus, diphtheria (low-dose diphtheria).

2002 to 2006: change from whole cell to acellular pertussis; change from live attenuated to inactivated polio and provided in combination with DTaP/Hib and Td; introduction of PCV7; change in infant MenC schedule; introduction of Hib & MenC boosters.

2006 to 2015: change from PCV7 to PCV13; change of MenC schedule; introduction of rotavirus, influenza and HPV vaccines.

2015: addition of MenB and MenACWY.

booster doses generate greater responses that last longer.

Successful immunization of a population

High quality surveillance is vital to determine who is at risk of disease and therefore the ideal time for vaccination. For neonates, maternal immunization may be the only way to achieve adequate protection in the first weeks of life. Protection is achieved predominantly by transplacental transfer of IgG in the third trimester.

In a population, interruption of transmission also significantly contributes to disease control. Population-level immunity ('herd immunity') is only obtained with high levels of vaccine coverage, reducing transmission sufficiently that even unimmunized individuals will be protected. The more infectious a pathogen, the higher the coverage required to achieve herd immunity; for example, over 90% of the population needs to be vaccinated to achieve herd immunity against measles. Disease easily recurs if coverage drops, as demonstrated with pertussis (1970s/1980s) and

Table 15.9 Immunizations for those at risk

Age	Disease	Immunization
Birth	Tuberculosis	BCG (intradermal)
Birth, 1 month, 2 months and 12 months	Hepatitis B	Hepatitis B

measles (2000s) outbreaks in the UK and polio in Syria (2013).

Immunization programmes evolve to take account of epidemiological changes, disease reduction in a population and availability of new cost-effective vaccines (Tables 15.8–15.9). See Further reading for up-to-date information from Public Health England on vaccines and vaccine programmes.

Vaccine safety and adverse events

Most vaccines have predictable adverse events which are minor and resolve quickly. However, known but rare and unexpected adverse events can occur – in the UK, these should be reported via the Yellow Card scheme. Common adverse events can be localized (pain, erythema, swelling) or systemic (fever, malaise,

myalgia, anorexia). Vaccine safety is paramount and more important than immunogenicity when a vaccine is in development. Post-licensure surveillance is vital to ensure that rare adverse events (which would not be apparent during clinical trials) are identified. In all cases, a risk/benefit analysis determines if a vaccine should continue to be used. For example, a previous rotavirus vaccine was withdrawn from the market due to an increased risk of intussusception, which was not identified during clinical trials. As a result, trials for the current rotavirus vaccines involved very large numbers of participants to try to ensure the risk from intussusception was low. Vaccine safety and consequent public confidence is vital in ensuring the ongoing success of any immunization programme.

Vaccines have been one of the most successful global public health interventions of the 20th century. Their impact is considered in Chapter 33, Global child health. To ensure this continues, it is of utmost importance to use modern technologies to improve current vaccines and develop new ones. One of the most important future determinants of immunization success will be public perception and the ability to reach regions of socio-political unrest. Vaccine development and implementation must be made on a rigorous scientific basis and all healthcare professionals are responsible for emphasizing the importance of immunization.

Question 15.3

General principles of immunization

A baby is born to an HIV-positive mother by planned caesarean section at 39 weeks' gestation. Her viral load was <20 copies/mL at delivery and she is on antiretroviral therapy. The baby is started on zidovudine and blood is taken for HIV PCR from the baby. The mother originates from sub-Saharan Africa, from a country where there is a very high incidence of tuberculosis.

Which of the following statements is not true regarding the baby's immunizations? Select ONE answer only.

A. He can receive MMR vaccine according to the normal schedule

B. He can receive the rotavirus vaccine according to the normal schedule

C. He should receive the BCG vaccine in the neonatal period as he is in a high-risk group

D. He should receive the DTP-Hib-polio vaccine according to the normal schedule

E. If the mother is also hepatitis B positive, he should receive hepatitis B vaccine as soon as possible

Answer 15.3

C. He should receive the BCG vaccine in the neonatal period as he is in a high-risk group.

This child has a low risk of being HIV-infected, being born by caesarean section to a mother on antiretroviral therapy who has an undetectable viral load – the risk of perinatally-acquired infection is between 1:500 and 1:1000. In babies born to mothers with an undetectable viral load at 36 weeks' gestation or later and who is on therapy, treatment is 4 weeks of zidovudine (AZT). Testing of the infant (proviral DNA PCR and/or RNA PCR) should be performed during the first 48 hours of life, 2 weeks after stopping zidovudine (at 6 weeks of age) and 2 months after stopping zidovudine (at 12 weeks of age). A final antibody test should be done at age 18 months – prior to this, there may be a false positive due to the presence of maternal antibody, whereas a positive antibody after 18 months indicates infection of the child. Note that these timings are based on a child who is not breastfeeding.

In terms of vaccination of HIV-infected infants, they should receive all routine childhood immunizations with the following exceptions:

- BCG: there have been reports of disseminated BCG in HIV-positive individuals. In those children where neonatal BCG is indicated (as in this case), this should be delayed until the negative PCR test at 12 weeks of age. If all tests have been negative, then BCG can and should be given.

- Measles: fatal disease has been reported following measles vaccination in one severely immunosuppressed HIV-positive adult. Current recommendations are that measles vaccine should not be given to HIV-infected individuals with moderate–severe immunosuppression, based on their CD4 count. Age-specific reference ranges are available and should be consulted. Most children in this setting will not be HIV-infected and the results of PCR testing will be known by the time of the first MMR vaccine at 12 months, so in most cases like this, MMR can be safely given at 12 months.

Hepatitis B vaccine should be given in the neonatal period according to the accelerated schedule in all babies born to hepatitis B-positive mothers irrespective of the mother's HIV status.

Further reading

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John O Warner, Paul J Turner

CHAPTER

Allergy

16

Allergy and immunity

The immune system primarily protects the host from microbial attack without causing harm to that host. It has two interacting components: the innate and the acquired systems, summarized in Table 16.1.

The immune system is tightly regulated – too little immunity can result in immunodeficiency while inappropriate/excess immune function will cause harm to the host. Allergy can be considered a consequence of an inappropriate immune response (Fig. 16.1): the immune system 'reacts' to an otherwise innocuous substance (allergen), e.g. pollen grain. 'Hypersensitivity' reactions to these substances are usually to protein or protein fragments, recognized by the immune system, which results in a clinical reaction. However, the immune mechanism is no different to an appropriate immune response to a parasite.
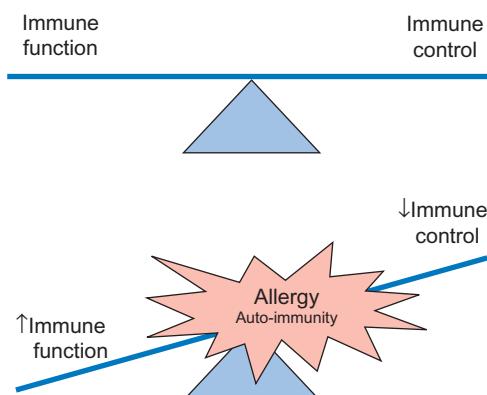
Fig. 16.1 Allergy can be thought of as a consequence of an inappropriate immune response to an otherwise innocuous stimulus, due to a malfunction in normal immune-tolerance induction.
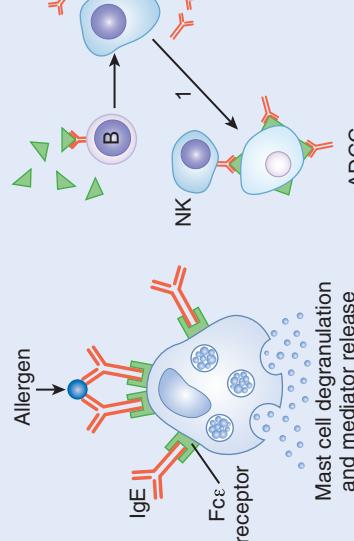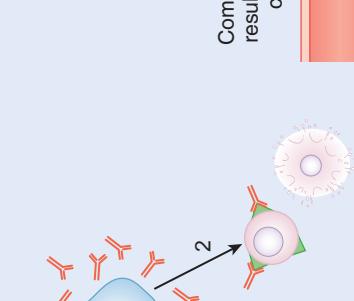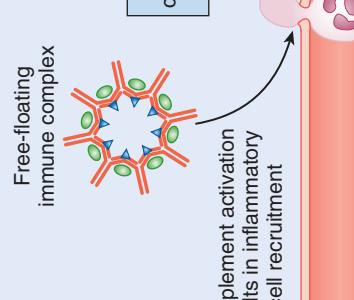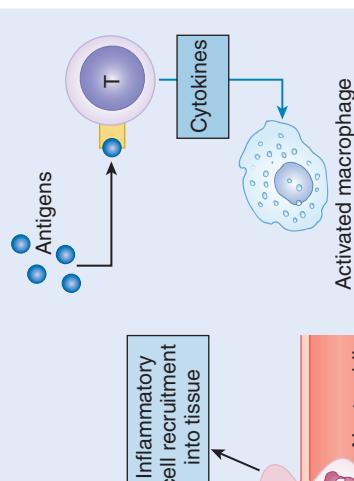
Hypersensitivity reactions and 'allergy'

There are four main mechanisms (originally characterized by Gell and Coombs) by which a hypersensitivity reaction can occur (Table 16.2). Most classical allergic

Table 16.1 Components of the immune system

Feature	Innate	Acquired
Recognition	Pattern recognition molecules reacting to pathogen-associated molecular patterns (PAMPs), e.g. lipopolysaccharide	Large range of specific molecules (or fragments of molecules)
Speed of response	Immediate	Fast, as cellular migration and interaction required
Memory	None	Efficient memory function
Humoral components	Complement	Antibodies
Cellular components	Neutrophils, eosinophils, basophils, mast cells, epithelial cells, macrophage, innate-responding lymphocytes NB: Some cells (e.g. mast cells, eosinophils) which traditionally have been classified as innate cells are now known to be involved in both innate and acquired immune responses. Similarly, some lymphocytes are now known to be involved in innate immune responses.	B and T lymphocytes

Table 16.2 Hypersensitivity reactions (Gell–Coombs classification) and how these relate to inappropriate hypersensitive responses*

	I Immediate	II Antibody-mediated cell cytotoxicity	III Immune complex	IV Delayed/cell-mediated
Antigen	Soluble	Cell-associated	Soluble	Soluble
Effector mechanism	IgE production by B cells, which subsequently binds to effector cell, e.g. mast cells through the IgE-Fc receptor. Antigen subsequently binds to IgE causing cross-linking of IgE resulting in effector cell degranulation.	Antigen part of or bound to the cell surface is recognized by IgG or IgM resulting in cell death by one of two mechanisms: 1) Activation of complement causing cell lysis 2) Cytotoxic T cell-mediated cell death.	IgG binds to antigen causing soluble immune complex formation. These are deposited in local tissues, where complement activation occurs, resulting in recruitment of inflammatory cells, e.g. neutrophils.	Soluble antigen is recognized by T cells causing an immune response mediated through cytokine release resulting in recruitment of effector cells (cytotoxic T cells, macrophage).
Examples	Allergy: food, venom, aeroallergens, some drugs Atopic asthma Anaphylaxis	Haemolytic disease of newborn due to Rh incompatibility Graves' disease Myasthenia gravis Goodpasture's syndrome Pernicious anaemia	Serum sickness SLE Rheumatoid arthritis Post-streptococcal glomerulonephritis Extrinsic allergic alveolitis	Graft-versus-host disease Some autoimmune diseases Tuberculin reaction Contact dermatitis

*N.B. Each mechanism also plays an important role in the host response to pathogens.
(Line drawings from Male D, et al. Immunology, 8th edition, Saunders 2013, with permission.)
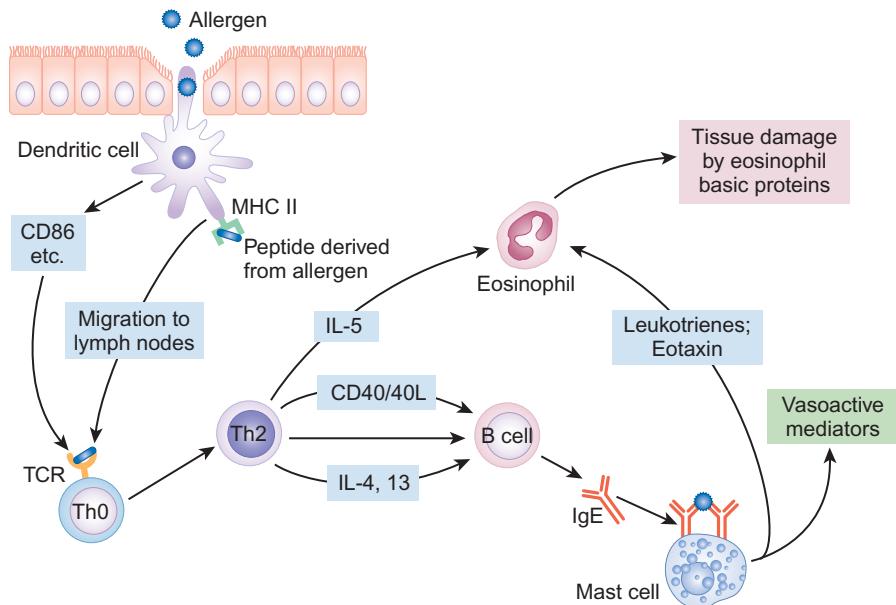
Fig. 16.2 A schematic representation of the process of primary allergic sensitization and the subsequent adaptive response to later exposure to the same allergen. Allergen is processed by antigen-presenting cells (APC), e.g. dendritic cells, and presented to the immune system. Multiple signals between the APC and T cell, in conjunction with antigen presentation on MHC class II to the T-cell receptor (TCR, CD3), dictate the differentiation of that T cell towards a typical cytokine-secreting pattern, which simplistically can be thought of as T-helper 1 or 2 phenotypes. In the presence of pro-allergy cytokines secreted by T-helper 2 cells (referred to as Th-2 type cytokines, which include interleukin-4, and -13), B cells switch from IgM to antigen-specific IgE production. Subsequent allergen exposure causes cross-linking of IgE molecules on adjacent IgE receptors, resulting in cell (e.g. mast cell) activation and the release of vasoactive mediators such as histamine, which cause the classical symptoms of IgE-mediated allergy. Other mediators such as cysteinyl leukotrienes, from the arachidonic acid to lipoxygenase pathway; and eotaxins from granules cause eosinophil influx. Note, however, that not all allergy is mediated through IgE, in particular to foods (see below).

conditions involve a type 1 hypersensitivity reaction, and require an initial 'sensitization' step in which antigen-specific IgE antibody is produced by B cells and plasma cells (Fig. 16.2). IgE subsequently binds to receptors on mast cells and basophils. Upon subsequent re-exposure to the allergen, IgE on the surface of mast cells recognizes and binds to the allergen.

Many allergic responses, particularly those mediated by IgE, consist of two acute phases:

- *The early phase response* occurs rapidly, often within minutes of allergen exposure, and is caused by the release of histamine and other vasoactive mediators from tissue-resident mast cells. This response resolves spontaneously within 1–2 hours
- *A late phase response (LPR)* in around 50% of reactions – well characterized in the upper or lower airways, but less so in skin or food allergy – there is a late phase response which is slow to peak (4–6 hours) and slow to resolve. In the nasal airway, this causes sustained nasal congestion; in the lower airways, LPR manifests as cough and wheezing, which persists for at least 24 hours and can cause increased bronchial hyper-responsiveness for 1–2 weeks. It is

associated with initial neutrophil influx and, later, more persistent eosinophilic inflammation.

LPR should be distinguished from chronic allergic inflammation. Continued exposure to the allergen induces a state of chronic inflammation. This is characterized by the development of allergen hyper-responsiveness, where the tissues (for example, lower airways) become more sensitive and responsive to any trigger (both allergen itself, and non-specific mediator release) causing an amplification of allergic reactions.

The spectrum of paediatric allergy

Up to 40% of children in the UK suffer from some form of allergic disease, including atopic eczema, food allergy, allergic rhino-conjunctivitis, asthma, insect sting hypersensitivity and drug allergy.

Why has paediatric allergy increased in prevalence?

Allergic diseases have become the commonest chronic conditions affecting children and young adults. They

mostly begin in early life and pose a major health economic burden, which has increased dramatically in developed countries over the last 30–50 years and is now also impacting on developing countries. The conditions cause considerable morbidity and occasional mortality, and are the consequence of complex gene–environmental interactions. Most are partially controllable but not curable, which emphasizes the need to understand the mechanisms leading to the development of allergy, as this could identify potential targets for future prevention.

Increases in allergic diseases were initially seen in affluent Western world countries, most notably the UK, Australia, New Zealand, USA and Canada. This trend was first noted in respiratory allergy (asthma and hay fever), and in some countries, prevalence now appears to have plateaued. The increase in the prevalence of eczema and particularly food allergy has occurred more recently, which suggests that perhaps there are different mechanisms involved in the development of sensitization to aeroallergens compared with foods.

It has long been known that allergic conditions run in families. This has led to the use of the term *atopy* as a descriptor of genetic susceptibility to develop allergic sensitization and disease. With the spectacular developments in genomics, it has been possible to identify a host of genes associated with susceptibility to developing allergic sensitization and/or allergic disease. However, genetic susceptibility must be assessed both in relation to the interaction with environment and to understand that independent genetic factors are associated with susceptibility to allergic sensitization, compared with those associated with susceptibility to specific allergic conditions such as asthma or eczema.

Initially, genetic studies identified potential candidate genes based on an understanding of function in relation to immune responses. For example, a number of associations with allergic sensitization have been identified close to the genes for IL-4 and IL-13, important cytokines for switching B-cell production from IgM to IgE. More recently, genome-wide association studies (GWAS) have reversed the process, by mapping the whole genome of individuals and identifying differences in those with a particular disease compared with those without. GWAS have identified many polymorphisms associated with allergic disease which fall outside the conventional mechanistic understanding of allergic sensitization, and provide evidence for different mechanisms associated with the onset of allergic disease such as asthma or eczema. The most well-known example are polymorphisms in the gene for the protein, filaggrin (expressed in skin

epithelial cells), which result in excessive leakiness of the skin making it susceptible to water loss, skin drying and penetration by irritants, infectious agents and allergens. There are strong associations with eczema and food allergy. This has led to the concept that food allergy may result from a primary exposure to food allergens through the skin, rather than the gastrointestinal route. The strongest association with asthma is with polymorphisms in the gene *ORM-DL3*, expressed in airway epithelium.

Some genetic polymorphisms are only associated with increased risks of a specific allergic manifestation in relation to particular environmental exposures. Thus, patients with polymorphisms in glutathione methyl-transferase genes only have a higher risk of asthma if they either live in a high pollution environment or are exposed to environmental tobacco smoke. In the absence of these exposures, the genetic polymorphism is not associated with an increased risk of asthma.

Environmental factors increase the risk of allergic disease

Given the very rapid increases in prevalence of allergic diseases in less than one generation, changes in DNA sequences are clearly not the explanation. Factors associated with an evolving affluent environment are likely to be critical and include diet, allergen, pollutant and microbial exposure.

There are subtle differences in the immune responses of neonates who subsequently develop allergic disease. Having an allergic mother confers a higher likelihood of allergy in the offspring than if the father is allergic. Thus, the immunological environment generated by the mother impacts on the fetus's evolving immune responses, committing them towards an allergic phenotype. Maternal nutrition in pregnancy has been identified as an important factor; strong associations have been identified between some allergic manifestations and lower omega-3 to omega-6 polyunsaturated fatty acid ratios, reduced fresh fruit and vegetable intake, and vitamin D deficiency. To date, these epidemiological associations have not translated into favourable outcomes from intervention studies of fish oils in pregnancy, modifications of fresh fruit and vegetable intake, and vitamin D supplementation.

Allergen avoidance during pregnancy and in early infancy would seem to be a reasonable approach to prevention, but outcomes from many trials have been spectacularly disappointing. House dust mite avoidance during pregnancy may have a small effect in reducing early infant wheeze, but has had no impact

on subsequent development of atopic asthma. Mothers were previously advised to avoid allergens such as nuts in pregnancy and in the infant's diet. The concern originally arose from the observation that some children appeared to react to food allergen at first exposure, implying that the initial exposure (causing sensitization) must have occurred prior to birth, i.e. *in utero*. However, epidemiological evidence indicates that, if anything, avoidance may be associated with an increased risk of allergy. Rather than a linear relationship between the level of allergen exposure and sensitization, there appears to be a bell-shaped curve, where very low and high exposures are associated with a lower risk. High exposure may result in the induction of immunological tolerance and may be a more appropriate approach to allergy prevention in the future.

In the postnatal period, the focus has been on early infant feeding. Exclusive breastfeeding (for at least four months) has been associated with a reduced risk of eczema and food allergy in some but not all studies. The impact on later development of asthma is less clear. In non-breastfed infants, there is limited evidence that the use of extensively hydrolysed milk formula results in a reduced risk of eczema, but not asthma. Paradoxically, delaying the introduction of allergenic foods during weaning may be associated with an increased risk of food allergy. Intervention trials assessing the optimal time for introduction of potentially allergenic foods are currently underway, to establish whether this is a cause-and-effect relationship.

The hygiene hypothesis

The demographic trends in reduction in infectious diseases over the last half century have been mirrored by a progressive increase in non-communicable diseases, including allergy and autoimmune conditions. Allergic diseases occur more commonly in firstborn than second and subsequent children in a family. This led to the formulation of the hygiene hypothesis, which states that early exposure to infections (such as occurs in later-born children exposed to their older siblings) reduces the risk of allergic sensitization and disease. This hypothesis has been substantiated by a number of other epidemiological associations, including high use of antibiotics during pregnancy and the postnatal period, which increases the risks of asthma, while babies born into Bavarian farming families exposed to high levels of endotoxin have a lower risk of allergy and allergic disease. It has been suggested that the latter may be due to ingestion of unpasteurized milk by mothers and by their infants during

weaning. Unpasteurized milk contains a range of bacteria, which could have a probiotic effect. The use of probiotics during pregnancy and in infants to prevent the onset of allergic disease has been studied, but there is significant heterogeneity in results and there is still no convincing evidence that this approach will alter the development of allergic disease. Recent studies utilizing prebiotic oligosaccharides (which occur in human breast milk) suggest this approach might reduce the risk of allergic sensitization and eczema, but more trials are needed to confirm this.

The allergic march

Many infants initially presenting with food allergy and eczema subsequently develop allergic rhinitis and/or asthma. This has been termed the allergic or atopic march (Fig. 16.3). However, there are other subjects who only ever have early eczema, sometimes with food allergy, and never develop subsequent allergic problems, while others with allergic asthma have never had preceding eczema. Nevertheless, there is some mechanistic credibility to the concept of the allergic march. Filaggrin gene polymorphisms, leading to excessive skin permeability, are not only associated with increased risk of food allergy and eczema but also with an increased risk of subsequent asthma. The mechanistic concept would be that sensitization to aeroallergens has occurred through the skin with subsequent homing of sensitized lymphocytes to the airway.

Case history

The allergic march

CJ was a full-term normal delivery of high birth weight. He developed facial and flexural eczema at three months of age, having been exclusively breastfed during that time. It became apparent to his mother that when she drank milk or ate eggs in the two hours prior to a breastfeed, his eczema flared. CJ had positive skin prick tests, demonstrating the presence of IgE antibodies to milk, egg proteins and house dust mite at six months of age. By two years, the milk allergy had completely resolved. His egg allergy had, however, persisted. At 24 months he presented with a paroxysmal nocturnal cough inducing vomiting, which had persisted for ten days during an upper respiratory infection. Subsequently he was heard to have wheezing when upset, occasionally in association with a cough at night. On further questioning, his parents had noted that he had experienced excessive sneezing and rhinorrhoea
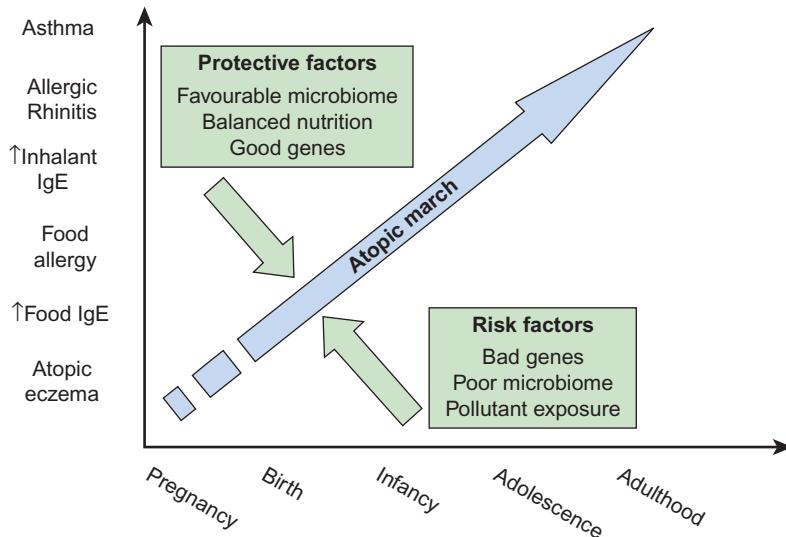
Fig. 16.3 A representation of the current understanding of the atopic (allergic) march.

for several months before the onset of the cough and wheeze.

Asthma was well controlled with low-dose inhaled steroids and occasional use of beta-agonists. At 12 years of age, he presented with an acute episode of stridor, wheeze, generalized urticaria and angioedema five minutes after eating a Brazil nut. On assessment in A&E, he was noted to be hypotensive but had a very rapid improvement after an intramuscular injection of 0.3 mg of intramuscular adrenaline. Allergy skin tests were negative to Brazil nut. On further questioning, the Brazil nut had been picked out of a bowl of mixed nuts, and he was actually allergic to peanut.

Anaphylaxis

Many allergic reactions are local, with symptoms only at the location of allergen exposure. Where symptoms are seen at a location remote to the site of allergen exposure, this is termed a 'generalized' or systemic reaction; if those symptoms are potentially life-threatening, e.g. involve the respiratory and/or cardio-vascular system, the reaction is termed anaphylaxis. Anaphylaxis represents the most severe manifestation of an IgE-mediated reaction. It can be defined as 'a severe, potentially fatal generalized or systemic hyper-sensitivity reaction'. The most common triggers of ana-phylaxis are food in children and adolescents, and insect venom or medications in adults.

The precise mechanism of anaphylaxis remains unclear. Antihistamines do not prevent anaphylaxis, so other mediators (e.g. other mast cell proteases, platelet activating factor) must be involved. Fortu-nately, there is good anecdotal evidence that adrena-line (epinephrine) can be very effective in halting an anaphylactic reaction; it is for this reason that children at risk of anaphylactic reactions are commonly pre-scribed adrenaline auto-injector devices for use in the community. The mechanisms by which adrenaline acts are likely to include:

- Alpha-adrenergic effects resulting in vasoconstriction, increasing blood pressure and reducing plasma extravasation
- Beta-adrenergic effects, causing broncho-dilatation in the airways
- Mast cell stabilization, preventing further degranulation and release of vasoactive mediators.

Food allergy

Food allergy affects up to 10% of preschool children worldwide, and continues to increase in prevalence in many countries. Current UK estimates for the preva-lence of peanut allergy are between 2 and 4% in school-aged children.

Food allergy involves an immune response to an otherwise innocuous food protein and must be distin-guished from food intolerance, now better termed non-allergic food hypersensitivity (Fig. 16.4). While many genuine food allergies are associated with
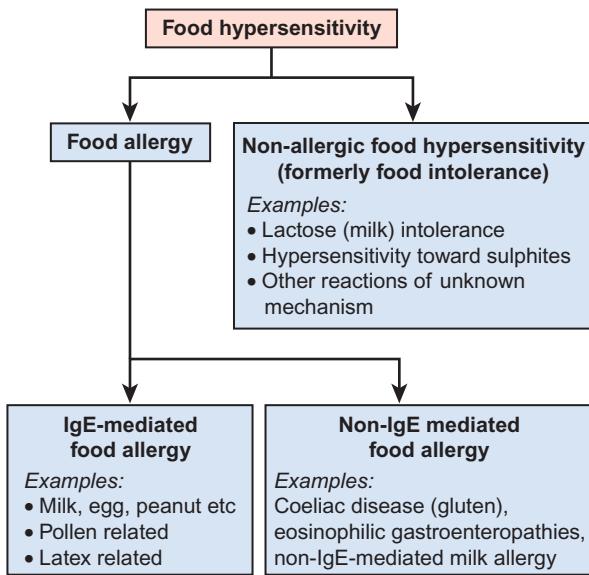
Fig. 16.4 Food hypersensitivity syndromes.

(Figure contents:)

Food hypersensitivity

Food allergy

Non-allergic food hypersensitivity (formerly food intolerance)
Examples:
• Lactose (milk) intolerance
• Hypersensitivity toward sulphites
• Other reactions of unknown mechanism

IgE-mediated food allergy
Examples:
• Milk, egg, peanut etc
• Pollen related
• Latex related

Non-IgE mediated food allergy
Examples:
Coeliac disease (gluten), eosinophilic gastroenteropathies, non-IgE-mediated milk allergy

specific IgE antibody, other immune mechanisms may sometimes be involved. Non-allergic food hypersensitivity reactions are typically transient and often result from the gastrointestinal tract being unable to metabolize non-protein food constituents. A classic example is secondary lactose intolerance resulting from a lack of the enzyme lactase (e.g. following gastroenteritis), which results in accumulation of lactose sugar in the gut causing osmotic fluid retention leading to abdominal discomfort and diarrhoea. The crucial difference is that the immune system is not involved, and thus food intolerances (while potentially debilitating) do not result in life-threatening, immune-mediated reactions. While food allergy can occur on exposure to tiny doses, in general intolerance symptoms only occur with a large-dose exposure.

Food allergy and intolerances should be distinguished from psychological food intolerance, which is common and may follow genuine food allergy which has resolved. Adverse reactions to food may also mimic food allergy, for example the response to scombroid food poisoning (which occurs with badly-stored fish such as tuna and is due to a high histamine content) and food contaminated with staphylococcal endotoxin, which results in acute vomiting.

IgE-mediated food allergy

Food allergy has been reported to almost every food known to man, including to fruit and vegetables,

herbs, spices and to carmine, a food colour produced from the cochineal bug. In practice, over 90% of food allergy is caused by 8 foods:

• Cows' milk
• Hens' eggs
• Peanuts
• Tree nuts and seeds
• Fish
• Shellfish
• Soya
• Wheat

Over 80% of children who develop food allergy present in the first year of life; many have atopic eczema. In fact, over 40% of infants with moderate eczema will have food allergy, most commonly to egg or milk. This observation has contributed to the epicutaneous hypothesis of food allergy: that exposure to environmental food allergen through a damaged skin epithelium results in sensitization and potential clinical allergy. Food allergy is more common where a child has at least one first-degree relative with some form of atopy. A child with one atopic parent has a fourfold higher risk of food allergy, while having a sibling with a food allergy results in a sevenfold higher risk.

Diagnosis of IgE-mediated food allergy

The gold standard for diagnosis is a double-blind, placebo-controlled food challenge (DBPCFC), in which increasing doses of the food (or placebo) are given under medical supervision. The DBPCFC can be difficult to perform in clinical practice due to the need for two separate hospital visits, and the need to 'blind' the taste of the food. In reality, most paediatric centres instead perform un-blinded, open food challenges as a more pragmatic alternative. Such challenges are still time-consuming and, in practice, IgE-mediated food allergy is frequently diagnosed through surrogate measures, through demonstration of food-specific IgE either by allergy 'skin prick' testing (SPT; see Fig. 16.5) or assay of circulating specific IgE from a blood test.

By comparing the size of the SPT wheal or level of specific IgE in the blood to food challenge outcome, allergists have been able to set 95% predictive values, above which a child has >95% likelihood of an allergic reaction should they eat the food to which they have been tested. It can therefore be assumed that a child with >95% likelihood of reaction is truly allergic and does not need to undergo a food challenge to demonstrate clinical reactivity.

Question 16.1

Food allergy in a young child

A 3-year-old girl is referred to the clinic with the following history:

- Itchy hives and swollen lips/face within minutes of exposure to peanut butter

- Red erythematous rash around her mouth, noticed around 30–60 minutes after eating strawberries, which she has done on multiple occasions

She is avoiding all cows' milk, having had loose stools and faltering growth as an infant when weaned onto cows' milk-based formula. Her GP recently recommended that the family try some dairy foods in her diet, and on each occasion she developed loose stools and variable abdominal pain occurring hours after eating dairy foods. She undergoes skin prick testing to peanut, cows' milk and strawberry – the results are shown in Fig. 16.5.

Which of the following is the most likely scenario? Select ONE answer only.

A. IgE-mediated food allergy to peanut and strawberry, lactose intolerance

B. IgE-mediated food allergy to peanut and strawberry, non-IgE-mediated to cows' milk protein

C. IgE-mediated food allergy to peanut, non-IgE-mediated to cows' milk protein, not allergic to strawberry

D. IgE-mediated food allergy to peanut, non-IgE-mediated to cows' milk protein and strawberry

E. IgE-mediated food allergy to peanut, non-IgE-mediated to strawberry, lactose intolerance

Fig. 16.5 The skin prick test (SPT): a drop of allergen extract is placed on the skin and then 'pricked' into the dermis using a lancet. The allergen will bind to any specific IgE present on mast cells resident in the dermis, causing histamine release. This manifests as a raised area of localized oedema (wheal) with surrounding erythema (flare) within 15 minutes.

Answer 16.1

C. IgE-mediated food allergy to peanut, non-IgE-mediated to cows' milk protein, not allergic to strawberry.

The child has a history consistent with IgE-mediated symptoms to peanut and an SPT wheal indicative of IgE-sensitization to peanut. The history is indicative of delayed/non-IgE-mediated symptoms to cows' milk protein, and the SPT to cows' milk is negative. Lactose intolerance is unusual in the absence of a previous significant episode of gastroenteritis. Almost all peri-oral reactions in this context are contact reactions due to chemical irritation and not due to immune mechanisms. Strawberry and tomato are common causes of peri-oral erythema. The borderline SPT wheal is common for irritant allergens and is negative (the wheal is not 2 mm larger than the negative control), which is further evidence against an IgE-mediated mechanism.

In practice, many children will have a positive skin or blood test but of a size below the 95% cut-off. This presents a diagnostic dilemma, because sensitization does not always correlate with clinical reactivity. For example, in a study of 2848 unselected infants in Australia, under 50% of children with a positive skin test to peanut were actually allergic to peanut when tested at a food challenge. This can result in a high rate of over-diagnosis (false positives), causing unnecessary dietary restriction and anxiety. Where the allergen is a major food group (e.g. cows' milk, wheat), it is even more important to confirm the presence or absence of clinical food allergy at a food challenge, to minimize the impact on the family. This is particularly vital where the child may have sensitization to multiple foods and dietary restriction might therefore have significant nutritional consequences.

Many children with an allergy to one food are also allergic to others, due to cross-reactivity between different food proteins, because the patient's IgE binds similar peptide fragments on different food proteins. Examples of this are shown in Figure 16.6. IgE testing can be used to determine which foods might be potential allergens in this scenario, although, as before, the detection of specific IgE does not always correlate with clinical reactivity.

It is unclear why many children have IgE to a food (either in the skin or in blood) but do not have clinical allergy, i.e. they tolerate the food in question. This is an important area of current research; if it is possible

If allergic to:	Risk of reaction to at least one:	Risk
A legume — Peanut	Other legumes — Peas, Lentils, Beans	5%
A tree nut — Walnut	Other tree nuts — Brazil, Cashew, Hazelnut	37%
A fish — Salmon	Other fish — Swordfish, Sole	50%
A shellfish — Shrimp	Other shellfish — Lobster, Crab	75%
A grain — Wheat	Other grains — Rye, Barley	20%
Cows' milk	Beef — Hamburger	10%
Cows' milk	Goats' milk — Goat	92%
Cows' milk	Mares' milk — Horse	4%
Pollen — Birch, Ragweed	Fruits/vegetables — Apple, Peach, Honeydew	55%
Peach	Other rosaceae — Apple, Plum, Cherry, Pear	55%
Melon — Cantaloupe	Other fruits — Avocado, Banana, Watermelon	92%
Latex — Latex glove	Fruits — Kiwi, Banana, Avocado	35%
Fruits — Kiwi, Banana, Avocado	Latex — Latex glove	11%

Fig. 16.6 Common cross-reactivities. *(From Sicherer SH. Clinical implications of cross-reactive food allergens. Journal of Allergy and Clinical Immunology, Volume 108, Issue 6, December 2001, Pages 881–890 with permission. © Elsevier.)*

to block the events that lead to the development of allergic disease in a sensitized child, then we may be able to prevent the transition from sensitization to clinical food allergy. Furthermore, if these 'tolerizing' events can be induced in children with food allergy, it may be possible to 'cure' established food allergy.

Management of food allergy

The prognosis of IgE-mediated food allergy is variable; 50% of children with allergy to cows' milk or egg will probably outgrow the allergy before the age of 5 years, while most (up to 80%) nut allergies persist into

Diagnosis of food allergy using population cut-offs

The following (A-J) is a list of possible answers to the scenarios which appear below:

A. Child has <1% likelihood of peanut allergy; no need to avoid peanut.

B. Child has 40% likelihood of peanut allergy; a food challenge is needed to clarify diagnosis.

C. Child has 40% likelihood of peanut allergy; food challenge is not needed to clarify diagnosis.

D. Post-test probability is 20–30%; a food challenge should be performed to make the diagnosis.

E. Post-test probability is 60–70%; a food challenge should be performed to make the diagnosis.

F. Post-test probability is 60–70%; food challenge is probably not indicated at this time.

G. Post-test probability is 85–90%; a food challenge must be performed to clarify the diagnosis.

H. Post-test probability is 85–90%; food challenge is probably not indicated at this time.

I. Post-test probability is >99%, confirming allergy – no food challenge needed.

J. Post-test probability is >99%; definite allergy should be confirmed by performing a food challenge.

Use the nomogram (Fig. 16.7) to determine the post-test probability and select the best answer for each of the following scenarios:

1. A 2-year-old with two recent reactions in the last month to peanut, typical of IgE-mediated allergy. He has a high pre-test probability of peanut allergy (99%), although his SPT is only 2 mm (likelihood ratio ~2).

2. A 5-year-old, never eaten peanut. The child has a sibling with peanut allergy, and thus has a 1 in 10 probability of having peanut allergy himself. The SPT to peanut is 4 mm (likelihood ratio ~6).

3. A 2-year-old girl with eczema and egg allergy. She has never eaten peanut, because her parents are concerned that she may have peanut allergy

on the basis of a skin prick test of 5 mm (likelihood ratio ~18). One third of 2-year-olds with eczema and egg allergy are thought to have peanut allergy as well.
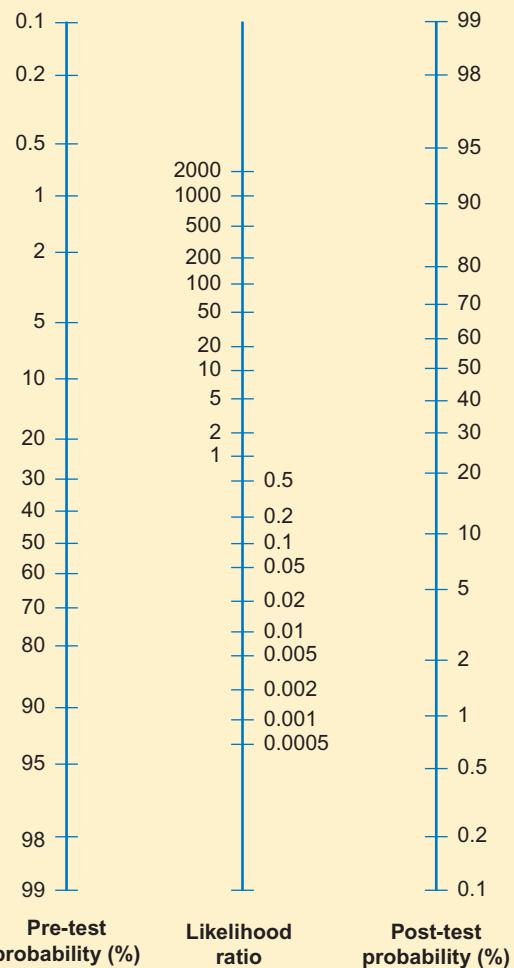
Fig. 16.7 Nomogram which can be used to establish the post-test probability of a test, using the pre-test probability and likelihood ratio (LR). In this context, LR is the chance that a person with the allergy will have a positive test compared with the chance that a person without the allergy would have a negative test.

1. I. Despite a borderline SPT, the clinical history is clearly consistent with IgE-mediated food allergy and the post-test probability of peanut allergy is >99%. No confirmatory food challenge is needed in this context.

2. B. The child has a 40% post-test probability of clinical peanut allergy, and a food challenge is thus indicated to clarify whether this child should also avoid peanut and whether he/she should be prescribed rescue medication.

3. H. The post-test probability is >85%. The child already has one food allergy and is only 2 years of age. Determining true clinical reactivity at this age will not significantly impact on the child and challenge should be deferred until the child is older and more able to be compliant with a food challenge.

adulthood, with resolution uncommon after the age of 10 years. Management involves:

- **Dietary avoidance,** which frequently will require specialist dietetic input to ensure effective avoidance and nutritional adequacy
- **Provision of a personalized management plan, together with rescue medication** (which may include adrenaline auto-injector devices) in the event of an accidental reaction, since these are common following diagnosis
- Research is ongoing as to possible means of **desensitization** in food allergy, but these protocols are not currently suitable for clinical practice.

It is unclear why some food-allergic children develop anaphylaxis, while others just experience only mild symptoms. The dose of allergen is likely to be an important factor; up to 75% of peanut-allergic children develop anaphylaxis to significant oral peanut exposure, but will only experience 'mild' symptoms when exposed to small amounts. However, a whole host of other factors also contribute to the likelihood of a severe reaction, including the ability of an individual to compensate for an allergic response. Reassuringly, while anaphylaxis may be common, death from anaphylaxis is rare, with around 2–3 deaths per annum in children in the UK. Associations with a higher risk of life-threatening food-induced anaphylaxis include poorly controlled asthma, high dose of exposure, failure to use rescue adrenaline early, subcutaneous rather than intramuscular administration of adrenaline which delays systemic absorption, and co-exposure to other allergens, e.g. pollen during spring in subjects with hay fever.

> **Recent advances in science – food allergy**
>
> The epicutaneous route as an important concept in the development of food allergy: exposure of food allergens present in the environment through the skin may result in sensitization and food allergy, especially in children with eczema in whom the skin barrier is compromised.

Non-IgE-mediated food allergy

Non-IgE-mediated food allergy is an increasingly recognized entity, where children do not present with typical IgE-mediated symptoms, but instead have predominantly gastrointestinal symptoms (nausea, vomiting, food aversion, poor weight gain) and coexisting atopy (e.g. eczema) which improve with dietary elimination of a particular food (often cows' milk) and then recur with subsequent exposure (Table 16.3). The precise mechanism(s) are generally poorly described, with the exception of coeliac disease (see Chapter 14, Gastroenterology). As a consequence, diagnosis currently depends on the demonstration of symptom resolution with dietary elimination, with recurrence when the triggering allergen is re-introduced.

The clinical phenotype of non-IgE-mediated food allergy is best defined for three distinct entities:

- *Eosinophilic oesophagitis*: Children classically present with a variety of non-specific symptoms, depending on their age. Infants and young children often have non-specific abdominal pains, exhibit food refusal behaviours (including slow eating with prolonged chewing of foods) and may develop faltering growth. In infants, this condition has been associated with Sandifer syndrome, with tonic neck posturing and back arching during and after feeds. Older children may have recurring abdominal (classically epigastric) pain, emesis, dysphagia and food bolus obstruction, which may be triggered by specific foods. Endoscopy with biopsy is needed for diagnosis, revealing areas of eosinophilic inflammation (white dot disease) and strictures in severe cases. Diagnosis is through evidence of eosinophils on biopsies according to internationally-agreed criteria. It is considered to be a progressive, chronic condition, which responds to both dietary elimination (where the causative food(s) can be identified, something not always possible) as well as immunosuppressant therapy, best achieved using topical steroids (which are swallowed). Some cases are responsive to proton pump inhibitors.
- *Food protein-induced enterocolitis syndrome (FPIES)* (see Case history on the next page): This is an acute food reaction which tends to present with profuse vomiting and diarrhoea 2–4 hours after consumption of the triggering food, in the absence of classical IgE symptoms. Significant fluid shifts can occur resulting in a clinical picture which can mimic septic shock; there is a rapid and excellent response to fluid resuscitation. Anti-emetics such as ondansetron can also be helpful. FPIES can be divided in solid-food FPIES (e.g. rice, chicken, legumes) and non-solid triggers (cows' milk, soya). The fact that rice (normally a 'safe' weaning food) is a relatively common trigger can delay the diagnosis. Cross-reactivity can be common, and patients are best managed by specialists experienced in the condition. Fortunately, most children with FPIES outgrow

Table 16.3 Features of IgE- and non-IgE-mediated food allergy (FA)

Feature	IgE-mediated FA	Mixed IgE/non-IgE and non-IgE-mediated FA
Onset of symptoms	Usually within 30 minutes of ingestion, <1–2 hours	Mostly 2–72 hours after consumption
Symptoms: – Gastrointestinal	• Vomiting • Diarrhoea • Abdominal cramps	• Vomiting • Excessive crying ('colic') • Altered gut transit causing loose/frequent stools/constipation • Abdominal cramps • Food refusal/aversion • Blood/mucous in stools • Faltering growth
– Extra-gastrointestinal	Skin: erythema, urticaria and angioedema Respiratory: rhinitis, wheeze and cough Cardiovascular: hypotension/dizziness	Skin: eczema Cardiovascular: very unusual, the only exception being FPIES where shock (pallor, lethargy) occurs (probably secondary to large fluid shifts within the gut)
Diagnosis	• Skin prick testing • Specific IgE testing • Oral food challenge	Trial elimination of suspected food protein +/– re-introduction
Management	• Dietary elimination of causative food protein • Dietetic support as needed • Written management plan with rescue medication (non-sedating antihistamine +/– adrenaline auto-injector)	• Dietary elimination of causative food protein • Dietetic support
Prognosis	Often persist into late childhood and adulthood	Typically resolve in early childhood, although some forms persist into adulthood, e.g. eosinophilic oesophagitis

FA, food allergy; FPIES, food protein-induced enterocolitis syndrome.

the condition by 3–4 years of age, particularly where the cause is cows' milk protein.

- *Milk-induced proctocolitis*: This classically presents with blood in the stool in infancy, in the absence of any features to suggest malabsorption, e.g. faltering growth. Symptoms resolve with exclusion of cows' milk protein. The condition classically resolves by 1 year of age.

Case history

Food protein-induced enterocolitis syndrome

A five-month-old female presents with a 6-hour history of recurrent, profuse non-bilious vomiting and increasing lethargy. She has not passed stools in the previous 48 hours. She is normally completely well and there are no sick family members. On examination, she is pale, quiet and lethargic. Her temperature is 35.6°C, HR 160, BP 84/59. There is no rash, but she has cool peripheries and the central capillary refill time is 5 seconds. Her mother comments that this presentation is very similar to one which occurred a month earlier, for which she was admitted to hospital for intravenous antibiotics for 48 hours. She is noted to have a high neutrophil count on the full blood count and a raised CRP.

She receives 20 mL/kg 0.9% saline as a fluid bolus, which results in reversal of her lethargy and complete normalization of her clinical parameters. She is commenced on intravenous antibiotics as a precautionary measure. On direct questioning, her mother reveals that while she continues to breastfeed her daughter, she has recently commenced weaning. The first presentation one month ago occurred two hours after eating rice cereal for the first time. Today was the second time she had been given porridge containing oats and sultanas.

You are suspicious that a food might have triggered the reaction, and contact the paediatric allergist who confirms that the reaction would be consistent with food protein-induced enterocolitis syndrome, particularly because of the common association in clinical reactivity with rice and oats in this condition. You refer the child for further management.

Allergy and aberrant behaviour

A population study of perceived intolerance to food additives in over 18,000 respondents in the UK found that 7.4% believed themselves to have a 'problem' with food additives. A wide range of symptoms were reported, from conventional allergic symptoms such as urticaria through to headache, behaviour and mood changes and musculoskeletal problems. A

subgroup of the respondents had double-blind challenges suggesting a calculated population prevalence of reproducible adverse reaction to food additives of 0.026%, equating to only 4% of people who believed themselves to react adversely to additives actually doing so at formal challenge. While food aversion is common, and reproducible reactions to foods on challenge are less frequent, the concept of food affecting behaviour should not be dismissed. Large quantities of caffeine will, for biochemical reasons, have an impact on wakefulness and irritability. There are many other neuro- and vasoactive constituents of natural foods which will impact on behaviour and performance. This is normal and predictable and will occur in the majority of the population given sufficient intake.

Case history

Overactive 7-year-old

RB, a 7-year-old girl, presented to the allergy clinic with a one-year history of overactivity and extreme irritability and aggressiveness after eating large quantities of colouring-containing foods, particularly at children's parties. The parents were told by several health professionals that this was a psychological problem induced by the excitement of attending a party. After referral to an allergy clinic, it was decided to do a formal double-blind placebo-controlled challenge with a number of azo colourings and benzoate preservatives. During the active challenge period, she did indeed become very irritable and overactive. However, examination revealed that she had a significant urticarial eruption induced by the colourings, but this was only seen when her clothes were removed. The intense itching is likely to have affected her behaviour.

Feingold was the first to report the potential association between behavioural disorder and dietary factors in a group of children with learning difficulties and behavioural problems. He claimed a 68% improvement on a diet eliminating artificial food colourings, preservatives and so-called salicylate-containing fruits and vegetables. This observation has not been replicated on subsequent studies and the concept was dismissed. However, a meta-analysis of studies investigating an association between exposure to food colourings and behaviour disturbance indicated a significant though rather small effect. Two subsequent studies in children, utilizing double-blind placebo controlled challenges of food colourings and preservatives, also found an association. *In vitro* studies suggest that high doses of certain food colourings can induce IgE-independent mast cell and basophil activation leading to the release of mediators such as histamine. A group of researchers in Southampton found that the effect of the food additives was only apparent in individuals with polymorphisms in genes associated with the histamine degradation pathway. As the histamine H_3 receptor in the brain has been suggested to contribute to behavioural aberration and other neurological problems, there is a credible mechanistic pathway to explain the association between high-dose additive exposure and an effect on behaviour, particularly in individuals with an abnormality in histamine degradation.

Case history

Attention deficit hyperactivity disorder

JW, aged 9, was diagnosed with attention deficit hyperactivity disorder (ADHD), severely compromising his education. He had disruptive behaviour with poor concentration, easy distractibility and periodic aggressive outbursts. He had no evidence of atopic disease, nor indeed was there any in the family. However, a range of psychosocial problems were identified. Treatment with methylphenidate produced a partial improvement in behaviour. However, additional support was required to facilitate his assimilation back into schooling having previously been expelled because of his disruptive behaviour. His mother was convinced that 'E numbers' aggravated abnormal behaviour and that avoidance led to further improvement. His mother would not consent to him having a supervised controlled additive challenge.

This is a typical history of ADHD. It would be very easy to dismiss the concept of food additives as an aggravating factor, and supporting the parental belief might be viewed as inappropriate collusion. However, his mother's use of the diet had empowered her to take action for herself and had indirectly probably improved the attention she gave to her child. Supporting the family and keeping an open mind may make it more likely that they will accept the additional help and treatment that is required to achieve a favourable outcome. Clearly only a double-blind placebo-controlled food challenge would have clarified the issue, but parents are understandably reluctant to allow this if they perceive that it will have an adverse effect on their child.

Allergic skin diseases

Urticaria and angioedema are not always caused by foods, as many other allergens by contact, inhalation and injection can also cause cutaneous reactions, which can be associated with anaphylaxis. However, in many cases they occur as an isolated phenomenon without further systemic progression. There are many other non-allergenic causes of the same response, including a host of physical factors such as cold exposure, heat, pressure, sunlight and exercise. Careful history-taking should discriminate the cause. Occasionally, it may be necessary to use a relevant provocation test in order to establish cause and effect. This is easily done in relation to cold urticaria, where the application of an ice cube to the skin for five minutes will result in a wheal in sensitive individuals. Episodes of urticaria/angioedema may also be triggered by acute infections, both viral and bacterial (the most classical being beta-haemolytic streptococcal tonsillitis). The response often lasts for days, in contrast to that induced by allergen, which typically resolves within a few hours.

Chronic urticarias

Most urticaria in childhood is intermittent. The occasional case is more persistent or chronic. One underlying cause is an autoimmune process with antibodies generated against IgE or the IgE receptor. In some cases, it is possible to confirm the diagnosis by performing a so-called autologous serum skin test. This involves separating patient serum and then skin testing with this, initially by prick test and, if negative, an intradermal injection. The more persistent or frequent recurrent and chronic cases of urticaria may well require treatment with continuous H_1 antagonists of which the non-sedating varieties are recommended. In very resistant cases, the addition of H_2 antagonist can sometimes provide additional benefit. There is increasing evidence that the anti-IgE monoclonal antibody omalizumab can be effective in controlling more resistant cases.

Hereditary angioedema

There is a dominantly-inherited form of recurrent angioedema in which there is either defective function or an absolute deficiency of C1 esterase inhibitor. This results in unregulated production of vasoactive kinins, typically associated with consumption of the fourth component of complement (C4). Kinin overproduction can result in episodes of angioedema which involve the airway, bowel as well as cutaneous swelling (but no urticaria). This can result in life-threatening respiratory compromise and severe colicky abdominal pains. Acute, life-threatening episodes are amenable to treatment with recombinant C1 inhibitor concentrate or kinin receptor antagonists, which may also inhibit kinin production, such as icatibant. Prophylaxis may be achieved in some with very low dose anabolic steroids or tranexamic acid.

> **Recent advances in science – hereditary angioedema**
>
> The role of bradykinin pathway in hereditary angioedema provides the potential for bradykinin receptor antagonists as a treatment for life-threatening reactions.

Eczema (atopic dermatitis)

Eczema is an intensely itchy maculo-papular erythematous chronic skin condition with a characteristic distribution which varies with age. In infants, it often affects the face (but not the nose) and trunk, while in older children skin flexures are most affected.

The identification of polymorphisms in skin barrier genes associated with susceptibility to eczema has changed the concepts and understanding of eczema. Thus, allergy is not the primary cause of the skin defect, but a consequence of the increased risk of allergic sensitization through an impaired skin barrier. Once sensitization has occurred, it drives inflammation, thereby increasing the severity and persistence of the eczematous process. In addition, these defects can allow abnormal exposure to aeroallergens with subsequent circulation of sensitized lymphocytes to the airway, thereby providing a mechanism to explain the allergic march from eczema to asthma. Most commonly, eczema appears in early infancy and at this stage is often associated with food allergy. Around 60% of cases have developed a complete remission by 3 years of age. However, one third have either continuing intermittent or persistent problems. Persistence is predicted in infancy by severity and the presence of allergic sensitization.

Management should initially focus on good skin care in order to build the skin barrier by the generous use of moisturizing and appropriate skin cleansing to avoid infection. Topical corticosteroids can be used with a focus on low potency if at all possible. Topical calcineurin inhibitors, tacrolimus and pimecrolimus, have provided additional modalities for more difficult cases. This is described in more detail in Chapter 25, Dermatology.

The relative importance of allergy in eczema is contentious. A pragmatic approach is to consider allergic causes in moderate–severe eczema, particularly where onset is under the age of 2 years and in those who have a history of exacerbation after specific exposure to allergens. Conventional allergy tests are usually unhelpful in determining the food triggers in eczema,

as IgE-mediated reactions are usually not involved. Under such circumstances there is no reliable diagnostic test, though some advocate the use of a so-called atopy patch test, where allergens are applied to the skin in the same way as contact antigens to establish whether they induce an eczematous response. For the majority of cases, trials of dietary exclusion (over 2–4 weeks) based on the history and focusing on likely common allergenic triggers is the usual diagnostic and therapeutic procedure.

United airways disease

The conventional representation of the allergic march shows asthma appearing in early childhood followed later by seasonal allergic rhino-conjunctivitis. However, it has become clear that allergic rhinitis often precedes the onset of asthma. This has been most obviously demonstrated in occupational lung disease, where exposure to an occupational allergen leads to sensitization and the first manifestations are either in the skin or nose, with asthma occurring at a later stage.

Many cases of asthma, particularly in adulthood, have no associated allergy. Even in children, some 20% of cases appear to be non-allergic. This has focused attention on genetic polymorphisms independent of immune responses which increase susceptibility to asthma. Thus, in a similar way to eczema, there are airway structure and function defects which predispose to airway inflammation and asthma, independent of allergy. However, allergy is the most pervasive and persistent drive to inflammation in the airway and therefore more persistent and severe disease.

While wheezing is the cardinal symptom associated with asthma, there are many other causes of wheezing. In the first two years of life, around 15–20% of all infants will have episodes of viral-associated wheezing, which is not associated with asthma beyond infancy. Infants who develop RSV bronchiolitis have recurrent wheezing through early childhood, which rarely persists beyond 5 years of age. Childhood asthma, on the other hand, can have an early, intermediate or late onset (Fig. 16.8) and in most cases this is associated with evidence of allergic sensitization, particularly to inhalant allergens such as house dust mite, cat, dog, pollens, and moulds. Thus, allergy, either in the form of eczema or positive allergy skin tests, is useful in determining prognosis in an infant with recurrent wheezing and, if present, indicates the need to commence asthma prophylaxis early.

Allergy and viral infection

While the role of viral infections in the development of asthma is unclear, the overwhelming majority of patients admitted to hospital with acute exacerbations of asthma have evidence of acute rhinovirus infection. There is good mechanistic evidence of an interaction between allergy and rhinovirus. Allergic sensitization and exposure to allergen increases the expression of a molecule known as intercellular adhesion molecule-1 (ICAM-1) on airway epithelial cells. This is the receptor to which rhinovirus attaches in order to gain access to cells, where it triggers an innate immune response including interferon production, which induces cell apoptosis, thus restricting spread of the rhinovirus. However, asthmatics have high ICAM-1 expression and an inefficient innate interferon response to the virus, which then replicates and can spread further down the airway. This explains the unique susceptibility of the asthmatic to rhinovirus infection, and is now leading to the identification of new therapeutic targets.
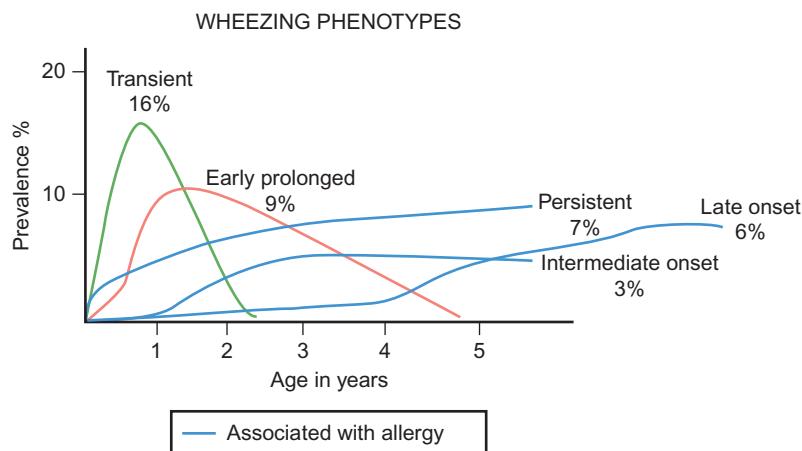
Fig. 16.8 **The prevalence of different wheezing phenotypes by age.** *Data based on the Avon longitudinal birth cohort study. 41% of children fit into one of 5 wheezing phenotypes. 59% did not have a wheezing phenotype: approximately 14% had 'infrequent wheeze', in 45% no wheeze was reported. Allergy tests facilitate prognosis and therefore treatment. (Henderson J, et al. Thorax 2008;63:974–980.)*

Allergen avoidance

Given the strong association between allergy and asthma severity and persistence, it would seem self-evident that allergen avoidance should be a primary strategy in management. However, avoidance of house dust mite, the commonest allergenic trigger to asthma in the UK, has a chequered history. Successive Cochrane reviews have concluded that there is insufficient evidence to recommend current chemical and physical methods aimed at reducing exposure. There is heterogeneity of outcomes, which suggests that some physical methods might, under some circumstances, be of value. Most recently, a unique environmental system, which provides a zone of filtered air over a person's upper torso and face while sleeping, has been trialled in children and adults with perennial inhalant allergen associated asthma with impressive beneficial effects. Unfortunately, avoidance of other allergens is very difficult or impossible. Those with cat allergy are recommended not to have a cat, but cat allergen is ubiquitous in the environment and can be found on seats in buses, trains, cinemas and in beds in hotels. Avoidance of pollen can only be achieved by wearing the equivalent of a space helmet!

Question 16.3

Urticaria and wheeze

A 12-year-old girl with a history of severe asthma and hay fever is admitted to the children's emergency department with an acute wheezing episode in summer. She felt well in the morning but her PE teacher insisted that she run across her school playing fields just after the grass had been cut. She has a widespread urticarial rash and is initially wheezy and hypoxic. She responds well to salbutamol and antihistamines.

Which of the following BEST describes the likely underlying pathologies? Select ONE answer only.
Immediate histamine release in the:

A. Alveoli is followed by grass pollen binding to IgG, which leads to an alveolitis

B. Smooth muscle of only the large bronchi will be followed within hours by a combined eosinophilic/neutrophilic response

C. Nasal airway will be followed within minutes by eosinophilic activation in the lower airways

D. Respiratory epithelium will be followed within hours by a predominantly neutrophil-induced inflammatory response in the first instance

E. Skin and gastrointestinal tract passes into the blood and results in severe bronchospasm

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Answer 16.3

D. Immediate histamine release in the respiratory epithelium will be followed within hours by a predominantly neutrophil-induced inflammatory response in the first instance.

This highlights the basic pathophysiology in a clinical context. Whilst allergen-triggered asthma often resolves quickly, there is frequently a late phase response (LPR). To an extent, this can be ameliorated with treatment with oral steroids, but the course of the late phase response is not entirely predictable and it would be prudent to consider a longer period of observation before letting this child home.

Grass pollen does not typically reach the alveoli and hence does not result in an alveolitis, but likewise is not limited to just large bronchi. The late phase response is associated in the first instance with neutrophil recruitment and activation, although subsequent eosinophil recruitment results in a predominantly eosinophilic infiltrate by 12 hours later. Systemic mast cell activation, while unusual, can occur following aeroallergen exposure causing systemic signs such as urticaria.

Pharmacotherapy

As allergen avoidance in asthma is unlikely to be effective in isolation, the mainstay of treatment becomes regular prophylaxis with inhaled corticosteroids (ICS) for the overwhelming majority of cases to control airway inflammation, thereby improving quality of life (Fig. 16.9). The addition of short-acting beta-agonists during exacerbations and before significant exercise is appropriate. Some children with more severe disease require more complex treatment combinations, for example a long-acting beta-agonist together with ICS. However, ICS remain essential, as continuous beta-agonist alone has been associated with heightened bronchial hyper-responsiveness and an increased risk of severe and life-threatening asthmatic reactions. Thus, long-acting beta-agonists should never be used in isolation. Successive confidential enquiries into UK asthma deaths have shown that very high usage of beta-agonist and lack of use of prophylactic ICS are the principle avoidable causes.

Cysteinyl leukotriene receptor antagonists (e.g. montelukast) do have a role as add-on therapy in more difficult cases and have also been shown to have some impact in reducing viral-induced exacerbations. They can be used as regular prophylaxis or just during viral infections, the latter can be particularly effective in pre-school children, with around 60% benefiting from this strategy. In the most difficult cases, relative insensitivity
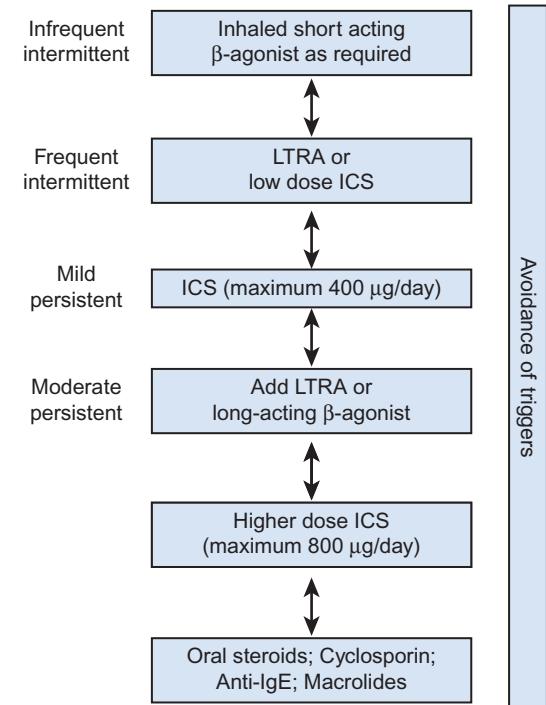
Fig. 16.9 A suggested therapeutic algorithm for paediatric asthma management. LTRA, cysteinyl leukotriene receptor antagonists (e.g. montelukast); ICS, inhaled corticosteroids. *(Adapted from the Third International Pediatric Consensus statement on the management of childhood asthma, 1998.)*

to steroids occurs. This can be associated with either eosinophilic or neutrophilic inflammation. For the former, where IgE-mediating mechanisms are involved, anti-IgE therapy using omalizumab can be highly effective for children over the age of 6 years. Those with chronic neutrophilic inflammation have sometimes benefited from the use of prophylactic macrolide antibiotics such as clarithromycin or azithromycin.

Finally, while allergen immunotherapy, particularly to house dust mites, cat, dog and pollens, has been shown to benefit asthma in terms of reducing exacerbations, its place in the therapeutic algorithm remains contentious. There is concern that allergen immunotherapy is more likely to induce severe and life-threatening anaphylactic reactions in those with poorly controlled asthma. Over the years there have been deaths reported from immunotherapy specifically in patients with asthma. Thus, in the UK, the recommendation is that allergen immunotherapy should be reserved for those with allergic rhinitis alone or those with venom allergy. The advent of newer, safer modified allergens for use in immunotherapy may well change this perspective in future. Sublingual immunotherapy is another option with a lower likelihood of inducing severe reactions than when the allergen is administered subcutaneously.

Question 16.4

Anti-IgE therapy

An 8-year-old patient with severe asthma is reviewed by her medical team. Her symptoms are exacerbated during the hay fever season; other triggers include exercise, viral infections and exposure to cold air. She is now requiring regular treatment with bronchodilators in addition to high-dose inhaled corticosteroids, and has poor sleep due to frequent wakening. The paediatrician is considering the child for anti-IgE therapy.

Which ONE of the following best summarizes the mechanism of action of anti-IgE in asthma?

A. Binds to mast-cell associated IgE resulting in mast cell stabilization

B. Blocks IgE receptor

C. Inhibits allergen penetration through the airway epithelium

D. Reduces free circulating IgE and IgE-receptor density

E. Reduces the production of allergen-specific IgE through an action on airway epithelial cells

Answer 16.4

D. Reduces free circulating IgE and IgE-receptor density.

Anti-IgE binds to free circulating IgE causing a complex which can no longer bind to and cause cross-linking of IgE-receptors. It also has been shown to reduce the number of IgE receptors on the surface of effector cells such as mast cells.

Allergic rhinitis

Allergic rhinitis (AR) affects up to 40% of children. It is often underdiagnosed, and frequently coexists with asthma (most studies reporting over 50% of asthmatic children also having AR). Untreated, it can predispose to rhino-sinusitis, otitis media, impaired hearing (secondary to Eustachian tube dysfunction), disordered sleep and adverse consequences on school performance. Evidence suggests that children with active AR will drop a grade in school exams (occurring during the pollen season) compared to their peers.

Symptoms are caused in a similar manner to other IgE-mediated allergens. Exposure to allergen in sensitized individuals induces the release of inflammatory mediators via an IgE-dependent mechanism, resulting in symptoms. Ongoing allergen exposure induces nasal airway hyper-responsiveness (NAHR), a hallmark of allergic rhinitis. NAHR is a pathophysiological state whereby the response of the nasal airway to

both allergen and inflammatory mediators (such as pollutants, histamine and bradykinin) is increased compared to normal. Thus, in experimental terms, the same level of exposure to antigen and other mediators results in increased nasal obstruction, tissue oedema and production of secretions. While a variety of pharmacological agents can be used to treat the initial inflammatory response, only corticosteroids are effective in preventing NAHR. The ability of corticosteroids to treat AR in patients with hay fever depends on when the medication is commenced; maximum effect is achieved only if steroids are commenced prior to the pollen season, before NAHR is established.

AR is traditionally classified as either perennial (PAR) or seasonal (SAR; 'hay fever'), dependent on whether symptoms occur throughout the year or in relation to seasonal exposure to allergen (Table 16.4). This distinction is important as the response to medication, particularly antihistamines, will often depend on the causative allergen.

The assessment of symptoms according to the ARIA (allergic rhinitis and its impact on asthma) classification (Fig. 16.10) is also useful in guiding treatment.

Skin prick testing (SPT) can be helpful in determining the cause for symptoms and, as with screening for food allergens, it has a high negative predictive value, but false positives are also common. Up to 30% of children have a positive SPT to house dust mite (HDM) but less than half will develop symptoms when exposed to HDM during an intranasal challenge. Furthermore, it is now known that patients can have 'local' AR, where IgE is present only in the nasal airway and not elsewhere, thus skin testing is negative. The use of 'panels' to test large numbers of allergens is at best unhelpful, generating confusion and impacting adversely on families who undertake inappropriate attempts at allergen avoidance. Any mismatch between symptoms and allergy tests (for example, a child with

symptoms in springtime but SPT positive only to HDM, an allergen which causes perennial symptoms) should prompt consideration of other allergic or non-allergic causes. In this case the house dust mite exposure could well have caused NAHR and the springtime exposure is to ozone generated by photochemical reactions in the atmosphere.

Specialist services offer a number of objective methods to assess the nasal airway, including nasal endoscopy, rhinomanometry and rhinometry (which

Table 16.4 Features of allergic rhinitis (AR) depending on cause

Feature	Perennial AR	Seasonal AR (hay fever)
Allergen	House dust mite Animal dander: cat, dog, etc.	Tree pollen Grass pollen
Symptoms	Nasal obstruction prominent	Nasal pruritus and sneezing, with relatively low nasal obstruction
Temporality	Perennial, i.e. throughout the year	Typically seasonal, though seasons can be prolonged and in some areas persist throughout the year
Eye symptoms	Infrequent	Common
Mediators involved	Kinins > histamine	Predominantly histamine
Response to antihistamine	Poor	Good
Response to steroid	Good	Good
First line treatment for mild disease	Nasal corticosteroids	Oral antihistamine
First line treatment for moderate–severe disease	Nasal corticosteroids	Nasal corticosteroids + oral antihistamine

ARIA CLASSIFICATION

Intermittent:
<4 days/week
and <4 consecutive weeks

Persistent:
>4 days/week
and >4 consecutive weeks

Mild:
Normal sleep
+ no impairment of daily activities, sport, leisure
+ no impairment of school
+ no troublesome symptoms

Moderate – severe:
One or more items
• Abnormal sleep
• Impairment of daily activities, sport, leisure
• Impairment of work and school
• Troublesome symptoms
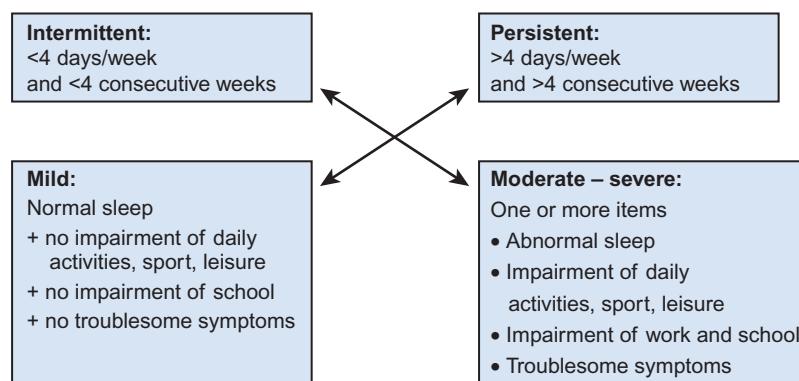
Fig. 16.10 Classification of symptoms of allergic rhinitis according to the ARIA (allergic rhinitis and its impact on asthma) consensus. *(Adapted from the Journal of Allergy and Clinical Immunology 2006;117:404–410. DOI: (10.1016/j. jaci.2005.10.032).)*

assess nasal airflow), exhaled nitric oxide (a marker of inflammation and/or nasal polyposis) and cytological evaluation (nasal smear, lavage and biopsy). However, their use in children can be challenging. Lung function should be considered in children with persistent rhinitis who are able to comply with testing, in order to identify concurrent asthma.

Drug hypersensitivity

Many children are reported to experience 'drug allergy', but in practice the rate of true drug hypersensitivity in children is low. Many research studies have reported that the majority of children reported to have had an allergic reaction to a drug usually tolerate the medicine when given at formal challenge. It is thought that many drug reactions are actually manifestations of the clinical disease for which the drug was prescribed; for example, viral exanthems may be misdiagnosed as a drug allergy, the most well-known example perhaps being amoxicillin-triggered exanthem in children with Epstein–Barr virus infection. Often, a detailed history helps distinguish between viral-triggered symptoms and drug hypersensitivity.

As with all hypersensitivity reactions, drug reactions have been described which correspond to the type I–IV mechanisms outlined in Table 16.5. Some medicines are too small in size to stimulate an immune response alone. These molecules are known as haptens, and need to bind to a larger carrier, often a serum protein such as albumin, in order to trigger a hypersensitivity reaction. The penicillin molecule is such a hapten.

Some medicines do not cause symptoms of hypersensitivity reaction via an immune-mediated response, but through direct degranulation of mast cells. Many children experience pruritus in response to opiates such as morphine. The opiate directly causes partial degranulation of mast cells, but this is not a hypersensitivity reaction. Vancomycin-triggered 'red man' syndrome is a similar entity, which can be difficult to distinguish from IgE-mediated allergic reactions to vancomycin. The former often responds to lowering the infusion rate of vancomycin, as well as antihistamines.

Children with genuine drug allergy may need to avoid not just that drug but others to which they are cross-reactive; for example, a child with allergy to the β-lactam ring in penicillins may need to avoid other drugs with a similar β-lactam structure (Fig. 16.11). However, many children are instead allergic to the side-chains attached to the β-lactam; alternatively, the side-chains may physically prevent IgE binding to the β-lactam ring for some antibiotics in some children. It is for this reason that children with a drug allergy should be assessed and undergo appropriate testing where possible. The diagnosis of drug hypersensitivity can be complicated, and involves a careful history and, in selected cases, skin testing (usually intradermal testing, though patch testing can be helpful in some cases of delayed hypersensitivity reactions).

In the emergency situation, the vast majority of children with penicillin allergy are able to tolerate third or fourth generation cephalosporin antibiotics, such as cefotaxime and ceftriaxone. Whether this is because the child was not allergic to the penicillin in the first instance (e.g. the 'rash' was actually a viral exanthem) is unknown. Temporary drug desensitization is possible where needed (for example, in the management of haematological malignancy), but should not be attempted outside specialist centres.

There are also a number of severe, life-threatening idiosyncratic drug reactions for which the mechanism is unknown and which do not currently 'fit' into the

Table 16.5 Mechanisms of drug hypersensitivity

	I Immediate	II Antibody-mediated cell cytotoxicity	III Immune complex	IV Delayed/cell mediated
Effector mechanism	IgE-mediated degranulation of mast cells, etc.	IgG/IgM-mediated cell lysis	IgG binds to antigen causing immune deposition	Cell-mediated inflammatory response: • T cells • Eosinophils • Neutrophils • Macrophage
Clinical symptoms	Urticaria, angioedema, bronchospasm, anaphylaxis	Blood cell dyscrasia	Serum sickness: fever, arthritis	Eczema flare Exanthems: maculopapular, bullous, pustular Organ failure: hepatitis, nephritis, myocarditis
Onset of reaction	Usually under 1–2 hours	5–14 days	Around 7 days	Days to weeks
Examples	Most antibiotics, contrast media	Ceftriaxone, piperacillin, β-lactamase inhibitors	Cefaclor	Antibiotics, aromatic anti-epileptics, azathioprine
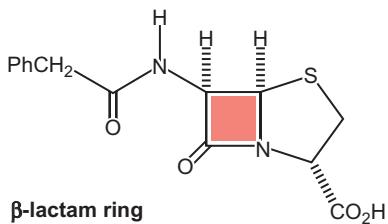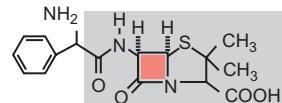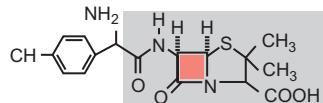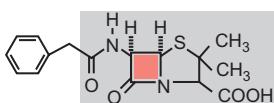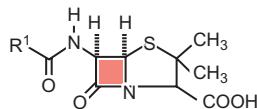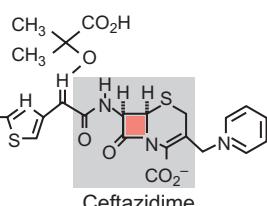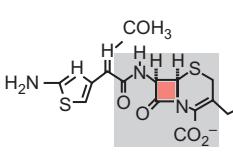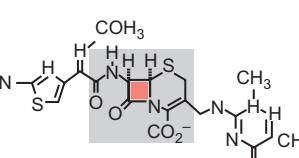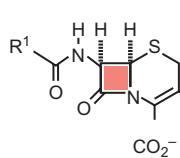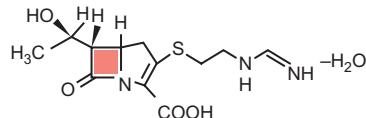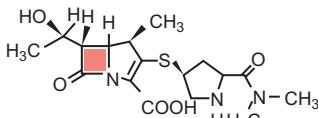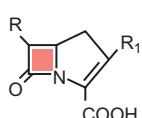
Fig. 16.11 Structure of different β-lactam antibiotics showing similar β-lactam structure.

above classification. Examples of these include Stevens–Johnson syndrome/toxic epidermal necrolysis and DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome. In these entities, the drug triggers an immune response which can cause multi-organ failure and even death. Drug testing in these conditions is generally contraindicated, due to concerns over triggering a further life-threatening reaction with repeat exposure. Preliminary research studies have suggested that patch testing or *in vitro* testing using lymphocyte stimulation with the drug may identify the cause.

Insect venom

Severe allergy to insect stings (most commonly bees and wasps, but also ant species in countries such as USA, Asia and Australia) is relatively uncommon in children. Many stings cause large local reactions, but these are not life-threatening and such children are unlikely to experience severe reactions in the future. Between 10–25% of children with true sting allergy will experience a severe systemic reaction (with shock

and/or respiratory involvement); they should be prescribed an adrenaline auto-injector, and given advice as to appropriate avoidance strategies. Even 20 years later, these children still have a 30% chance of a similar reaction, and should therefore be referred to a specialist clinic for venom immunotherapy.

Further reading

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Respiratory medicine

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Know about the embryology of the respiratory system
- Know the anatomy of the respiratory system
- Understand the physiology of respiration
- Know the physical signs and symptoms and presentation of respiratory illness
- Understand the changes in the respiratory system during sleep
- Be able to select and interpret appropriate respiratory investigations
- Know the aetiology and management of respiratory diseases of childhood
- Understand the pharmacology of agents commonly used in those diseases
- Know the respiratory complications of other system disorders

Embryology

The respiratory tree arises from the ventral surface of the foregut. The phases of lung development are shown in Figure 17.1. Abnormal embryological development may result in congenital thoracic malformations (CTMs), which include:

- Failure of complete separation of foregut and bronchial structures, leading to different types of tracheo-oesophageal fistula
- Congenital pulmonary airway malformations (CPAM), previously known as congenital cystic adenomatoid malformations (CCAM), from abnormal development of alveolar or bronchial tissues
- Pulmonary sequestration from an abnormal blood supply to part of the lung (usually systemic rather than pulmonary)
- Congenital diaphragmatic hernia from maldevelopment of the pleuroperitoneal canal with or without associated deficiency of the diaphragm itself
- Cysts, bronchogenic or foregut
- Congenital lobar emphysema from partial obstruction of the developing airway, most commonly due to a deficiency of bronchial cartilage development
- Lung agenesis/bronchial atresia from maldevelopment of the tracheobronchial tree in early fetal life.

> ### Question 17.1
>
> **A wheezy infant**
>
> Following normal delivery at term, birth weight 3.6 kg, a 6-month-old boy is referred with persistent wheeze. His mother says he feeds well but vomits after almost every feed.
>
> What is the most likely explanation for his wheezing? Select ONE answer only.
>
> A. Congenital cystic adenomatoid malformation
> B. Cystic fibrosis
> C. Gastro-oesophageal reflux
> D. Laryngomalacia
> E. Tracheo-oesophageal fistula
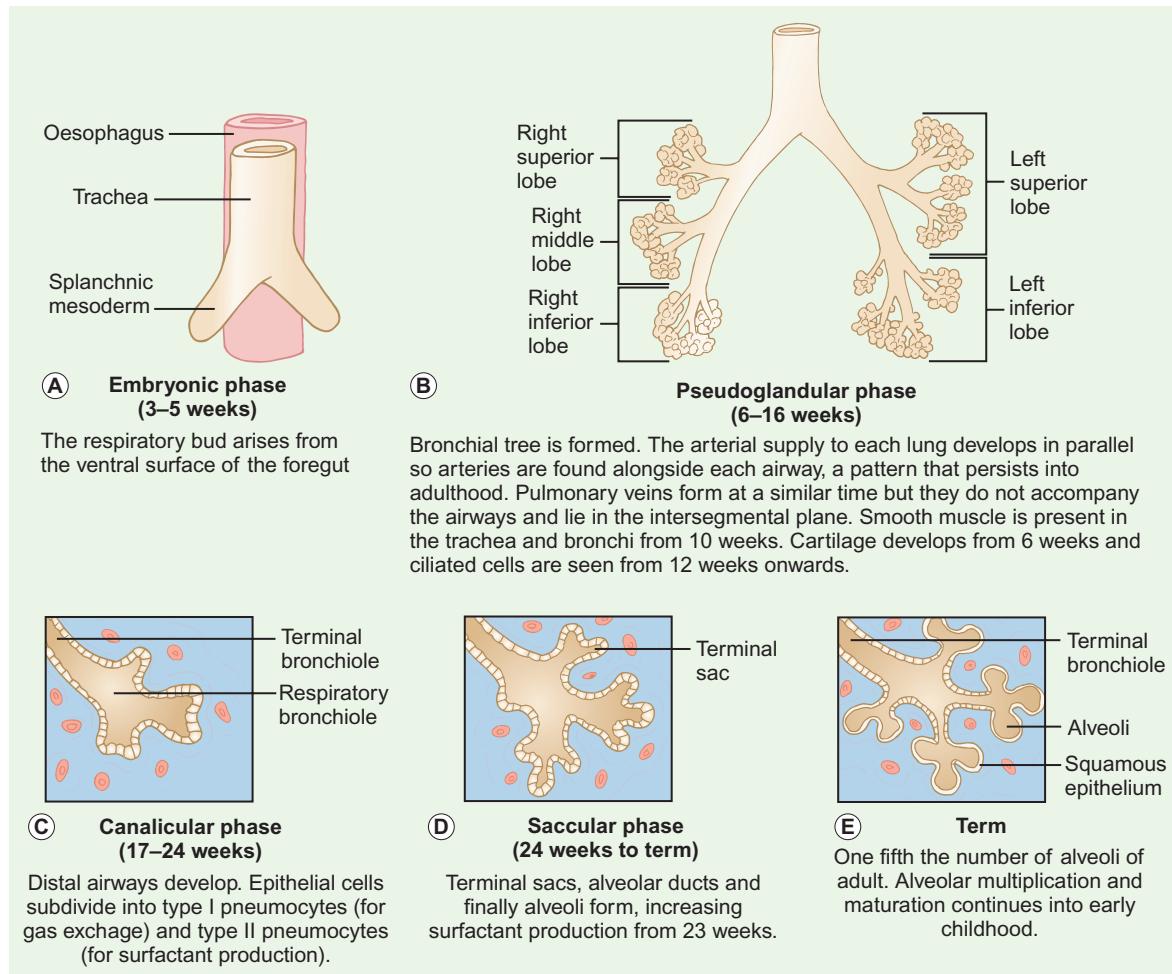
Fig. 17.1 **Phases of lung development.** *(From Lissauer T, Fanaroff AA, Miall L, Fanaroff J. Neonatology at a Glance, 3rd edition. 2015, Wiley-Blackwell, with permission.)*

Answer 17.1

C. Gastro-oesophageal reflux.

The shared origin of the lower respiratory tract and the foregut includes innervation. Gastro-oesophageal reflux in infancy leads to vagal stimulation, which may cause airway smooth muscle contraction and respiratory fluid and mucus secretion, thus presenting with wheezing or cough. Cystic fibrosis usually causes infection.

In tracheao-oesophageal fistula, there is persistence of connections between the respiratory and gastrointestinal tracts, but H-type fistulae are very rare and usually cause recurrent infection or coughing during feeds rather than wheeze.

Anatomy

The respiratory system is split into three major parts: the upper airways, the conducting airways and the lower respiratory tract. Whilst they are smaller than the final adult configuration and the relative size of the component parts is somewhat different (e.g. the epiglottis is relatively large and floppy) at birth, the upper and conducting airways are fairly well developed. In contrast, the lower respiratory tract is significantly different from the adult constitution with far fewer alveoli and proportionately more conducting airways.

The upper airway (Fig. 17.2) is made up of the nasal cavity (the nose is the natural airway for all of us but young children in particular require a clear nasal passage to breathe), sinuses, the pharynx and the larynx. The entire upper airway and the conducting airways are lined with ciliated (respiratory) epithelium. Abnormalities in the cilia lead to blockage and obstruction, as these are required to ensure clearance of mucus (see Ciliary dyskinesias, below).

The main functions of the nasal portion of the airway are filtration, humidification and warming. Particles larger than 10 μm in diameter tend to impact in the upper airway and most are not inhaled into

Frontal sinus
Opening of ethmoid sinus
Nasal cartilage
Opening of maxillary sinus
Vestibule
Anterior nares
Upper lip
Mouth and oropharynx

Olfactory nerve and bulb
Sphenoid sinus
Adenoid vegetations
Opening of Eustachian tube in nasopharyngeal fold
Nasopharynx
Soft palate

Fig. 17.2 **Gross anatomy of the upper airway.**

the lower airway. The air reaching the trachea varies in temperature from around 6 to 30°C depending upon the minute ventilation, size of the child and ambient temperature. It is warmed to 37°C in the trachea and lungs. Heat from gases expired through the nose is extracted by use of a countercurrent exchange system.

Loss of control of the pharyngeal muscles, either due to pathology (e.g. cerebral palsy, muscular dystrophies) or deep sedation, leads to intermittent upper airway obstruction (stertor). Narrowing at the larynx leads to fixed upper airway obstruction (stridor – see later). In babies, the airway is maximally open when the head is held in a neutral position. As the relative size of the head decreases, the airway becomes maximally opened with increasing degrees of neck extension.

The conducting airways are made up of the trachea, bronchi and bronchioles that make up the first sixteen branches of the tracheobronchial tree. Cartilage is an important constituent of the larynx and the conducting airways and at birth this is significantly more floppy than in later life.

The trachea divides into two bronchi. The right bronchus is wider than the left and it is more vertical. Therefore, inhaled objects tend to fall into the right main bronchus. The bronchi divide into four lobar bronchi, which, in turn, subdivide into 16 segmental bronchi. After 16 subdivisions, we reach the terminal bronchioles which are capable of limited gas exchange.

The lower airways (divisions 16–23 of the airways) are where most gas exchange takes place. The formation of the lower airways is only partly complete at birth and alveolarization (the formation of new alveoli) continues until at least 2 years of age.

The lungs are surrounded by the visceral pleura. This is separated by a thin layer of pleural fluid from the parietal pleura, which covers the thoracic walls and upper surface of the diaphragm. Due to the considerable surface tension that exists, the pleura usually remain closely opposed. However, they can still slide easily over each other (think of two glass microscope slides separated by a little fluid – they slide easily over each other but are hard to pull apart). Fusion of the two layers by the production of fibrin leads to pain on movement (pleurisy). Separation of the pleura by either fluid (pleural effusion) or gas (pneumothorax) can also lead to pain, particularly on inspiration.

Physiology

Airway resistance and compliance

Airway resistance is a result of the frictional force which opposes the flow of air. Airway resistance must be overcome for air to flow. The resistance for laminar flow (most airflow in the airways is laminar under normal conditions) is described by Poiseuille's equation:

$$\text{Resistance} = \frac{8 \times \text{length} \times \text{viscosity of the gas}}{\pi \times (\text{radius})^4}$$

This predicts that resistance increases dramatically as diameter decreases. However, most resistance to airflow is offered by the trachea and larger bronchi. Although counterintuitive, this is due to the branching of the tracheobronchial tree, which means that the combined cross-sectional area of the smallest airways is sufficiently large to provide little resistance to flow. Whilst the airway diameter at the 23rd branching is only 0.4 mm in diameter, the total cross-sectional area is 4 m^2 as there are 300 million airways of this size. In contrast, the tracheal cross-sectional area is just 3 cm^2. Thus, under normal circumstances, most of the total airway resistance is offered by just 10% of the total lungs – the large conducting airways. This becomes important when considering the results of lung function testing (spirometry) – see below.

In young children, the decreased size of the airways results in overall increased resistance to flow. This is

coupled with a reduction in chest wall compliance. Under these circumstances the chest wall can become drawn inwards with each breath even in health. Obviously, this worsens if there are any additional factors that further increase airways resistance (e.g. bronchiolitis).

The compliance of the lung is a measure of how easily it can be distended. It is given by the formula:

$$\text{Compliance} = \frac{\text{Change in volume}}{\text{Change in pressure}}$$

During the first part of inspiration, a relatively greater pressure is required to generate airflow. Therefore, compliance varies depending upon the exact lung volume.

Compliance also varies with age. A newborn child has stiff lungs with very low compliance compared to a young adult. A typical adult male will have lung compliance of between 0.09 and 0.26 L/cmH_2O, whilst a newborn infant will have lungs that are more than 20 times less compliant with values of 0.005 L/cmH_2O.

Control of breathing

The primary control of breathing (Fig. 17.3) is via the autonomic nervous system. It is mediated mainly, but not exclusively, through neural centres in the brainstem. Recent studies have shown, however, the existence of other chemosensitive cells in, for example, the hypothalamus and the cerebellum, that are exquisitely sensitive to changes in hydrogen ion concentration. Carbon dioxide in the blood diffuses rapidly into the cerebrospinal fluid, where it reacts with water to release hydrogen ions. This accounts for the rapid respiratory response to changes in arterial carbon dioxide levels. Afferent input also occurs via peripheral chemoreceptors sensitive both to oxygen and carbon dioxide, which are located in the carotid and aortic bodies, irritant receptors in the upper and lower airways and mechanical receptors in the lungs and chest wall. These receptors facilitate the response to hypoxia, which is much less rapid than the response to carbon dioxide. As excess H^+ will only cross the blood–brain barrier slowly, therefore metabolic acidosis tends to be incompletely and slowly corrected. Autonomic control can be overridden by conscious control enabling, for example, speech and breath-holding to occur. Voluntary conscious signals are generated in the cortex and conducted to muscles of breathing via the corticospinal tract.

The rate and depth of normal quiet (tidal) breathing are controlled within the brainstem. During tidal breathing, the distribution of air within the lungs is determined by regional variation in airway resistance and lung compliance. In an upright child, the weight of the lungs ensures that the pleural pressure is more negative at the apex. This leads to relative over-distension at the apices with relatively reduced volumes at the bases. This is most prominent in
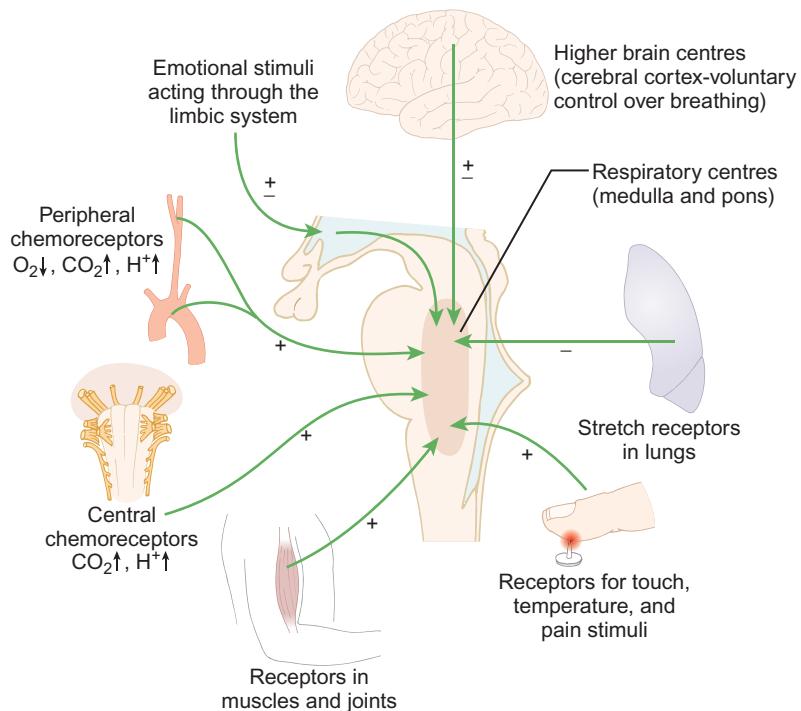
Fig. 17.3 **Control of breathing.** *(Adapted from Atlas of Clinical Sleep Medicine, Saunders 2010.)*

Emotional stimuli acting through the limbic system

Higher brain centres (cerebral cortex-voluntary control over breathing)

Respiratory centres (medulla and pons)

Peripheral chemoreceptors $O_2\downarrow$, $CO_2\uparrow$, $H^+\uparrow$

Central chemoreceptors $CO_2\uparrow$, $H^+\uparrow$

Stretch receptors in lungs

Receptors for touch, temperature, and pain stimuli

Receptors in muscles and joints

infancy and early childhood but is opposed by the rigid chest wall and stronger respiratory muscles in adult life. During infancy, any increases in airway resistance (usually as a result of airway narrowing, e.g. smooth muscle thickening and/or airway cell oedema) will result in a greater effort of breathing. The relatively weak intercostal muscles and compliant chest wall are unable to oppose the stronger contraction of the diaphragm, leading to the abdominal breathing and sternal/intercostal recession seen in infants with respiratory distress.

Question 17.2

Desaturation during sleep

A 14-year-old boy with Duchenne muscular dystrophy is admitted at 18.00 for a routine sleep study. You are called to review him at 02.00 during sleep because his oxygen saturations, which were 95% at the start of the study, are now dropping to 90%. He appears to be sleeping quietly. What is the most likely cause? Select ONE answer only.

A. Dependence upon accessory muscles to maintain ventilation

B. Diurnal variation in cortisol production leading to bronchoconstriction

C. Movement artefact

D. Obstructive sleep apnoea

E. Thromboembolic event due to immobility

Answer 17.2

A. Dependence upon accessory muscles to maintain ventilation.

Physiological recordings during sleep are more sensitive markers of respiratory failure in children with muscular dystrophies, as during the day they can 'assist' respiratory effort by recruiting accessory muscles. During sleep, this occurs to a lesser degree, thus normal daytime oxygen saturations are a much less sensitive measure of clinical status. Whilst additional oxygen will improve oxygenation, it will not address the likely coexistent hypoventilation. Although obstructive episodes can occur, they would be likely to be accompanied by an increased effort during attempted inspiration.

The role of the diaphragm

The major muscle of respiration is the diaphragm. At birth, fatigue-resistant striated muscle fibres account for only 10% of its muscle mass. This increases to 50% by early adulthood. Infants, therefore, will tire more

quickly and are at increased risk of apnoea and respiratory failure if the work of breathing needs to increase for more than a few minutes for any reason e.g. bronchiolitis or heart failure due to ventricular septal defect (VSD). The more compliant chest wall predisposes the immature airway to partial closure, particularly at the lung bases, leading to intrapulmonary shunting of blood through non-ventilated areas.

The diaphragm and accessory muscles are affected differently by sleep. During sleep, diaphragmatic function is largely preserved. This is essential for maintenance of adequate ventilation. Accessory muscle function is reduced, particularly during REM sleep. This may contribute to hypoventilation and ventilation–perfusion mismatching resulting in oxygen desaturation.

Positioning and oxygenation

The matching of ventilation with perfusion takes place within the airways and alveoli. Sudden changes cannot be instantly compensated for and may lead to ventilation–perfusion mismatch. The clinical consequences are not always obvious. Placing a child with respiratory distress in a horizontal position (lying them flat) leads to an immediate reduction of ventilation in the dependent lungs. This is not immediately accompanied by a change in lung perfusion, causing mismatch and potentially decreasing oxygen saturation levels.

Minute volume, tidal volume and lung capacities

In normal breathing, the volume of inspired air and expired gases that move in and out of the lungs each minute (minute volume) is a product of the volume of each breath (tidal volume) and the respiratory rate (breaths per minute).

From the age of five, lung volume changes can be measured using a spirometer (Fig. 17.4). The vital capacity (VC) and the forced expiratory volume in 1 second (FEV_1) can be measured spirometrically, but total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV) require different techniques (see below).

Gas exchange and diffusion

Exchange of gas across a surface is dependent upon the gradient of partial pressure across it, the surface area, and the magnitude of the diffusion distance. Gas transfer occurs by diffusion. Carbon dioxide is very water-soluble so diffuses more readily than oxygen across the membranes and is less affected by increases in diffusion distance, as occurs in pulmonary oedema. The differential changes seen in blood carbon dioxide
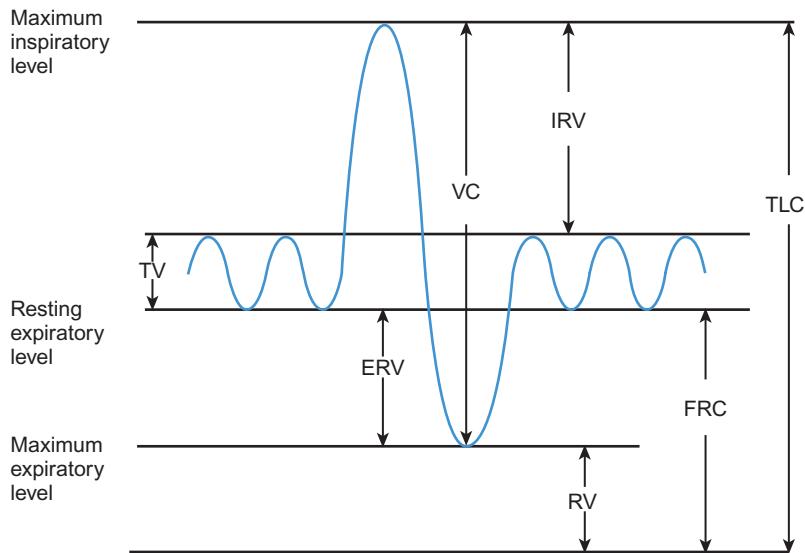
Fig. 17.4 Spirograph tracing showing tidal breathing followed by a deep inspiration and full expiration. The total lung capacity (TLC) is the maximum amount of air the lungs can accommodate. The tidal volume (TV) is the amount of air inspired and expired at each breath (usually 6–8 mL/kg). The expiratory reserve volume (ERV) is the amount of air that can be exhaled after normal, quiet expiration. The residual volume (RV) is the volume of air that remains in the lungs at the end of maximal voluntary expiration. The inspiratory reserve volume (IRV) is the amount of air that can be inhaled at the end of normal tidal inspiration. The vital capacity (VC) is the sum of IRV, TV and ERV.

Table 17.1 Causes of hypoxia and their response to oxygen supplementation

Cause of hypoxia	Effect of increase in FiO_2	Arterial CO_2
Alveolar hypoventilation	Correction of hypoxaemia	Increased
Impaired diffusion	Correction of hypoxaemia	Normal or decreased
Right–left shunt or ventilation–perfusion imbalance	Little change or no change	Decreased

and oxygen content in respiratory failure allow us to understand where a problem is likely to be occurring (Table 17.1). Children may present with a combination of problems.

Oxygenation of blood

Whilst some oxygen is dissolved in the plasma (3 ml/L of arterial blood) the vast majority is transported bound to haemoglobin. Oxygen saturation describes the percentage of haemoglobin molecules that are bound to oxygen. When all the possible sites for oxygen binding within haemoglobin are occupied, oxygen saturation is 100%. Oxygen saturation and oxygen content of blood do not share a linear relationship. The relationship is shown by the oxygen dissociation curve (Fig. 17.5). The sigmoidal shape demonstrates how haemoglobin is an effective carrier of oxygen.

Physiology of respiratory signs

The rate and pattern of breathing

Normal tidal volume is proportional to weight throughout life; usually 6–8 mL/kg. Energy requirements and therefore oxygen demand and carbon dioxide production are relatively higher in younger children. Respiratory rate is therefore higher in younger children and decreases with age.

The normal breathing pattern in children is variable. In an awake child, it is modulated by various baseline physical activities and is under conscious control. During sleep, physiological changes occur that vary with sleep state and are influenced by maturational changes in respiratory mechanics and control of breathing. Studies of healthy infants show that pauses and gaps in breathing up to 15 seconds during sleep are common but may be exaggerated in illness. The response to hypoxia is biphasic in infants, with an initial increase in respiratory rate followed by a decrease, often in association with apnoea.

In well children, minute ventilation falls 15% during sleep. In addition, during rapid eye movement (REM) sleep, there is an automatic decrease in accessory muscle activity accompanied by an increase in upper airway resistance as the muscles supporting the upper airway relax. Newborn infants sleep for approximately two thirds of the time, 60% spent in REM-equivalent sleep. By six months of age, most children sleep 11–14 hours per day, one third being REM sleep.

The typical adult sleeps 8 hours a day, 20% being in REM sleep.

Question 17.3

Respiratory signs in childhood

The following is a list of clinical respiratory signs:

A. Brassy cough
B. Clubbing
C. Coarse crackles
D. Crepitations
E. Grunting
F. Harrison's sulci
G. Moist cough
H. Stertor
I. Stridor
J. Wheeze

For each of the following statements, choose the most likely clinical sign from the list above. Note: each answer may be used once, more than once or not at all. Select ONE answer only for each question.

1. Narrowing of the small to moderate airways
2. Partial collapse of the upper airway
3. Acute accumulation of mucus in the moderate and large airways

Answer 17.3

1. J. Wheeze
2. H. Stertor
3. C. Coarse crackles
   See below for discussion.

Grunting and forced expiratory braking

It would be inefficient for airways and lungs to collapse completely during expiration, as re-inflation requires much more energy than widening/expanding a partially closed airway. Under normal circumstances, airway closure is opposed by maintenance of functional residual capacity (FRC) at a level above the point at which airways collapse. Collapse is increased in surfactant deficiency, bronchiolitis and pneumonia. FRC is reduced when lying supine, during anaesthesia and sleep.

Three factors influence the FRC: elastic recoil of the lung, the time allowed for expiration and the expiratory flow rate. Elastic recoil increases with age during childhood, making older children less susceptible to complete airway closure. Younger children oppose airway collapse by having higher respiratory rates, thus
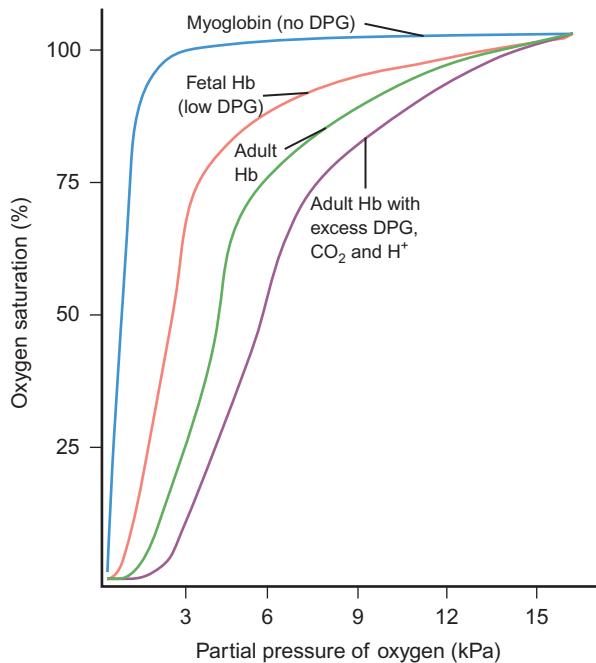
Fig. 17.5 The oxygen dissociation curve for myoglobin, fetal and adult haemoglobin (Hb) and the effect of acidosis, carbon dioxide and 2,3-DPG. Adult Hb (dark green line) unloads most of its oxygen between 6.5 and 2.5 kPa. Fetal Hb unloads its oxygen over a lower range (5.2 and 1.3 kPa). This is partly because fetal Hb does not bind 2,3 DPG efficiently and thus will tend to 'hold on' to oxygen at the expense of maternal Hb during pregnancy. Both will still deliver oxygen to the tissues as the tissue store for oxygen is myoglobin whose dissociation curve is even further to the left. If Hb binds oxygen more strongly, then the dissociation curve is shifted to the left. In these circumstances, oxygen is less readily delivered to the tissues. The oxygen dissociation curve is altered by the presence of hydrogen ions (the Bohr effect), 2,3-diphosphoglycerate (2,3-DPG) and carbon dioxide. Increases in these molecules shift the dissociation curve to the right. The net effect of this is that less oxygen remains bound to the Hb molecule at the same partial pressure of oxygen, therefore oxygen tends to be delivered better to areas with higher concentrations of hydrogen ions and carbon dioxide. Newly transfused blood is less efficient at delivering oxygen as it is low in 2,3-DPG.

reducing the time allowed for expiration. If this is insufficient to maintain FRC then infants will attempt to reduce expiratory flow rates using partial closure of the glottis or upper airway. This leads to grunting, as seen in neonates with respiratory distress, where glottic closure maintains a positive expiratory pressure but reduces expiratory flow.

Cough

Reflex or voluntary coughing requires coordination of a complex series of events. It begins with opening the glottis and a short inspiration to increase lung volume. Recruitment of lung volume is essential to maximize expulsion, as this allows elastic recoil of the lung to

assist muscular contractions. Next, the glottis closes and respiratory muscles contract, generating high intra-thoracic pressures. Shortly after closure, the glottis re-opens causing rapid decompression of the airways and a high velocity expulsion of gas. These rapid shifts in airway volume also cause a degree of small airway closure and compression, physically squeezing mucus and other intraluminal contents into the larger proximal airways. As expired air flows from the alveoli to the mouth, pressure within the airway falls. If there is airway obstruction, this pressure drop is greater, with a tendency for more proximal airways to collapse. This flow-related collapse during a forced expiration accounts for the brassy sound that occasionally occurs during maximal forced expiration in healthy subjects. It is more common if there is narrowing of the larger airways or if they are less rigid than usual as in bronchomalacia.

Cough is an important symptom in childhood. It is often informative to hear a cough (or see video recording of a cough), allowing one to distinguish between dry and wet coughs and wheezy or brassy coughs. Wet coughs suggest increased mucus within the airways, whereas the presence of wheeze suggests smaller airway obstruction. A brassy or barking cough suggests narrowing of the larger airways (this results in the barking cough of croup) and/or a degree of bronchomalacia.

Children with muscular weakness have reduced ability to cough. It is possible to measure the force of coughing by asking the child to cough as hard as they can into a peak flow meter, either using the mouthpiece or a mask. A cough expiratory flow of >270 L/minute in adults or older children predicts adequate cough strength. Physiotherapy may assist airway clearance in children with inadequate cough strength. Cough assist devices work on the same principle by generating a positive pressure followed by a negative pressure upon initiation of cough. They assist complete expansion of the airways and chest. This increases

airway clearance as the natural elastic recoil rapidly empties the chest. At the same time a degree of negative pressure is applied via a tightly applied face mask. With cooperation and practice, most children with weak cough find this a useful aid.

The cough reflex itself has peripheral and central components. Cough receptors exist throughout the respiratory system. There are irritant receptors in the larynx and large airways and stretch receptors within the lung parenchyma that stimulate cough in response to mechanical irritation or over-distension of the lung. The cough pathway involves cough receptors, mediators of sensory nerves, an afferent limb, the vagus nerve, the central cough centre and an efferent limb.

Normal breath sounds, crackles, stridor and wheeze

Normal breath sounds are described as vesicular. Dampening of the sound as it travels through normal lung tissue ensures that, as the lung deflates and flow diminishes, there is little or no sound towards the end of expiration (Fig. 17.6). In pneumonia, the lung parenchyma becomes filled with inflammatory cells and fluid, which conduct sound from the central airways more efficiently. Expiration is longer and the breath sounds on auscultation harsher and similar to airflow heard by listening over the trachea.

Crackles are discontinuous, non-musical additional respiratory sounds. There are two types of crackles. Coarse crackles are the easiest to hear, occurring when fluid or secretions collect in the large airways. In addition, coarse bubbling sounds can be heard that often clear or alter after coughing or taking a deep breath. Fine crackles or crepitations are higher pitched, explosive sounds. They are thought to occur when small closed airways suddenly open during inspiration. They are often obscured by other respiratory noises and are dampened by hyperinflation or the thicker chest wall of older children.

NORMAL VESICULAR BREATHING

Very short gap in sound at end of inspiration before expiration starts

Acoustic intensity

Inspiration   Expiration

BRONCHIAL BREATHING

Longer gap in sound as first part of expiration now is almost silent

Acoustic intensity

Inspiration   Expiration
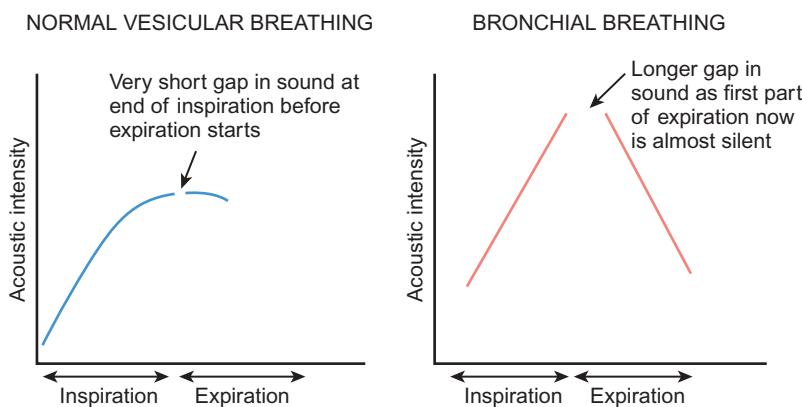
Fig. 17.6 Schematic representation of bronchial and vesicular breathing.

Wheeze is primarily heard during expiration and is a musical sound caused by flow limitation in the small intra-thoracic airways. It represents oscillation of the airway walls at the site of narrowing. In severe airway obstruction, wheezing also occurs in inspiration.

Obstruction of the extrathoracic airways results in either stridor (if it is fixed) or stertor (if it is intermittent). As with wheezing, if obstruction becomes severe it may become biphasic. As severity increases, flow reduces, as do the abnormal noises. A silent chest may indicate very severe airway obstruction.

Investigations

The investigation of respiratory disease can be complex. However, there are some non-invasive tests that can provide very useful information to the clinician. The following gives an overview of the types of investigation that may be encountered and a brief description of how they might apply to clinical practice.

Common investigations are:

- Oxygen saturation – for detection of hypoxaemia and monitoring response to oxygen therapy. Non-invasive and allows continuous monitoring (see Chapter 3, History and examination).
- Vital signs – heart rate, respiratory rate and temperature.
- Blood gases – for direct measurement of arterial pH, PaO_2 and $PaCO_2$. Especially important in intensive care for patients on respiratory support and when sample is taken from an arterial line. Samples taken from a peripheral artery need to be interpreted in conjunction with clinical features, as will be affected by the infant crying.
- Oxygenation index – see Chapter 6, Paediatric emergencies and critical care.
- Spirometry – widely used in outpatient settings.

Spirometry and other tests of lung function

Question 17.4

Pulmonary function tests

Concerning pulmonary function tests, which ONE of the following measures is the most sensitive marker of small to moderate airways obstruction:

A. Forced expiratory flow (FEF_{25-75})

B. Forced expiratory volume in 1 second (FEV_1)

C. FEV_1:FVC ratio

D. Forced vital capacity (FVC)

E. Peak expiratory flow rate (PEFR)

Answer 17.4

A. Forced expiratory flow (FEF_{25-75}). See below for discussion.

Question 17.5

Spirometry

Which ONE of the following measurements can be obtained with a spirometer:

A. Forced vital capacity

B. Fractional excretion of nitric oxide

C. Functional residual capacity

D. Residual volume

E. Total lung capacity

Answer 17.5

A. Forced vital capacity. See below for discussion.

A peak expiratory flow meter and spirometer (Fig. 17.7) allow the measurement of:

- Peak expiratory flow rate (PEFR)
- Forced vital capacity (FVC)
- Forced expiratory volume in 1 second (FEV_1)
- Forced expiratory flow (FEF_{25-75})

The forced expiratory flow (FEF_{25-75}) is the mean maximal flow in the middle 50% of the FVC and is more sensitive but more variable than FEV_1 or PEFR in assessing obstruction of the small- to moderate-sized airways.

To generate a PEFR, a child must give a short sharp expiration into the device. The measured value reflects the maximal flow able to be generated in litres per minute. PEFR is much less sensitive a marker of airway obstruction than FEV_1 or indeed the shape of the flow–volume curve and is used less than in the past.

To generate an adequate flow–volume curve, a child must take a maximal inspiration and then exhale into a mouthpiece as hard as possible and for as long as possible. The volume and flow of exhaled breath are measured; for reproducibility, there should be three attempts producing results within less than 5% error. Most children are able to perform good quality spirometry/flow–volume loops from 5 years of age. The first 25–35% of expiration, which includes measurement of the PEFR, is effort dependent. The remaining two thirds of the flow–volume curve is effort independent.

Spirometry is a sensitive way to assess airway narrowing. Two main patterns are recognized – obstruction and restriction. The most common is an obstructive picture (Fig. 17.8). Asthma causes reversible
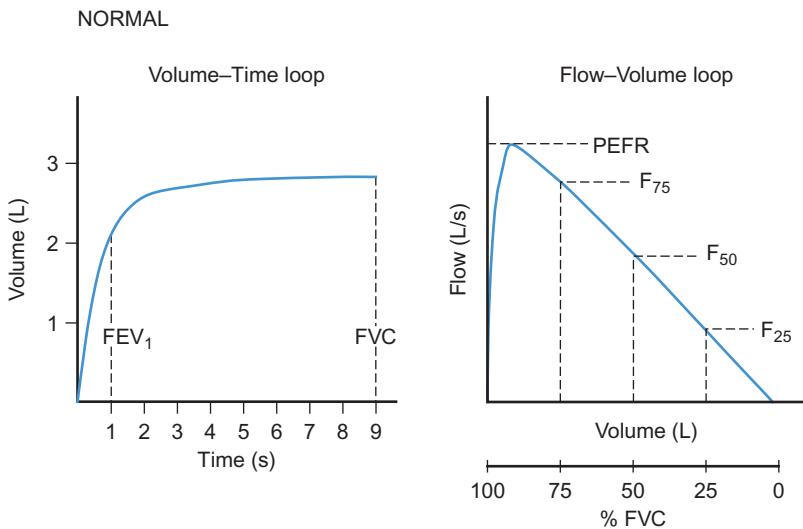
NORMAL

Fig. 17.7 Normal volume–time and flow–volume loops.

OBSTRUCTIVE AIRWAY DISEASE
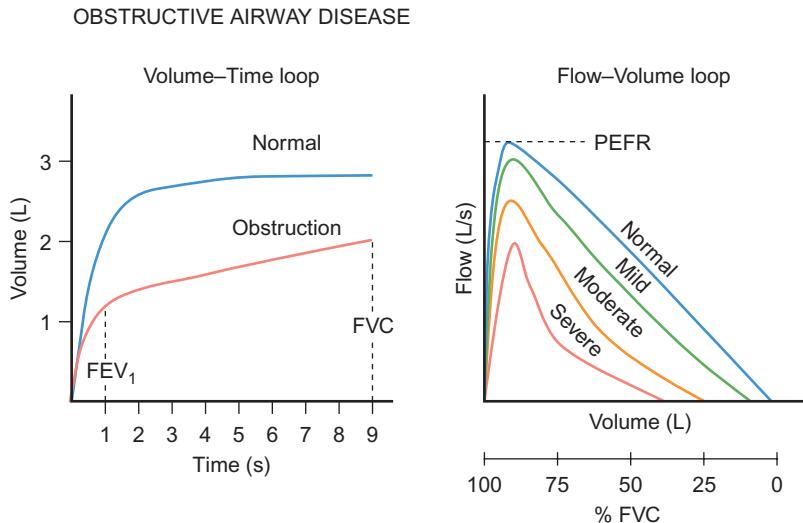
Fig. 17.8 Typical volume–time and flow–volume loops in obstructive airway disease. In obstruction, flow is reduced compared to normal values (or the personal best value of the child measured previously), but there is relative preservation of the total lung volume. Thus, FEV_1 is reduced more, as a proportion of the expected value, than the FVC.

obstruction, hence the value of diagnosis confirmed spirometrically before and after salbutamol usage to show improvement in the post-salbutamol measurement. Depending upon the guideline used, an increase of more than 8–12% in FEV_1 following a bronchodilator is considered clinically significant and confirms a diagnosis of asthma.

Airway smooth muscle is seen from birth and functional β-adrenoceptor activity has been documented from infancy. Whilst the FEV_1 is reduced in obstructive airway disease, the FEF_{25-75} is reduced even more (see Fig. 17.8). The ratio of FEV_1 to FVC is a useful measure,

as it not only gives an indication of severity but 'tracks' throughout life. Older children with severe persistent asthma tend to have lower levels of this ratio (<45%) than those with moderate or mild disease (70–75%).

The second, less common abnormality detected is that of restriction (Fig. 17.9), in which there is a reduction of both flow (FEV_1) and total lung volume (FVC). The flow–volume loop is the same shape as normal but is smaller. Diseases where restriction is seen are muscular weakness states, where the chest wall is more rigid or where there are interstitial changes, as in sarcoidosis.

Fig. 17.9 Typical volume–time and flow–volume loops in restrictive airway disease.
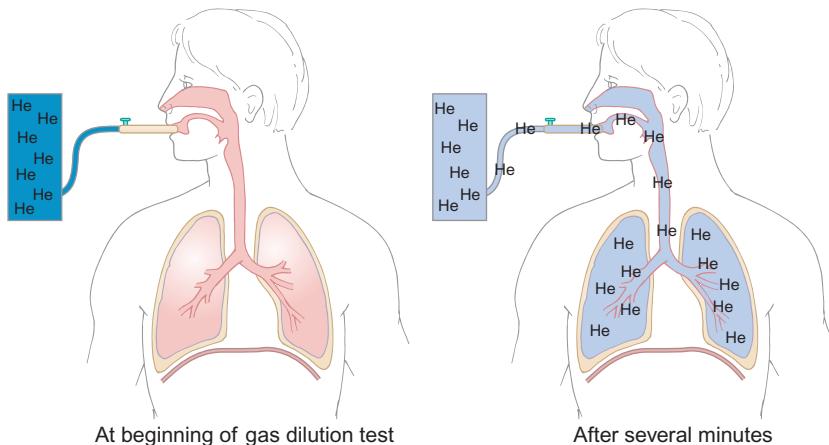
Fig. 17.10 Principles of the gas dilution technique. Gas dilution is a method of determining those lung volumes that cannot be determined from spirometry. The subject is connected to a spirometer containing a known concentration of helium, or other inert and insoluble gas. After several minutes of breathing, gas concentrations in the lung and spirometer equilibrate. From the law of conservation of matter, we know that the total amount of helium before and after is the same. Therefore, the fractional concentration × the volume before = the final fractional concentration × the volume.

Gas dilution and whole body plethysmography (Fig. 17.10)

FRC, TLC and RV can be determined using gas dilution methods or whole body plethysmography.

Although gas dilution methods are relatively simple to perform and interpret, they are time-consuming and only valid if there is no leak around the mouthpiece. They are less commonly used than whole body plethysmography (Fig. 17.11). This technique relies on Boyle's law, which states that for a given mass of gas, the product of the volume and the pressure is a constant. Thus, by measuring pressure and volume changes during breathing against a closed shutter, lung volumes can be calculated.

Lung clearance index

Lung clearance index (LCI), also known as the 'multiple breath inert gas washout technique' is a recently developed, highly sensitive, measurement of lung function, which can be performed at any age from infancy to adolescence and throughout adult life. Its principal use is to detect inhomogeneity of expired gas excretion either due to structural abnormalities or long-term lung disease. The patient inspires an inert
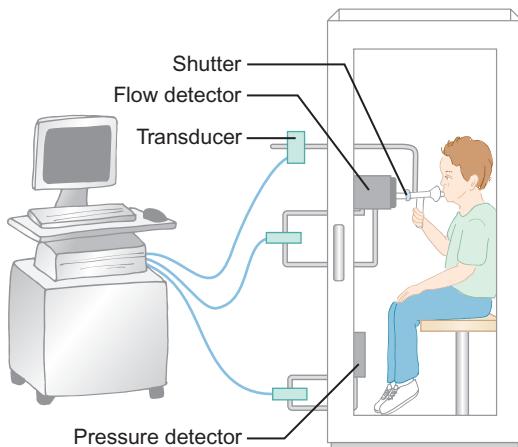
Fig. 17.11 A patient using a whole body plethysmograph. The child sits within a sealed rigid transparent box and breathes through a mouthpiece, which contains a shutter and pressure transducer. Asking the child to breathe (pant) against a closed shutter at the end of a normal tidal breath allows measurement of alveolar pressure. The small pressure changes produced by compression of the trapped air by respiratory muscles can be converted to changes in lung volume and FRC can be calculated by comparison with the effect on a known volume of air within a calibration device. Body plethysmography can measure the total volume of air in the chest, including gas trapped in bullae and it can be performed quickly. Drawbacks include the complexity of the equipment as well as the need for the patient to sit in a small enclosed space.

tracer gas such as sulphur hexafluoride (SF_6) and the LCI is calculated as the ratio of the cumulative expired volume needed to clear the lungs of the tracer gas divided by the FRC. Normal values are remarkably constant throughout life. It is an excellent tool for the detection of early abnormalities in cystic fibrosis and for long-term follow up of chronic lung diseases over many years.

In restrictive lung diseases, lung expansion is reduced and TLC is smaller than expected for age, gender and height. RV (residual volume), which reflects airway closure on expiration, is increased with airway narrowing. The ratio of RV to TLC is a sensitive and early indicator of hyperinflation, which is seen in obstructive lung diseases.

Measuring the alveolar–arterial gradient

The alveolar–arterial gradient is often used in the ITU setting when the exact nature of the underlying respiratory pathology is sought. It is relatively simple to calculate and is sometimes calculated automatically and displayed on arterial blood gas results.

> **Box 17.1 Clinical examples of (A–a) DO$_2$**
>
> **Example 1**
>
> A 12-year-old boy with progressive muscle weakness presents with respiratory failure. He has an arterial PaO$_2$ of 18.5 kPa in 32% oxygen and a PaCO$_2$ of 8 kPa.
>
> His (A–a) DO$_2$ = 32 (0.94) – (8 / 0.8) – 20 = 30 – 10 – 18.5 = 1.5 kPa.
>
> There is pure alveolar hypoventilation as the (A–a) DO$_2$ is normal and the PaCO$_2$ is raised.
>
> **Example 2**
>
> A 4-month-old girl presents with bronchiolitis. She has an arterial PaO$_2$ of 12 kPa in 80% oxygen (via headbox) and a PaCO$_2$ of 8 kPa.
>
> Her (A–a) DO$_2$ = 80(0.94) – (8 / 0.8) – 12 = 75 – 10 – 12 = 53 kPa.
>
> This child has a combination of alveolar hypoventilation (raised CO$_2$) and ventilation–perfusion mismatching.

In healthy children without right-to-left shunting, the diffusion of oxygen across the alveolar membrane is remarkably efficient and can be determined by comparing the difference between the alveolar oxygen concentration (close to the inspired oxygen concentration) and the arterial oxygen concentration. This value, the alveolar–arterial gradient, is small, usually 1–2 kPa. The alveolar oxygen concentration is approximately given by the formula:

$$\text{Alveolar O}_2 = \text{Inhaled O}_2 - [0.8 \times \text{Arterial CO}_2]$$

Water vapour in the alveoli reduces the alveolar oxygen concentration by 6%. The alveolar–arterial PO$_2$ difference (A–a) DO$_2$ is approximated by the formula:

$$(\text{A}-\text{a})\,\text{DO}_2 = [\text{Inspired oxygen \%} \times 0.94] - [\text{Arterial CO}_2/0.80] - [\text{Arterial O}_2]$$

Some clinical examples of alveolar–arterial PO$_2$ difference are shown in Box 17.1.

In most disease states, the alveolar–arterial gradient cannot be relied upon to determine the cause of hypoxaemia as it is also influenced by ventilation–perfusion mismatching and right-to-left shunting of blood within the lungs. Therefore, a marker gas is required to study this in many circumstances. The diffusion capacity of the lungs is more reliably estimated by examining the diffusion of carbon monoxide from a single inhalation (the single breath carbon monoxide diffusion test).

Diseases and disorders of the respiratory tract

Respiratory diseases are common and account for >25% of acute medical care. They can be placed into four groups: acute infections, chronic infections, inflammatory states and other causes.

Respiratory infections

Epidemiology and aetiology

The respiratory tract is the commonest source of childhood infections, including otitis media, nasopharyngitis, tonsillitis, sinusitis, bronchiolitis and pneumonia. Whilst many viruses are capable of causing symptoms, the most frequent pathogen is the rhinovirus (RV), which belongs to a family of small RNA viruses (picornaviruses). Respiratory syncytial virus (RSV) is the commonest cause of bronchiolitis and is an important nosocomial pathogen during the winter. Pneumonia can be viral or bacterial, and infections can involve multiple viruses or viral/bacterial co-infection. Some pathogens are seasonal, such as RSV and influenza. Routine seasonal influenza vaccine for younger children was introduced in the UK in 2013 and should result in a decrease in the burden of infections. There are a number of vaccines against RSV under development.

Pathophysiology

Respiratory infections usually begin with invasion of the pathogen in the nasopharynx. The initial local immune response involves an influx of neutrophils and cytokine secretion, in particular IL-8, IL-1β and IL-6, resulting in coryzal symptoms. If the organism is particularly virulent or expresses the appropriate surface molecules for receptors found elsewhere in the respiratory tract, or if there is absence of systemic or mucosal immunity to the organism, the infection can spread. Pulmonary defence mechanisms include physical and physiological barriers (e.g. nasal hairs, humidification, mucus, cilia) in addition to the immune mechanisms described previously. Alveolar fluid contains antimicrobial compounds such as surfactant, complement and lysozyme, while IgA plays a major role in protection in the upper airway – hence children with IgA deficiency have increased respiratory infections.

Complications and outcomes

A common cold will usually resolve within 10–14 days. Viral infections, including bronchiolitis and pneumonia, generally only require supportive therapy. Bacterial otitis media can rarely progress to mastoiditis

and possibly meningitis. Sinusitis can develop into periorbital or orbital cellulitis and then intra-cranial infection if untreated. Bacterial pneumonia may be complicated by bacteraemia, empyema, necrotizing pneumonia, and lung abscesses. It is therefore important to differentiate bacterial from viral infections, although this is problematic due to the difficulty in obtaining sterile samples from the respiratory tract, and the presence of potential pathogens in the nasopharynx of healthy children. Rhinovirus infection leads to a more significant illness in children with asthma; the virus penetrates deeper into the lungs, as their interferon-gamma response is blunted. It accounts for up to 60% of asthma exacerbations during childhood.

Case history

Tonsillitis

A 3-year-old boy presents with a 2-day history of fever and anorexia. He does not appear toxic-looking and has enlarged red tonsils with no exudate. Examination is otherwise normal. He is discharged with a diagnosis of viral upper respiratory tract infection. He returns 2 days later with persistent symptoms. He remains systemically well, and has exudates on his tonsils and has developed tender cervical lymph nodes. He is treated with a 10-day course of oral penicillin V for presumed group A streptococcal tonsillitis.

What criteria are used to decide on antibiotic treatment of tonsillitis?

Management of pharyngitis/tonsillitis is guided by the Centor criteria in the UK. Antibiotic treatment is advised if 3 or more of the 4 criteria are present: tonsillar exudates; tender anterior cervical lymphadenopathy or lymphadenitis; fever; absence of cough. First line treatment is with amoxicillin or penicillin V orally for 10 days, which ensures elimination of Streptococcal species. While UK guidelines (NICE CG69, 2008) do not recommend testing, some countries include throat culture and/ or rapid antigen detection tests to help determine need for treatment.

Upper airway obstruction

This is common in childhood. Narrowing of the extrathoracic airway leads to increased respiratory effort and inspiratory respiratory noises. Intermittent obstruction of the nasopharyngeal area by tonsils, adenoids or the soft palate leads to stertor (snoring).

This is more evident during sleep, as relaxation of the pharyngeal muscles holding open the upper airway leads to a worsening of airway obstruction. Narrowing of the lower portion of the upper airway (epiglottis, larynx or trachea) leads to a more musical and continuous breathing from obstruction – stridor. As muscle tone contributes less to airway patency, it is less affected by sleep.

Most causes of acute onset stridor are inflammatory and will benefit from treatment with steroids (either oral or inhaled). Oral dexamethasone has the advantage of a significantly longer half-life (36 to 72 hours) than other treatments (prednisolone has a half-life of 12 to 36 hours). Studies have shown it to reduce need for hospitalization and re-attendance. Both work quickly and some relief will be apparent within 90 minutes. A more rapid improvement can be achieved with nebulized adrenaline. This adrenoceptor agonist causes local vasoconstriction. Deposition of larger droplets from a nebulizer into the upper airway (>5 μm) has an almost immediate effect on local blood flow, which increases airway diameter. Its effects are only short-lived but systemic absorption leads to tachycardia and agitation. In all causes of upper respiratory obstruction, if the child is upset, his clinical condition will deteriorate. Keeping calm and avoiding unnecessary examination is a very important part of any plan. Do not try to visualize the upper airway as it may precipitate respiratory obstruction.

View from back
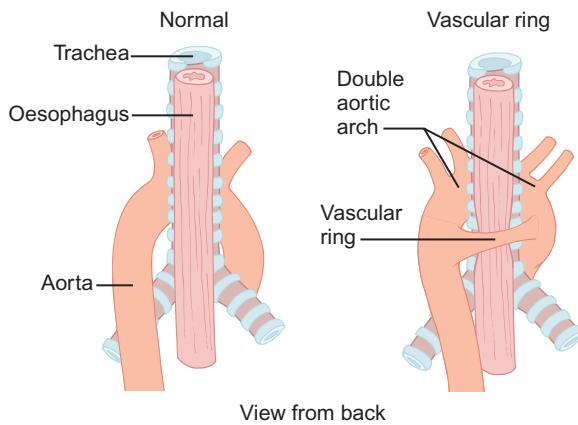
Fig. 17.12 **The anatomy of a vascular ring. Under normal circumstances, the arch of the aorta loops forward over the left main bronchus. A double aortic arch is one of many possible variations in the anatomy of the pulmonary or systemic vessels that can lead to entrapment of the trachea and prevent normal growth. Usually the oesophagus is also entrapped, which causes indentation of the posterior oesophageal wall on barium swallow, but only rarely causes difficulty in swallowing.**

Case history

Persistent stridor

Anna, 2 months old, has had persistent noisy breathing since the first week of life. The stridor was initially intermittent and only occurred with crying or when she was lying supine, but has now become more persistent and more severe, and has become more pronounced over the last 12 hours. Anna has a mild fever and some indrawing at rest, the stridor is both inspiratory and expiratory and you note that she lies with her neck extended. Her weight has dropped from the 25th to the 2nd centile.

What are the causes of her stridor?

She has persistent stridor, which may be caused by narrowing of the lower portion of the upper airway. In view of her age, this is most likely to be a congenital abnormality. Laryngomalacia accounts for at least 90% of cases, but other causes are subglottic stenosis, subglottic web, subglottic or laryngeal haemangioma, vascular ring, tracheal stenosis, vocal cord paralysis.

Why is she not thriving?

Her recent clinical deterioration may be due to an intercurrent respiratory infection. In addition, her chronic symptoms appear to be worsening. Persistent respiratory distress may hamper feeding and the increased effort of breathing will increase energy expenditure (and therefore calorie requirement). The worsening of symptoms suggest that either a lesion is enlarging within the airway (e.g. haemangioma) or that some part of the upper airway is not enlarging as Anna grows, such as a vascular ring (Fig. 17.12).

Bronchiolitis

Question 17.6

RSV bronchiolitis in children

Concerning respiratory syncytial virus (RSV) bronchiolitis in children, which of the following statements are true (T) and which are false (F)?

A. Initial infection produces life-long immunity
B. Is commonest in the first 2 months of life
C. Leads to persistent wheeze in the majority of infants
D. Occurs most commonly in the summer months
E. Results in neutrophilic inflammation within the airways

A. False; B. False (as maternal IgG antibodies offer passive immunity); C. False (although some do go on to wheeze); D. False; E. True. See below for discussion.

The bronchiolitis season in the UK is November to March (Fig. 17.13). Every year, 20,000 infants (usually in the first 6 months of life) are admitted to UK paediatric wards with bronchiolitis. There is a characteristic cough and on auscultation fine crackles and wheeze. As a clinical syndrome, the term bronchiolitis has different definitions in different countries. In the UK, the most widely accepted definition is 'a seasonal viral illness characterized by fever, nasal discharge and dry, wheezy cough'. There is no upper age limit for this diagnosis, but most hospital admissions occur in children in the first two years of life. The most common causative agent is respiratory syncytial virus (RSV), but human metapneumovirus, rhinovirus and adenovirus have also been implicated. Identification of the virus responsible is not helpful in reducing cross-infection or in influencing management decisions.

There are three major components of the immune response: innate immunity, a cell-mediated response and a humoral (antibody-mediated) response.

Pulmonary surfactant is the first line of innate lung defence. Surfactant protein A binds to surface oligosaccharides on a range of pathogens and enables both opsonization and complement activation. Neutrophils are the predominant airway leukocytes on histology. In RSV infection, neutrophil chemotaxis is dependent on the production of IL-8, by respiratory epithelial cells and macrophages. The role of the humoral immune system in bronchiolitis is complicated. All term babies have specific RSV-neutralizing antibodies following placental transfer of maternal immunoglobulin. This may offer early protection to infants but most severe

RSV disease occurs between 2 and 6 months of age, when protection from maternal antibody is declining. The individual's humoral response is important in protecting against re-infection. RSV infection provokes the production of serum antibodies in even the youngest children, although the titres in infants are low compared to older children and adults.

During primary infection, serum IgM antibody is present within a few days and remains detectable for 1–2 weeks. IgG antibody appears in the second week, peaks in the fourth week and declines after 1–2 months. Serum RSV-neutralizing antibodies appear to have a protective effect, as children with high titres (>1/100) are less likely to develop bronchiolitis than those with lower titres.

The pathological culmination of the inflammatory response to RSV infection in the lung is narrowing of the distal airways, sloughed necrotic epithelium, mucus secretion and mucus plugging. Alveolar hypoxaemia in young babies leads to apnoea. Oxygen is the only treatment of proven benefit. Nebulized hypertonic saline is being trialled but to date is non-proven. The increase in critical closing volume of the airways seen in babies with bronchiolitis can be partially opposed by chest hyperinflation by the infant or the provision of continuous positive airway pressure (CPAP).

For the majority, there is complete resolution. Some infants admitted to hospital continue with episodes of cough and wheeze over several years.

Inflammatory states

Asthma

Asthma is a complex polygenic disorder. It is the result of interactions between many genes and environmental triggers. Whilst some asthma aspects are heritable, monozygotic twin studies demonstrate a concordance rate of only 40–50%. Environment seems to play a pivotal role in determining overall asthma risk. Epidemiological studies focusing on the rapid urbanization of agricultural communities have revealed several clues about the origins of asthma, and these are discussed in Chapter 16, Allergy. Complementary laboratory studies have improved our understanding of its pathogenesis and of related atopic diseases, eczema, hay fever and food allergy.

Whilst asthma is common, there is no universally accepted clinical definition. Diagnosis can be particularly problematic in younger children. It causes variable obstruction of the small- to moderate-sized airways by a combination of eosinophilic and neutrophilic inflammation, together with contraction of the bronchial smooth muscle in response to a variety of stimuli. Not all parents report wheezing accurately
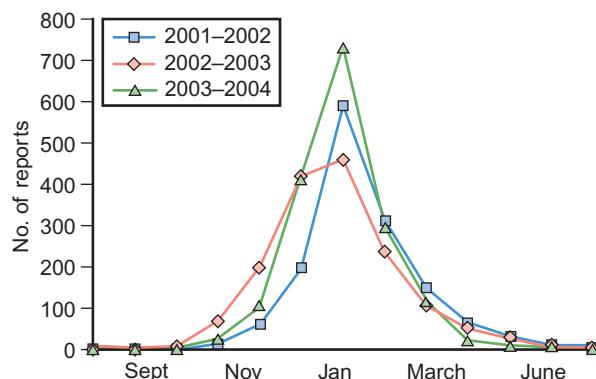
Fig. 17.13 RSV laboratory reports to Health Protection Scotland in a 4-week period between 2001–2004.

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and many children who wheeze do not have asthma (see Chapter 3, History and examination).

How should we treat asthma?

Asthma is an inflammatory disease which leads to airway hyperreactivity (AHR) and bronchospasm. Control of asthma is an important aspect of optimal care. The aim of therapy is to prevent symptoms (daytime, night-time and limitations of normal physical activity), prevent exacerbations (need for hospital admission or unplanned medical care and oral steroids) and maintain normal lung function. This should be achieved in most children with small doses of regular inhaled corticosteroids. The mechanism of action and the delivery of asthma medications are discussed in more detail later.

Parenchymal diseases

Chronic obliterative bronchiolitis

Chronic obliterative bronchiolitis (COB) is a rare condition where a child presents with cough, wheeze, pyrexia and tachypnoea which fail to resolve. Known causes include infection (particularly adenovirus) and chronic aspiration. It results in characteristic changes on the high resolution CT scan (HRCT), with patchy hyperinflation with a characteristic mosaic attenuation appearance of the lungs from adjacent lobes being either normal or hyperinflated.

Lung function shows very severe irreversible obstruction. Treatment is supportive, with many children requiring oxygen therapy and, in a few cases, eventual lung transplantation.

Interstitial lung disease (diffuse parenchymal lung diseases)

Interstitial lung disease (ILD) is exceptionally rare in childhood, affecting about 1 in 100,000 children. It occurs due to a wide variety of pathological causes. In the light of more recent understanding of these aetiologies, a new term – 'diffuse parenchymal lung diseases' (DPLD) – has been introduced. Approximately a third of patients present in the first two years of life and the aetiology of 40–50% remains unknown. Known genetic defects which cause DPLD include abnormalities in surfactant B (SP-B), surfactant protein C (SP-C), surfactant protein ABCA3 and thyroid transcription factor-1 (TTF-1). These disorders are characterized by inflammatory and fibrotic changes that affect alveolar walls. There is usually a gradual decrease in lung compliance that results in increased work of breathing followed by a fall in arterial oxygen saturation. The diagnosis is suggested by a combination of failed response to treatment, poor growth, cough, tachypnoea, reduced oxygen saturations, finger clubbing and fine crackles.

As with adults, DPLD in childhood may present as extrinsic allergic alveolitis. Care should be taken to ensure there is no exposure to potential allergens, particularly fungal spores and pigeon droppings. DPLD may complicate systemic diseases, including juvenile dermatomyositis, sarcoidosis, systemic lupus erythematosus and scleroderma. It can also occur as a reaction to drugs (azathioprine, methotrexate) or as a consequence of radiotherapy to the chest.

Radiological changes tend to be non-specific, including generalized ground glass shadowing with reticular nodular infiltrates and honeycombing on CXR. HRCT provides more detail, but to establish a specific tissue diagnosis, a lung biopsy is required.

Older children may present with any number of respiratory signs. They frequently have finger clubbing and a restrictive pattern on spirometry. Two thirds of children respond to a combination of corticosteroids with or without hydroxychloroquine.

Chronic infection

Bronchiectasis occurs when there is abnormal dilatation of the bronchi. It can be suspected on clinical grounds (persistent moist cough, clubbing and focal chest signs) but is usually diagnosed using HRCT scanning (Fig. 17.14). Bronchiectasis arises from chronic airway inflammation that is driven by persistent infection. This leads to intense neutrophilic inflammation within the airways. It has been proposed that most bronchiectasis arises because a vicious cycle of infection and inflammation develops within the lung leading to impaired mucociliary clearance, followed by bacterial proliferation and more inflammation. Any condition that results in either impaired mucociliary clearance or abnormal response to infection can lead to bronchiectasis. Once bacterial growth is established within the mucus, clearance will be impaired by a combination of factors.

Widening of the bronchi in the right middle lobe
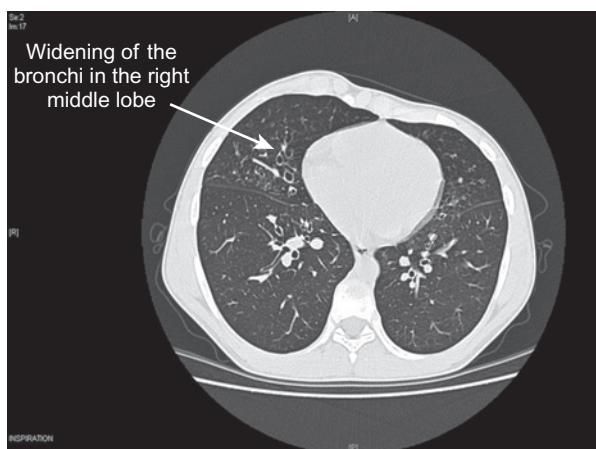
Fig. 17.14 High resolution CT scan of the chest demonstrating bronchiectasis.

Table 17.2 Causes of bronchiectasis

Post-infectious – measles, pertussis, severe pneumonia
Immune dysfunction – hypogammaglobulinaemia, neutrophil dysfunction, HIV infection
Impaired mucociliary clearance – primary ciliary dyskinesia, cystic fibrosis
Systemic disorders – rheumatic arthritis, inflammatory bowel disease
Undiagnosed foreign body or recurrent aspiration

Haemophilus influenzae, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* release mediators which directly inhibit ciliary function. They also lead to increases in local mucus production and the production of interleukin-8, which recruits neutrophils to the site of inflammation. In contrast to asthma, chronic infection is characterized by a neutrophilic inflammation. The causes of bronchiectasis are listed in Table 17.2.

Cystic fibrosis

Cystic fibrosis (CF) is a lethal single gene disorder inherited in an autosomal recessive manner. It is caused by mutations in a single gene on chromosome 7, which encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CFTR is an ATP-regulated channel which allows certain anions, in particular chloride, to flow down their electrochemical gradient. This is achieved through conformational changes which open and close a gate regulating transmembrane flow. CFTR is found in epithelial cells, where it allows chloride and other anions to move out of the epithelial cell into the mucus which covers it. Sodium ions will follow passively, increasing the mucus electrolyte concentration, and mucus will be viscid. As the epithelial cells line the lung, pancreas, skin and gastrointestinal and reproductive tracts, these systems are affected. CFTR is located on epithelial cell membranes but not on cilia. The chloride concentration in sweat is raised, the basis of the sweat test, the diagnostic test for cystic fibrosis before DNA analysis became available.

Approximately 1 in 25 Caucasians in the UK possesses one abnormal copy of the CFTR gene, which leads to a population frequency of approximately 1 in 2500 newborns. To date, over 1900 possible mutations of this gene have been described, of which 1300 are thought to be pathogenic. Specific mutation frequencies vary between different geographical locations and ethnic groups. Worldwide, very few CFTR mutations (<20) have a frequency of greater than 0.1%. ΔF508 (deletion of three nucleotides which code for phenylalanine at position 508 in the amino acid sequence) is the most common CFTR mutation. It accounts for nearly two thirds of the mutations in individuals with CF, with a clear gradient in distribu-tion even across Europe, with a frequency of 25% in Turkey rising to a frequency of 88% in Denmark. Although CFTR mutations are relatively common, *de novo* mutations are exceptionally rare.

CF screening is performed on the blood spot taken on day 5 of life. If the immunoreactive trypsinogen (IRT) is raised, a further sample is taken, and if again raised, genetic screening is performed.

Case history

Cystic fibrosis

Emma was diagnosed with cystic fibrosis following blood spot screening which confirmed that she is homozygous for the ΔF508 mutation. She was started on pancreatic enzyme supplements (Creon) and was following her growth centiles. At 18 months, she develop a cough and her mother brings her to your clinic. She has a fruity cough and on auscultation crepitations are heard on the right side of the chest. Her weight has also dropped slightly below her previous centile. She has a CXR and sputum is sent for culture and sensitivities. Emma's chest X-ray shows right lower lobe consolidation.

She is commenced on oral antibiotics initially and is reviewed one week later. She is still unwell and her recent sputum has grown *Pseudomonas aeruginosa* for the first time.

What respiratory pathogens is she particularly susceptible to?

She is particularly prone to infection with bacterial pathogens. Commonly isolated organisms include *Staphylococcus aureus* and *Haemophilus influenzae* in the early years, *Pseudomonas aeruginosa* later and *Burkholderia cepacia* and *Stenotrophomonas maltophilia* as lung disease progresses.

Her recent sputum has grown *Pseudomonas aeruginosa* for the first time. What treatment would you give her?

Initially, treatment with flucloxacillin or cephalosporins is often successful, but once *Pseudomonas* is isolated, antibiotic choices become more limited. *Pseudomonas aeruginosa* often becomes resistant to oral antibiotics (ciprofloxacin), as its genome hosts multiple resistance genes which are activated once colonization is established. Most of the bacteria present during infective exacerbations are found within the mucus itself. Mucolytics such as DNAse (dornase alfa) or a short course of hypertonic saline may aid breakdown of the mucus plugging, allowing physiotherapy to clear it more easily. Both reduce sputum viscosity and therefore improve its clearance.
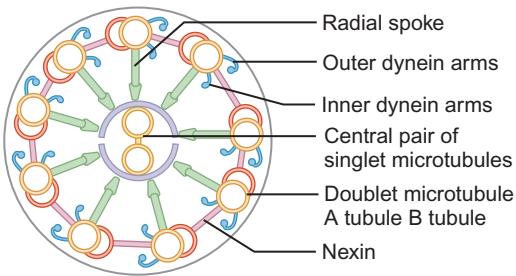
Fig. 17.15 Diagrammatic representation of normal ciliary ultrastructure.

Later reduced fertility; males and females

Clinical manifestations of primary ciliary dyskinesia

Fig. 17.16 Clinical manifestations of primary ciliary dyskinesias. Children with PCD have recurrent sinopulmonary infections. Boys may have reduced fertility due either to sperm immotility or vas deferens abnormalities. Almost half of all affected children have laterality defects such as situs inversus. This is thought to occur because the functional defects seen in PCD reduce the effectiveness of nodal cilia during embryogenesis. Normally functioning cilia have a fast 'upstroke' followed by a slower recovery phase in the opposite direction. The normal cilial beat frequency is between 12 and 14 times/ second. PCD is a genetic disease, but although several causative genes have been described, the mainstay of diagnosis remains the visualization of abnormal ciliary function demonstrated by electron microscopy of cilia from brush samples from inside the nose.

CF is a multi-system disease. Throughout life a number of organ systems can be affected. In early childhood there are problems with the exocrine pancreas (pancreatic insufficiency) in >90% of children. Ten per cent present at birth with meconium ileus. Others may need treatment with laxatives in childhood to prevent distal intestinal obstructive syndrome. CF-related diabetes presents increasingly with age, as does hepatic disease. Modern management has led to an increasing life expectancy, on average, of at least 40 years in the best treatment centres.

Ciliary dyskinesias

Mucus is one of many defence mechanisms within the lung which helps prevent infection and reduces direct chemical damage from toxins. A thin layer of mucus (approximately 5 μm thick) 'floats' on top of an even thinner layer of extracellular fluid. Mucus is produced by the goblet cells and is a complex mixture of glycosylated proteins called mucins. Inhaled particles of more than 2 μm diameter become trapped in this mucus layer. In healthy children, mucus is moved proximally by the effective coordinated beating of cilia. Cilial function is temporarily disrupted following exposure to environmental tobacco smoke, some inhalational anaesthetics, cold air or following bacterial or viral infections.

Epithelial cilia are hair-like appendages that line the human respiratory tract. Each ciliated epithelial cell has approximately 200 cilia. These are long enough to catch the base of the viscous mucus layer and propel it forward. They have a complex structure (Fig. 17.15). Primary ciliary dyskinesia (PCD) describes a heterogeneous group of conditions with a primary defect in the structure or function of the cilia (Fig. 17.16). PCD is mainly inherited as an autosomal recessive condition. The incidence is 1 in 15,000–30,000 live births.

Treatment for respiratory infection is similar to cystic fibrosis. Optimal management requires rapid treatment and airway clearance techniques.

Pharmacology of respiratory medicines used in children

General principles of inhaled medications

Particles of >10 μm in diameter deposit in the upper airway. Those <10 μm in diameter can be inhaled into the lung. The particle size is important in determining efficiency and most likely site for deposition within the lung. Very small particles (<1 μm) will be delivered widely, but fewer will be delivered to the medium-sized airways. In contrast, particles between 1–5 μm will deposit in the medium to small airways. Larger particles tend to deposit in the larger airways. There are three mechanisms of deposition: inertial impaction, sedimentation and diffusion (Fig. 17.17). For the particle size used in aerosol therapies (1–10 μm), only two mechanisms predominate – inertial impaction and gravitational sedimentation. Diffusion, is relevant in aerosol particles less than 1 μm in diameter.

Inertial impaction occurs at bifurcations of the bronchial tree, particularly in the larger central airways. It occurs mainly with large particles or high velocity particles, where they are unable to follow the airstream when it changes direction. Gravitational sedimentation occurs for smaller particles that follow the airstream and penetrate the more peripheral airways. The airstream is slower, allowing the particles to settle on the airway surfaces. Breath-holding is important for smaller particle sizes because of increased chance of exhalation as they can remain airborne for longer.

Nebulization leads to a range of particle sizes (Fig. 17.18). A 10 μm diameter particle contains much more drug than a smaller particle. The differences in particle size from different inhaled medications can lead to major differences in their effects.

Short-acting β_2 receptor agonists (SABAs)

β_2 receptors are found in the throat and down to the terminal airways. It is unclear where short-acting β_2 receptor agonists (SABAs) have their main actions, but it is thought to be primarily within the large- and medium-sized airways.

β Agonists were developed in the 1960s as analogues of epinephrine. Those such as isoproterenol were non-selective and hence cardiotoxic from their β_1 effects. Salbutamol was the first selective SABA to be introduced in the UK in 1968. It shows >500-fold separation in activity on β_2 compared to β_1 receptors. Inhaled salbutamol has its onset of action within 5 minutes, maximal effect by 20 minutes with a half-life of 90 minutes. It requires a 4–6 hourly dosing regime for continuous therapeutic effect.

Clinical uses

The clinical uses include acute asthma exacerbations, symptom relief in chronic asthma management and
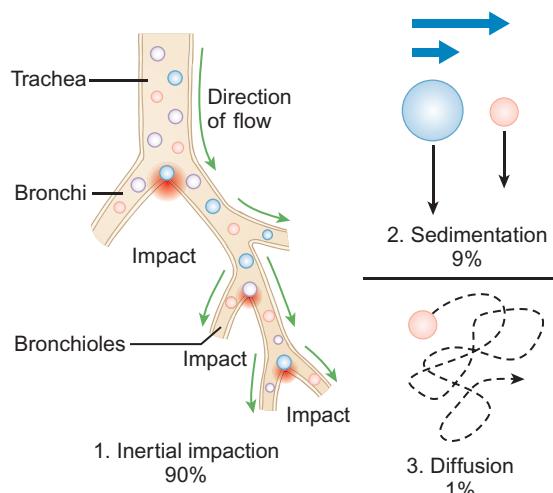
Fig. 17.17 **General mechanisms of deposition of aerosols in the human lung.** *(From O'Callaghan C, Barry PW. Thorax. 1997 Apr; 52 (Suppl 2):S31–S44.)*
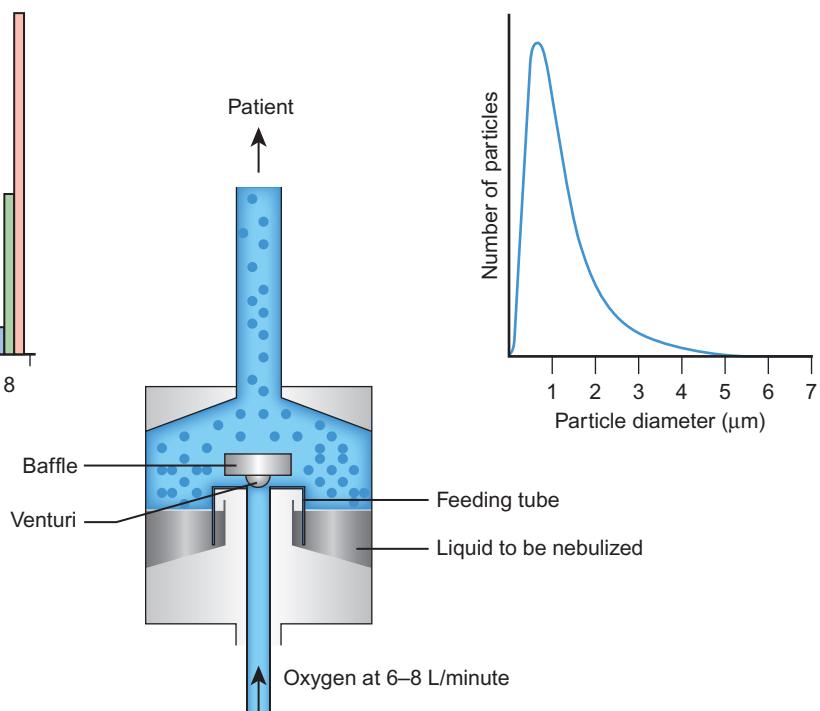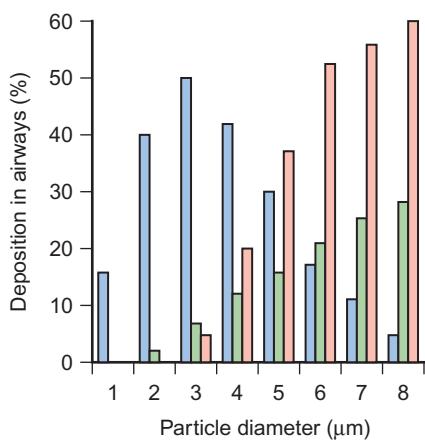
Fig. 17.18 **Nebulization and the effects of particle size on distribution throughout the airways.**

prevention of activity-related symptoms. They act directly on airway smooth muscle. Recommendations are for 'as required' treatment. Terbutaline has similar efficacy and safety profiles.

Routes of administration

Routes of administration include metered-dose inhaler (with spacer device), dry powder inhalation, via nebulizer and intravenously. Oral therapy is not recommended.

Long-acting β_2 receptor agonists (LABAs)

Binding of the β agonist molecule to the β adrenergic receptor leads to activation of the receptor, stimulation of adenylate cyclase and cyclic AMP formation.

Whereas SABAs are hydrophilic, salmeterol and formoterol (LABAs) are hydrophobic, salmeterol being 10,000 times more so than salbutamol. Both LABAs have higher affinity for β_2 receptors than SABAs. Salmeterol approaches the active site of the β_2 receptor through the cell membrane and is very slow to dissociate itself from the receptor, confirming its unique prolonged mode of action. The active head of the molecule attaches itself in an analogous way to salbutamol; its long flexible side arm embeds itself into the hydrophobic core of the receptor. This binding of the side chain enables the other end of the molecule to interact freely with the active site, reducing the possibility of desensitization or tachyphylaxis. Formoterol's length of action is different and can be explained by its high receptor affinity, efficacy and lipophilicity.

Neither LABA should be used as monotherapy, as use without an inhaled corticosteroid seems to increase mortality. National guidelines recommend using them with inhaled corticosteroids (ICSs), preferably in one combined inhaler (e.g. fluticasone/salmeterol or budesonide/formoterol combinations) to improve treatment adherence.

Anticholinergics

These are muscarinic receptor antagonists which prevent cholinergic nerve-induced bronchial constriction. The main one used in children is ipratropium bromide, given through a metered dose inhaler or a nebulizer. Clinical use is reserved for acute severe asthma exacerbations as an adjunct to SABA therapy.

Pharmacology of corticosteroids

Corticosteroids pass through the cell membrane of many inflammatory cells, including cells within the lung, probably by diffusion. In the cytoplasm, they attach themselves to glucocorticoid receptors and form complexes which then translocate into the cell nucleus. Here they bind to specific genes involved in inflammation resulting in increased transcription of those which suppress inflammation and reduced transcription of those which enhance inflammation. Corticosteroids are clinically very helpful, as they reverse hyperreactivity within epithelial cells (Fig. 17.19), which, if not treated early, leads to chronic inflammation and airway remodelling, a process which is non-reversible and produces permanent changes.

Clinical use

Oral corticosteroids are used as once daily therapy in an acute attack to speed recovery. Prednisolone is the corticosteroid of choice. It can also be used in acute viral croup but traditionally dexamethasone has been recommended, as studies demonstrating benefit were undertaken using this rather than prednisolone. Courses for both disorders are recommended for 1–3 days. In very severe asthma, low-dose prednisolone may be helpful on a once-daily or alternate-day basis.

Inhaled corticosteroid usage (beclometasone dipropionate, budesonide, fluticasone propionate, etc.) is first-line anti-inflammatory therapy in all ages, with asthma prescribed as a twice-daily inhaled regime.

Leukotriene receptor antagonists

High leukotriene levels occur in asthma. Cysteinyl leukotrienes (C4, D4 and E4) are derived from arachidonic acid using the enzyme 5-lipoxygenase; this inflammatory pathway is not modified by steroids and this is the scientific basis for leukotriene receptor antagonist (LTRA) use. Leukotrienes increase mucus production, bronchoconstriction, eosinophil recruitment and exudation of plasma (inflammatory processes). The LTRA montelukast, licensed for use in children, modifies the processes. It is a once-daily medication either in granule form for the very young or as a pink, chewy, cherry-flavoured once-daily tablet in children over 2 years old. It is used in allergic asthma and in viral-induced wheeze.

Clinical uses

Clinical uses include control of wheezing in children 6–24 months old, control of asthma in the 2–5 year age group (as first-line prophylactic treatment in both groups), and as adjunct to inhaled corticosteroids in school-aged children poorly controlled with low-dose ICS.

Anti IgE therapy

Omalizumab is a recombinant humanized monoclonal antibody which binds to circulating
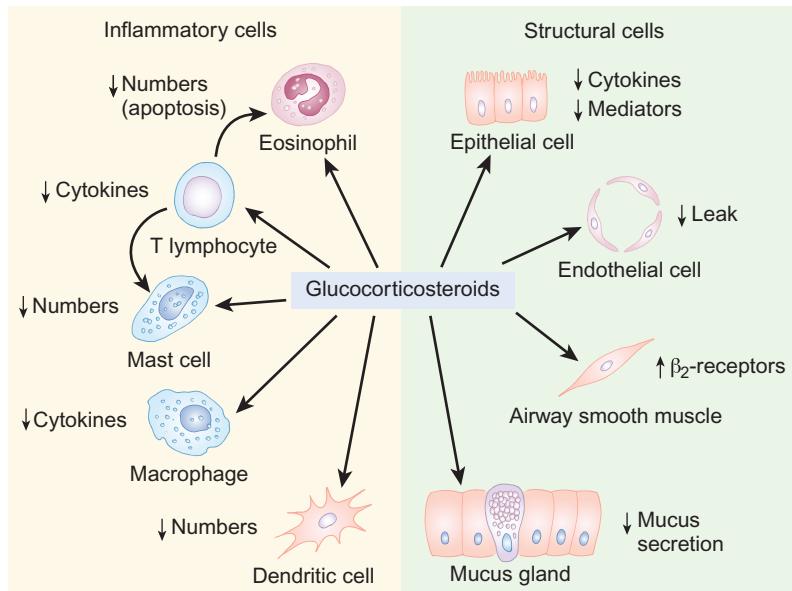
Fig. 17.19 Effects of corticosteroids on inflammatory and structural cells in the airways. *(From Barnes P. Drugs for airway disease. Medicine, Volume 36, Issue 4, April 2008, pages 181–190, with permission. © Elsevier.)*

immunoglobulin E (IgE). This binding prevents the IgE from activating IgE receptors on inflammatory cells, especially mast cells, and blocks responses to specific aeroallergens. Such treatment requires regular (2–4 weekly) subcutaneous injections. It reduces IgE levels, asthma symptoms and exacerbations. It is very expensive and should only be prescribed in children with extremely severe, difficult to control asthma attending a tertiary care clinic.

Theophyllines

These have been prescribed for decades in children with asthma. Their pharmacological effect is thought to be due to inhibition of phosphodiesterases, which results in an increase in intracellular cyclic AMP. This results in bronchodilatation. They may also act as antagonists to adenosine, a bronchoconstrictor. They are cheap but benefits are small. They have a narrow therapeutic range and toxicity can occur even at normal therapeutic serum levels.

Pharmacology of key respiratory medicines used in CF

Antibiotics

Colomycin (nebulized and intravenous)

Colomycin is used in the treatment of *Pseudomonas aeruginosa* infection and therefore is particularly useful in children with cystic fibrosis. It is derived from a

bacillus in the polymixin group; colistimethate is a cyclical polypeptide. It is a cationic agent which damages the bacterial cell membrane. All polymixins are lethal to bacteria which have a hydrophobic outer cell membrane.

This extracellular site of action means that resistance is less commonly acquired and continuous use is possible. The breakpoint for accepted clinical sensitivity of a bacterium is a mean inhibitory concentration (MIC) of 4 mg/L or less. An MIC of 8 mg/L or more infers bacterial resistance. *Burkholderia cepacia*, *Proteus* species, anaerobes, Gram-positive organisms and possibly *Enterobacter* and *Klebsiella* also fit the resistant category.

Absorption from the GI tract does not occur. Following nebulized therapy, absorption is variable but some systemic presence should be considered. Following intravenous (IV) treatment, protein binding is low. The antibiotic has a half-life of 1.5 hours and is converted to its base whose elimination is through the kidneys.

Tobramycin (nebulized, inhaled powder and IV)

All aminoglycosides have very similar kinetic properties with elimination half-lives of 2–3 hours. Clearance is mostly through glomerular filtration and is reduced in renal failure. Tobramycin is rapidly bactericidal and shows concentration-dependent killing. The upper limits are well above the peak concentrations reached in clinical practice. The theoretical benefits of

higher, less frequent dosings are better concentration-dependent killing, less post-antibiotic resistance and adaptive resistance. The best predictor of efficacy is the area under the curve over 24 hours (AUC24):MIC ratio. All aminoglycosides are nephrotoxic.

Mucolysis

Dornase alfa (DNAse)

Extracellular DNA is released into the airways by leukocytes in response to chronic bacterial infections. In patients with CF, this DNA can represent 10% of dry weight of respiratory secretions and can accumulate. Solutions containing this amount of DNA are very viscous. Deoxyribonuclease (DNAse) is a human enzyme found in saliva and other bodily fluids which breaks down DNA. On the basis that additional DNAse would help clear secretions and improve lung function, recombinant human DNAse (dornase alfa) was developed as nebulized treatment. Studies showed benefit over placebo but no clinical difference between once- or twice-daily regimes. Nebulized DNAse is increasingly used in younger children despite its relatively high cost.

Recent advances in respiratory paediatrics

Manipulation of the abnormal CF gene

Ivacaftor

About 5% of patients with CF have the missense mutation G551D, a class 3 mutation causing defective chloride channel opening or gating controlled by the CFTR protein. Ivacaftor increases stimulated chloride secretion and prevents dehydration of airway surface liquid and increases cilia motility. Studies in patients aged 6 years and above have normalized the sweat test and have shown clinical improvement in terms of reduced symptoms and improved lung function. Ivacaftor is extremely expensive (of the order of £120,000 per patient per year!). Peak plasma concentration is at 4 hours. High fat foods increase bioavailability up to fourfold. It is highly protein bound (99%) and undergoes hepatic metabolism, the majority of metabolites being in the faeces. Ivacaftor is a sensitive CYP3A substrate, so co-administration with CYP3A inhibitors (ketoconazole, voriconazole, itraconazole, grapefruit juice, etc.) increases exposure. With CYP3A inducers (rifampicin, carbamazepine, etc.), exposure is lower.

Inflammometry – measurement of exhaled nitric oxide

> ### Question 17.7
>
> **Fractional excretion of nitric oxide**
>
> Which of the following is most likely to result in a low fractional excretion of nitric oxide (<5 ppb)? Select ONE answer only.
>
> A. Atopic disease
> B. Contamination of sample from nasal sinuses
> C. Kartagener syndrome
> D. Poor adherence in a child with asthma
> E. Treatment with sildenafil

> ### Answer 17.7
>
> C. Kartagener syndrome. See below for discussion.

Whilst obstruction is relatively easy to measure, airway inflammation is less so. Nitric oxide (NO) is a biologically important molecule which is produced from the conversion of L-arginine to L-citrulline, a reaction catalysed by nitric oxide synthase (NOS). The inducible form of NOS (iNOS) is found in a number of inflammatory and regulatory cells within the airways and NO production is predictably increased in untreated childhood asthma. Eosinophilic inflammation in the conducting airways results in production of large quantities of NO. This results in an increase in the fractional nitric oxide concentration in exhaled breath (FeNO).

Whilst this can be clinically valuable in steroid-naïve patients, the level of FeNO falls promptly and dramatically in response to treatment with inhaled corticosteroids and therefore its value in routine clinical practice has been debated. In 2011, the American Thoracic Society produced recommendations for its use in adults and children (Table 17.3). It may have value in detecting poor medication adherence or undertreatment of asthma.

Continuous and high production of NO also takes place in the human nose and paranasal sinuses. Nasal NO levels are altered in several respiratory disorders. Reduced levels are seen in children with cystic fibrosis and allergic rhinitis. Very low values for nasal nitric oxide and exhaled nitric oxide are seen in children with primary ciliary dyskinesia, which has led to the suggestion this could be a screening test for this condition.

Table 17.3 General outline for exhaled nitric oxide (FeNO) interpretation in children

	FeNO <20 ppb	FeNO 20–35 ppb	FeNO >35 ppb
Diagnosis			
Symptoms present in last 6 weeks	Eosinophilic airway inflammation unlikely Consider alternative diagnosis Unlikely to benefit from ICS	Be cautious Evaluate clinical context Monitor change in FeNO over time	Eosinophilic airway inflammation present Likely to benefit from ICS
Monitoring			
Symptoms present*	Possible alternate diagnoses Unlikely to benefit from increase in ICS	Persistent allergen exposure Inadequate ICS dose Poor adherence Steroid resistance	Persistent allergen exposure Poor adherence Inadequate ICS dose Steroid resistance
Symptoms absent*	Adequate ICS dose Good adherence ICS taper	Adequate ICS dosing Good adherence Monitor change in FeNO	ICS withdrawal or dose reduction may result in relapse Poor adherence

*Symptoms refer to cough and/or wheeze and/or shortness of breath. ICS, inhaled corticosteroid.

Kartagener syndrome is a subtype of primary ciliary dyskinesia (with dextrocardia).

Atopy and male gender increase exhaled nitric oxide levels, as does exposure to viruses or allergen. Poor adherence with inhaled steroids results in increases in FeNO for children with asthma. Typically, nasal exhaled nitric oxide levels are much higher than those seen in the conducting airways.

Further reading

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Robert M R Tulloh, Jessica Green

Cardiology

Congenital heart disease is the most common group of structural malformations in children (8 per 1000 live-born infants) and knowledge of the anatomy and physiology of the cardiovascular system is necessary to understand the clinical manifestations, natural history and treatment options of these disorders.

The anatomy of the normal heart

Although conventionally described in terms of 'right-' and 'left-sided' chambers, in reality the heart does not hang down from the great vessels with the ventricles directly below the atria. Instead, it is tilted forwards and to the left so that the 'right' chambers have a more anterior position than the left (Fig. 18.1). This is further complicated by the twisted nature of the ventricular outflow tracts; the aorta, despite emerging from the left ventricle, has its valve in a right-sided and inferior position in relation to the pulmonary valve. In congenitally malformed hearts, when the chambers do not occupy their usual positions, the positional distinction of right and left becomes confusing and is avoided by referring instead to the 'morphological' right and left.

The morphological approach to examination of the heart enables easier description of congenital cardiac malformations. The basic mantra is that all hearts are built from three segments – the atria, ventricular masses and arterial trunks with the atrioventricular junction and the ventriculoarterial junction interposing between adjoining segments. A normal heart would therefore be described as situs solitus (i.e. the atria are in the correct orientation), concordant atrioventricular connection and concordant ventriculoarterial connection. Congenital abnormalities can be present in one or more of these segments.

The atria

The right atrium is slightly larger than the left atrium but its walls are thinner. The internal wall of the right atrium is composed of a smooth, posterior portion (into which the vena cava and coronary sinus drain) and a ridge-like, muscular anterior portion with characteristic pectinate muscles distributed down into the
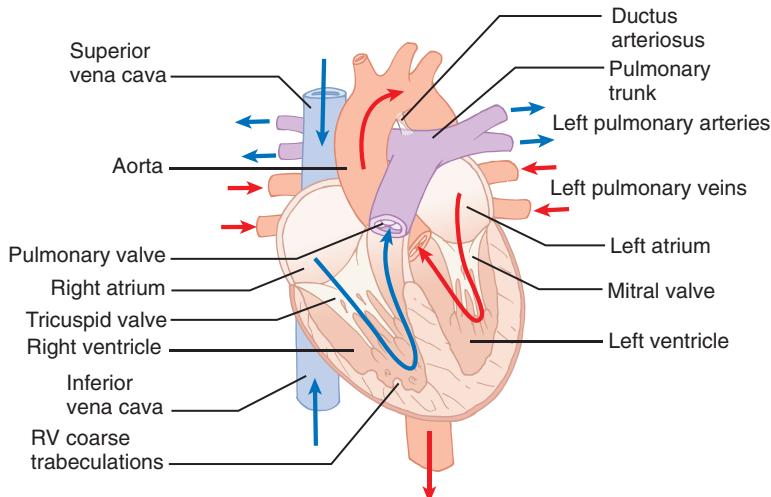
Fig. 18.1 Diagram of the heart demonstrating the anatomical relationship of the atria, ventricles, heart valves and major blood vessels.

vestibule of the tricuspid valve. The left atrium receives the four pulmonary veins into its smooth-walled posterior surface. The atria share a common wall – the atrial septum. This contains a flap valve of the fossa ovalis, which overlaps the atrial walls, so even if not fused, there will be no shunting across the septum, as long as the left atrial pressure exceeds that of the right atrium. The vestibule of the left atrium supports the leaflets of the mitral valve (two cusps) and is smooth.

The ventricles

The ventricles consist of inlet, apical trabecular and outlet components. The shape of the normal right ventricle is determined by the inlet being inferior and to the right of the outlet. The inlet surrounds and supports the leaflets and tension apparatus of the tricuspid valve. The right ventricle also has characteristic coarser trabeculations than those on the left. The pulmonary semilunar valve (three cusps) is supported by a muscular infundibulum. The inlet component of the left ventricle contains and surrounds the mitral valve, which characteristically has no cordal attachments to the ventricular septum. The apical part of the ventricle has fine criss-crossing trabeculations and a smooth septal surface. The three leaflets of the aortic valve are attached in a semilunar fashion but, unlike the pulmonary valve, the hinge lines attach in part to fibrous structures and in part to the muscular walls of the ventricle.

The great vessels

The aorta arises from the middle of the base of the heart and curves upwards to the aortic arch, where it gives rise to the brachiocephalic, the left common carotid and the left subclavian vessels. The three

sinuses of Valsalva support the leaflets of the aortic valve and two of these sinuses give rise to the right and left coronary arteries. The pulmonary trunk runs from the pulmonary infundibulum, where its sinuses support the leaflets of the pulmonary valve, to its bifurcation into the right and left pulmonary arteries. In the fetal circulation, the ductus arteriosus extends from the pulmonary trunk into the descending aorta and demarcates the isthmus of the aorta.

Peripheral blood vessels

The vessels of the peripheral circulation are made up of three layers (Fig. 18.2):
- Tunica intima – a single layer of flattened endothelial cells providing a smooth lining.
- Tunica media – elastic fibre and smooth muscle arranged in a circular fashion. It is thicker in arteries than in veins and allows vasoconstriction/vasodilation. The contractile activity of the smooth muscle in the tunica media is affected by the autonomic nerves supplying it and by vasoconstrictor substances in the blood, in particular angiotensin.
- Tunica adventitia – outermost, fibrous layer composed of connective tissue.

The pericardium

The heart and roots of the great vessels are encased in the pericardial sac, which consists of fibrous and serous parts. The outer fibrous part fuses underneath the heart with the central tendon of the diaphragm and also fuses with the ends of the great vessels as they enter or leave, so helping to anchor the heart in its
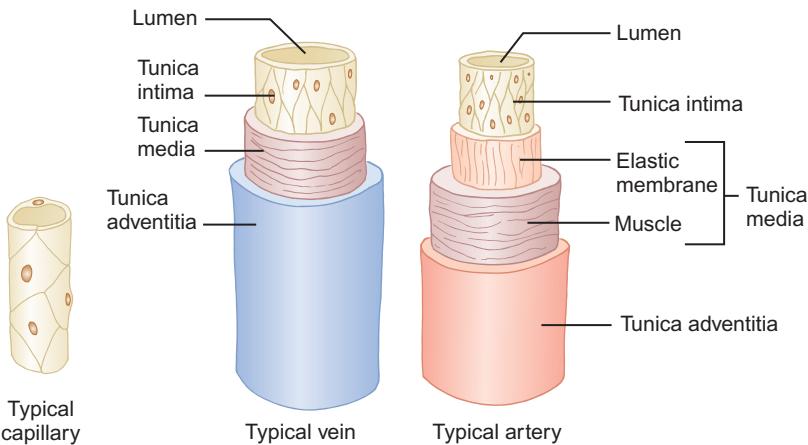
Fig. 18.2 Structure of a capillary, vein and artery.

central position. The inner, serous pericardium has two layers: the parietal layer that adheres to the inner surface of the fibrous pericardium; over the great vessels it becomes reflected onto the outer surface of the heart as the visceral layer or epicardium. The adjacent surfaces of the serous pericardium are kept lubricated by pericardial fluid, allowing the surfaces to glide over one another as the heart beats.

Embryology and its relevance to congenital heart disease

The heart is the first organ that functions within an embryo, by the 4th week of gestation, when the nutritional and oxygen requirements of the growing embryo can no longer be met solely by diffusion from the placenta. The embryo is made up of three germ layers: the ectoderm, mesoderm and endoderm. The heart develops predominantly from the mesoderm and is

---

Answer 18.1

A. The cilia (see below).
    The case very vaguely describes a child born with Kartagener syndrome (see also Chapter 17, Respiratory medicine).

---

remodelled throughout its development. Its early development is summarized in Figure 18.3. By day 22, coordinated contractions of the heart tube are present. Following fusion, the primitive heart tube develops a series of expansions separated by shallow sulci, forming the heart's various divisions: the sinus venosus, atrium (future atria), bulbus cordis (future right ventricle), ventricle (future left ventricle) and truncus arteriosus.

Case history

Dextrocardia is noted in an infant.

How does it arise?

Dextrocardia is the most frequent positional abnormality of the heart. If the heart tube twists to the left instead of the right, the heart is displaced to the right and there is transposition in which the heart and its vessels are reversed left to right. Polarity of the embryo is in part determined by cilia function with small hairs determining the orientation of the organs. Complete failure to determine polarity leads to dextrocardia with situs inversus; the process of heart formation has usually occurred correctly but in a mirror-image fashion to the usual order of events, thus the incidence of accompanying cardiac defects is low. If dextrocardia is isolated, e.g. the stomach remains on the left and the liver on the right, then the anomaly is usually complicated by severe cardiac anomalies, e.g. single ventricle, arterial transposition.

Question 18.1

Dextrocardia

A child is admitted at 6 weeks of age with bronchiolitis. She is hypoxic and has significant respiratory distress. A chest X-ray shows dextrocardia.
    Which organelle is most likely to be defective? Select ONE answer only.

A. Cilia
B. Golgi apparatus
C. Lysosome
D. Mitochondria
E. Peroxisome
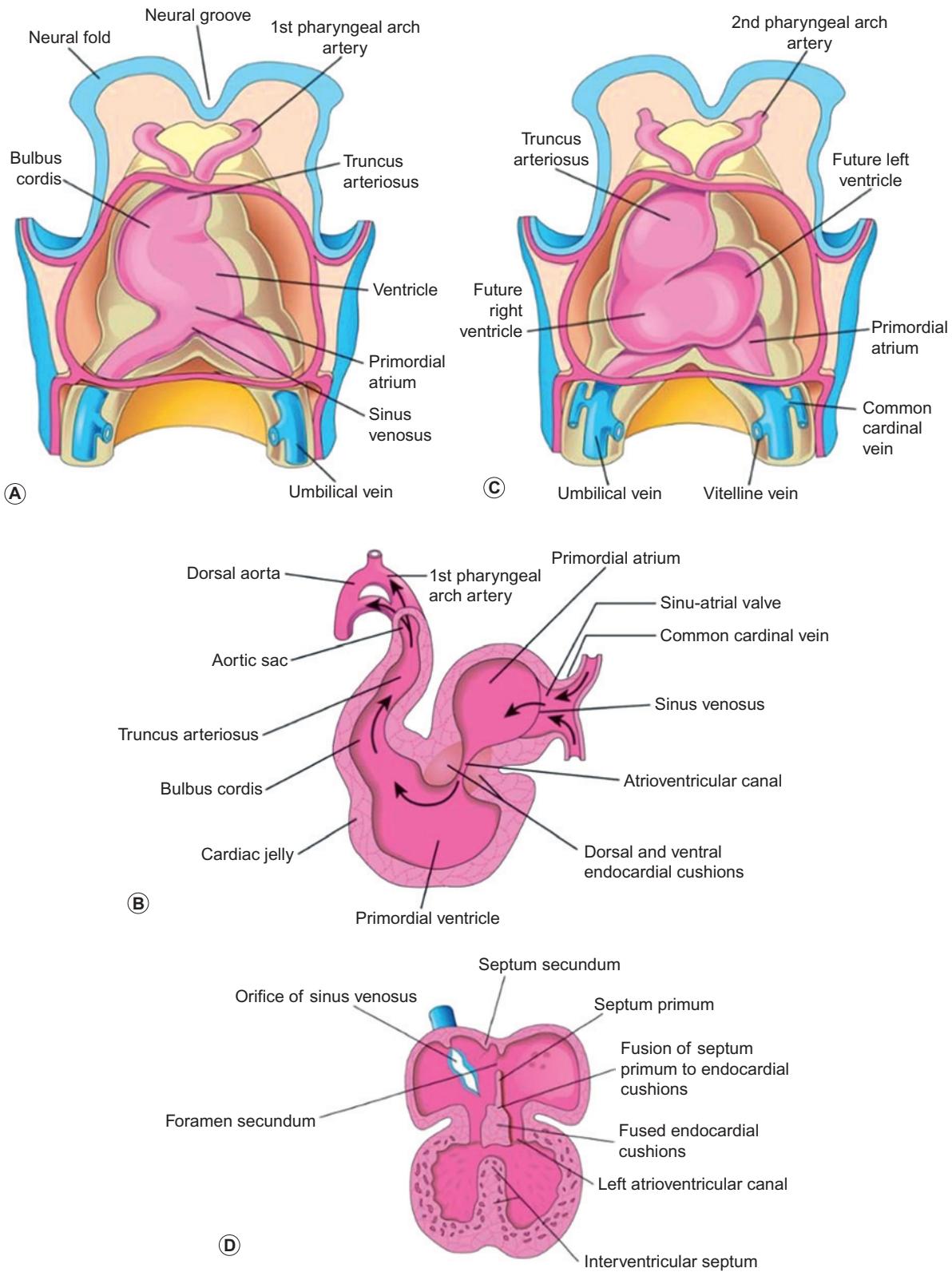
Fig. 18.3 **Embryology of the developing heart. A. The heart as a tube at around 22 days. B. Cross-sectional view. C. The heart bends on itself to form an 'S' shape. D. Partitioning of the heart (approximately 35 days) with formation of the septum primum.**
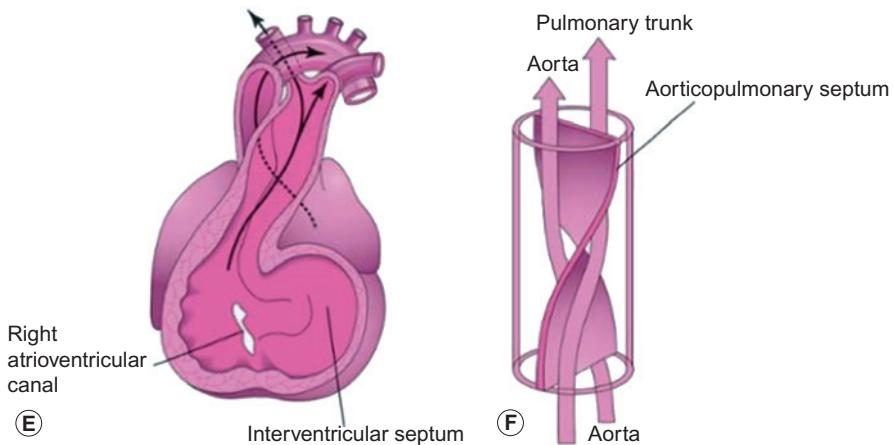
Fig. 18.3, cont'd **E. Partitioning of the bulbus cordis and truncus arteriosus and spiraling of the of the aorticopulmonary septum. F. During partitioning of the aorticopulmonary septum, the spiral arrangement results in rotation of the aorta and pulmonary artery.** *(From Moore KL, Persaud TVN, Torchia MG. Before we are born, 9th ed. Philadelphia: Saunders, Elsevier; 2015.)*

Early embryology of the heart

During weeks 4 and 5, the heart forms an 'S' shape, demonstrating left to right asymmetry. Looping brings the future left ventricle forward in continuity with the sinus venosus (future left and right atria), whereas the future right ventricle is shifted rightward and in continuity with the truncus arteriosus (future aorta and pulmonary artery). In weeks 5 and 6, the neural crest mesenchymal cells proliferate and migrate through the primordial pharynx and over the aortic arch arteries to reach the outflow tract, the aorticopulmonary septum forms and cleavage of aortic and pulmonary trunk occurs. The primordial pulmonary vein is incorporated into the left atrium from week 5. The vein develops as an outgrowth of the dorsal atrial wall and as the atrium expands, the primordial pulmonary vein and its main branches are gradually incorporated into the vein of the left atrium, forming the four pulmonary veins.

In total anomalous pulmonary venous connections, none of the pulmonary veins connects with the left atrium. They open into the right atrium or into one of the systemic veins or into both. In partial anomalous pulmonary venous connections, one or more pulmonary veins have similar anomalous connections; the others have normal connections.

Case history

An atrial septal defect (ASD) is diagnosed in an 18-month-old boy following identification of a heart murmur.

What is their embryological aetiology?

ASDs are common, the most common form being a *patent foramen ovale*. Incomplete adhesion between the flap-like valve and the septum secundum is present in up to 25% of people. Whilst normally not clinically significant, it may be forced open due to other cardiac defects and contribute to functional cardiac pathology. Defects in the area of the fossa ovalis are most common. They lie distant from the atrioventricular valves and usually do not disrupt their function. *Ostium primum defects*, or partial atrioventricular septal defects, lie anteroinferiorly to the fossa ovalis. These account for less than 10% of ASDs but are associated with abnormal atrioventricular valves and variable degrees of mitral regurgitation.

Atrioventricular septal defects (AVSD) are characterized by an interatrial communication between the bottom end of the atrial septum and the atrioventricular valves (primum ASD) and abnormal atrioventricular valves, with a regurgitant left tri-leaflet atrioventricular valve. 80% occur in children with Down's syndrome.

In weeks 6 and 7, the atrioventricular valves form and a ridge of tissue, the crista terminalis, forms superior to the right valve forming the conduction pathway from the newly identifiable sinu-atrial node to the atrioventricular node. Division of the primordial ventricle starts with formation of a median muscular ridge in the floor of the ventricle near its apex. The median walls of the enlarging ventricles approach one another and fuse to form the primordium of the muscular part of the intraventricular septum.

Later, there is active proliferation of myoblasts in the septum, which increase in size. Until week 7, there is a crescent-shaped interventricular foramen between the free edge of the intraventricular septum and the fused endocardial cushions, which permits communication between the right and left ventricles. It usually closes by the end of the seventh week, as the bulbar ridges fuse with the endocardial cushion. The membranous part of the intraventricular septum is derived from an extension of tissue from the right side of the endocardial cushion to the muscular part of the intraventricular septum. This tissue merges with the aorticopulmonary septum and the thick muscular part of the intraventricular septum. After closure to the interventricular foramen and the formation of the

membranous part of the intraventricular septum, the pulmonary trunk is in communication with the right ventricle and the aorta is in communication with the left ventricle.

In weeks 7 and 8, the truncus arteriosus (TA) is divided in two by a spiral process of central septation, forming the truncoconal septum, which results in the formation of the aorta and pulmonary trunk. This septum also grows into the ventricles, where it forms the membranous ventricular septum. Swellings develop at the inferior end of the truncus arteriosus, and these give rise to the semilunar valves.

Truncus arteriosus results from the failure of the truncal ridges and the aorticopulmonary septum to develop normally and divide the truncus arteriosus into the aorta and pulmonary trunk. In this defect, a single arterial trunk, the TA, arises from the heart and supplies the systemic, pulmonary and coronary circulations. A VSD is always present with the TA anomaly and the TA overrides the VSD.

Development of the venous system

At week 4, three systems of paired veins drain into the primordial heart:

- Vitelline system – returns poorly oxygenated blood from the yolk sac, later becomes the portal system
- Cardinal veins – carry poorly oxygenated blood from the body of the embryo, becomes the caval system
- Umbilical system – carries well-oxygenated blood from the placenta, involutes after birth

The umbilical veins run on each side of the liver and carry well-oxygenated blood from the placenta to the sinus venosus. As the liver develops, the umbilical veins lose their connection with the heart and empty into the liver. The right umbilical vein disappears during the 7th week, leaving the left umbilical vein as the only vessel carrying well-oxygenated blood from the placenta to the embryo. A large venous shunt – the ductus venosus – develops within the liver and connects the umbilical vein with the inferior vena cava and so forms a bypass through the liver, enabling most of the blood from the placenta to pass directly to the heart without passing through the capillary networks of the liver.

The inferior vena cava (IVC) forms from a series of changes in the primordial veins of the trunk that occur as blood returning from the caudal part of the embryo is shifted from the left to the right side of the body. The IVC is composed of four main segments, hepatic,

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Case history

A ventricular septal defect (VSD) is identified on echocardiography in an 8-week-old infant with pneumonia and a loud pansystolic murmur.

What are the different types of VSD and what is their embryological origin?
Ventricular septal defects are the most common type of congenital heart disease. They may occur in any part of the ventricular septum.
Perimembranous VSDs are the most common and result from the failure of the membranous part of the intraventricular septum to develop or from failure of the extension of sub-endocardial tissue.
Muscular VSDs are less common and may occur anywhere in the muscular part of the intraventricular septum. They probably occur due to excess cavitation of myocardial tissue during the formation of the ventricular walls and the muscular part of the intraventricular septum. *Complete absence of the intraventricular septum* results in a single or common ventricle, a rare defect, which results in a three-chambered heart where both atria empty into a single ventricle and the aorta and pulmonary trunk arise from the single ventricle.

pre-renal, renal and post-renal, each derived from different venous structures. Because of the many transformations that occur during the formation of the IVC and superior vena cava (SVC), variations in their adult form occur, the most common variant is a persistent left SVC, which drains into the right atrium through the enlarged coronary sinus. Less commonly, the IVC may have its abdominal course interrupted, so blood draining from the lower body returns to the heart through the azygos system.

Development of the arterial system

As the pharyngeal arches form during the 4th and 5th weeks, they are penetrated by arteries (aortic arches), which arise from the aortic sac and terminate in the dorsal aortae. Initially, the paired dorsal aortae run through the entire length of the embryo but they soon fuse to form a single dorsal aorta, just caudal to the pharyngeal arches. During weeks 6 to 8, they are transformed into the adult arterial arrangement of carotid, subclavian and pulmonary arteries.

Initially, there are approximately thirty branches of the dorsal aorta. However, with increasing gestation, most of these branches disappear whilst some fuse together and persist. In the neck they join to form the vertebral arteries, in the thorax they form the intercostal arteries, the lumbar arteries in the abdomen, the common iliac arteries and the sacral arteries in the sacrum. The unpaired ventral branches of the dorsal aorta supply the yolk sac, allantois and chorion. The vitelline arteries pass to the yolk sac and later the primordial gut, which forms from the incorporated part of the yolk sac. Three vitelline arteries remain: the coeliac trunk supplying the foregut, superior mesenteric artery to the midgut and the inferior mesenteric artery to the hindgut.

The paired umbilical arteries pass through the connecting stalk (later umbilical cord) and become continuous with vessels in the chorion. The umbilical arteries carry poorly oxygenated blood to the placenta. Proximal parts of the umbilical arteries become the internal iliac arteries, and superior vesical arteries whereas distal parts obliterate after birth and become the medial umbilical ligaments.

Because of the many changes involved in transformation of the embryonic pharyngeal arch system into the adult arterial pattern, there are a number of irregularities that may result from the persistence of parts of aortic arches that usually disappear (e.g. right arch of the aorta, double aortic arch), or from disappearance of parts that normally persist (e.g. anomalous right subclavian artery).

Case history

A 36-hour-old female infant is rushed to hospital as she has respiratory distress and her limbs have become mottled. Echocardiography identifies coarctation of aorta.

What is its anatomy?

Coarctation of aorta occurs in approximately 10% of children with congenital heart disease. It is characterized by a congenital narrowing or shelf-like obstruction of the aortic arch of varying length. The constriction is usually eccentric, distal to the left subclavian artery and juxta-arterial. Any condition leading to reduced anterograde flow through the aortic isthmus in fetal life may predispose to coarctation (e.g. VSD) and remnants of ductal tissue may exist within the wall of the aorta. Coarctation may develop when this tissue contracts during ductal closure. In an infant with severe coarctation, closure of the ductus results in hypoperfusion and rapid clinical deterioration. Prostaglandin E2 is given in an attempt to reopen the arterial duct and establish adequate blood flow to the lower limbs. The causes of coarctation are not clearly understood, but it is associated with a number of anomalies including bicuspid aortic valve, Turner's syndrome, renal anomalies and berry aneurysms.

Fetal circulation and transitional changes after birth

These are described in Chapter 10, Perinatal medicine.

Persistent ductus arteriosus (PDA)

This is the second commonest form of congenital heart disease, accounting for approximately 10% in term infants. Failure of involution of the ductus arteriosus by failure of contraction of its muscular wall after birth is the primary cause of patency. It may occur as an isolated anomaly or in association with cardiac defects. Large differences between aortic and pulmonary blood pressures can result in increased blood flow through the ductus arteriosus preventing normal constriction. Such pressure differences may be seen in coarctation of the aorta, transposition of the great arteries or pulmonary stenosis and atresia.

A 36-hour-old female infant is noted to have low oxygen saturation on screening for critical congenital heart disease. Her breathing is normal and congenital heart disease is suspected.

What are duct-dependent cardiac lesions and how are they managed?

A number of congenital heart defects are dependent on the patency of the duct in order to maintain survival of the infant. These can be divided into those that are dependent on the duct for adequate pulmonary blood flow and those that require the duct to maintain systemic circulation.

Ductal-dependent pulmonary blood flow:

- Critical pulmonary stenosis
- Pulmonary atresia
- Tricuspid atresia with pulmonary stenosis/atresia

Ductal-dependent systemic blood flow:

- Coarctation of the aorta
- Hypoplastic left heart syndrome
- Interrupted aortic arch

Ductal patency can be maintained by the administration of exogenous PGE1 (alprostadil) or PGE2 (dinoprostone). Both are potent vasodilators. They have a broad range of actions including apnoea. Although oral PGE2 can be used, both these drugs are rapidly and almost completely inactivated following passage through the lungs and their effective half-life is less than one minute. Therefore, they are best given by intravenous infusion and loading doses are not required.

Genetic and environmental factors in the aetiology of heart disease

Only a small percentage of congenital heart disease cases have identifiable causes:

- Primary genetic factors (e.g. chromosomal abnormalities, single gene abnormalities): 10%
- Environmental factors (e.g. chemicals, drugs, viruses, maternal disease (Table 18.1)): 3–5%
- Genetic–environmental interactions (i.e. multi-factorial): 85%

The recurrence risk of cardiovascular anomalies varies from 1–4% and is higher with the commoner lesions, e.g. the recurrence risk for VSD is 3% whereas Ebstein anomaly is 1%. With two affected first-degree relatives, the risk is tripled. Table 18.2 lists the syndromes associated with cardiac lesions.

Table 18.1 Prenatal maternal factors associated with cardiac disease in the neonate

Prenatal factor	Associated defect
Diabetes mellitus	LVOT obstruction, hypertrophic cardiomyopathy, TGA, VSD
Maternal phenylketonuria	VSD, ASD, PDA, coarctation of the aorta
SLE	Heart block, pericarditis, endomyocardial fibrosis
Rubella	PDA, branch pulmonary stenosis
Alcohol	Pulmonary stenosis, VSD, ASD, tetralogy of Fallot
Aspirin	PPHN
Lithium	Ebstein anomaly
Coxsackie B infection	Myocarditis
Diphenylhydantoin	Aortic stenosis, pulmonary stenosis

ASD, atrial septal defect; LVOT, left ventricular outflow tract; PDA, patent ductus arteriosus; PPHN, persistent pulmonary hypertension of the newborn; TGA, transposition of the great arteries; VSD, ventricular septal defect.

Cardiovascular physiology

Question 18.2

Cardiovascular physiology

Which of the following BEST describes the cardiac output? Select ONE answer only.

A. The product of the mean arterial blood pressure and heart rate
B. The product of the volume of blood ejected by both ventricles and the heart rate
C. The product of the volume of blood ejected by the right ventricle and the heart rate
D. The volume of blood ejected by the left ventricle in 1 minute divided by the heart rate
E. The volume of blood pumped out by both left and right ventricles per minute

Answer 18.2

C. The product of the volume of blood ejected by the right ventricle and the heart rate.

The heart is an electrically controlled and chemically driven mechanical pump. In order for the heart to function as a pump, its chambers must be filled with sufficient amounts of blood before each contraction. The heart fills passively but due to its limited pressure–volume compliance, it offers its own impediment to filling. By filling passively, the heart pumps

Table 18.2 Syndromes associated with cardiac lesions

Syndrome	Lesion
Trisomy 21/ Down's syndrome	Up to 50% will have congenital heart disease. VSD commonest followed by AVSD. Pulmonary vascular disease develops early.
Turner's syndrome XO	Bicuspid aortic valve – 33% Coarctation of the aorta
Noonan's syndrome (*PTPN11* gene on chromosome 12)	Pulmonary stenosis, ASD, hypertrophic cardiomyopathy
Williams syndrome (deletion of genes from the long arm of chromosome 7)	Supravalvular aortic stenosis, branch pulmonary artery stenosis
DiGeorge syndrome (22q11.2 deletion)	Aortic arch abnormalities, truncus arteriosus, pulmonary atresia, tetralogy of Fallot, familial VSD
CHARGE (*CHD7* gene on chromosome 8)	Tetralogy of Fallot, VSD, AVSD, double outlet right ventricle
VACTERL (abnormalities in structures derived from embryonic mesoderm; no known genetic or chromosomal cause)	Tetralogy of Fallot, VSD, coarctation of the aorta, PDA
Trisomy 18 – Edwards syndrome	VSD, ASD, PDA, coarctation of the aorta, bicuspid aortic valve, double outlet right ventricle
Trisomy 13 – Patau syndrome	VSD, ASD, PDA, coarctation of the aorta, bicuspid aortic valve, double outlet right ventricle
Marfan's syndrome (*FBN1* gene encoding connective protein fibrillin-1 on chromosome 15)	Aortic aneurysm, aortic regurgitation, mitral regurgitation
Ehlers–Danlos syndrome (defect in synthesis of type I or III collagen)	Aortic root dilation
Tuberous sclerosis (*TSC1* on chromosome 9 or *TSC2* on chromosome 16; code for tumour suppressor genes hamartin and tuberin, respectively; autosomal dominant)	Cardiac rhabdomyoma

ASD, atrial septal defect; AVSD, atrioventricular septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

out blood at a rate determined by the rate of blood coming to it. The venous return is the amount of blood flowing into the right atrium per minute from the systemic circulation. It is driven by:

- Peripheral vein compression from skeletal muscle activity, pushing venous blood into vessel segments closer to the heart.
- Respiration, which produces an alternating pressure gradient between the abdomen and thorax that favours venous return during inspiration (while the opposite effect during expiration is limited by the presence of semilunar valves in the veins).
- Active ventricular contraction, which shifts the atrioventricular border downwards in the direction of the cardiac apex and, as the atrioventricular valves are closed at this point, draws blood from the venae cavae and pulmonary veins into the atria.

The volume ejected by each ventricle (about 70 mL in the adult) is the stroke volume; with a heart rate of over 70 beats per minute over 5 litres of blood are pumped out of each ventricle every minute – this is the cardiac output. The cardiac output refers to the volume pumped out by *either* the right or left ventricle, not the total amount pumped by both. The cardiac output will vary with changes in stroke volume or heart rate and is governed by the central equation:

Cardiac output (litres/minute)
= stroke volume (litres) × heart rate (per minute)

The heart is able to modify its cardiac output by adjusting the number of contractions per unit of time and by moderating the volume of blood pumped by each contraction (stroke volume). These mechanisms are brought about through a number of intrinsic biophysical pathways as well as extrinsic control.

Heart rate

Acceleration of the heart rate can be achieved by decreasing the time taken to depolarize a pacemaker

cell. Catecholamines (noradrenaline and adrenaline) are positive inotropes. They bind to cardiac β1-adrenoceptors and act to increase the rate of diastolic depolarization by moving the threshold for action potential generation towards a more negative potential. Acetylcholine (parasympathetic), in contrast, binds to muscarinic M_2 receptors in the heart and acts inversely to slow the heart rate. Positive and negative inotropic factors are summarized in Table 18.3.

Specialized nerve receptors are constantly feeding back information to the reticular formation in the brainstem, which can initiate changes to the heart rate

Table 18.3 Positive and negative inotropic factors

Positive inotropic factors	Negative inotropic factors
Sympathetic nerve stimulation and catecholamines	Hypoxia, hypercapnoea
Increase in extracellular calcium	Decrease in extracellular calcium – calcium channel blockers
Decrease in extracellular sodium	Increase in extracellular sodium
Increased pH	Decreased pH
Increased temperature	Decreased temperature
Drugs, e.g. digoxin, glucagon, L-thyroxine	Drugs, e.g. beta blockers, anaesthetic agents

as necessary via the glossopharyngeal and vagal nerve supply (Fig. 18.4). Baroreceptors, located in the walls of the internal carotid arteries and in the arch of the aorta, constantly monitor the blood pressure and chemoreceptors in the carotid and aortic bodies monitor the amount of oxygen in the blood.

Preload

Increasing the preload (end-diastolic volume loading of the heart) stretches the sinuatrial (SA) node and increases heart rate via a reflex pathway and local stretch-activated ion channels that depolarize the pacemaker cells and increase the rate of diastolic depolarization. Outside the fetal period, stretch also increases the contractility of the working myocardium according to the Frank–Starling law (the energy of contraction is proportional to initial length of cardiac muscle fibre, i.e. length-dependent activation).

Increasing the end-diastolic volume increases the load experienced by each muscle fibre and augments contraction by increasing the affinity of troponin C for calcium and causes a greater number of actin–myosin cross-bridges to form within the muscle fibres. It is affected by length of diastole, venous return, atrial systole and myocardial compliance. An example of this is in premature ventricular contraction, which causes early emptying of the left ventricle. This
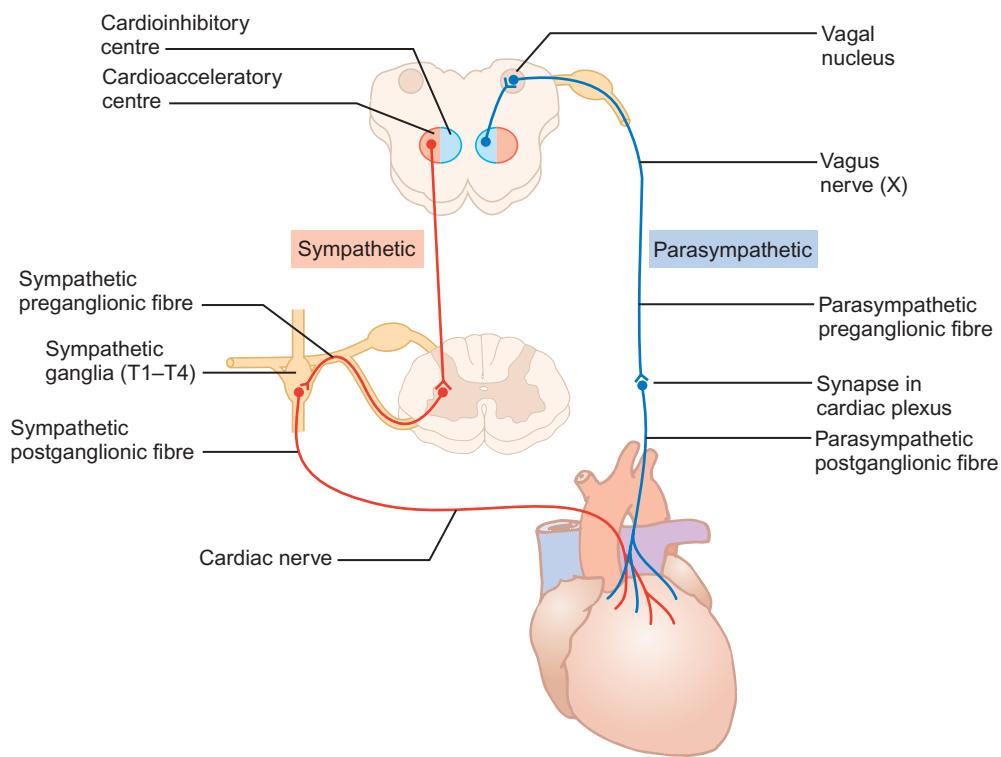
Fig. 18.4 Sympathetic and parasympathetic innervation of the heart.

Radius (*r*)   Wall thickness (η)

Wall tension (σ)

$$\sigma = \frac{Pr}{\eta}$$
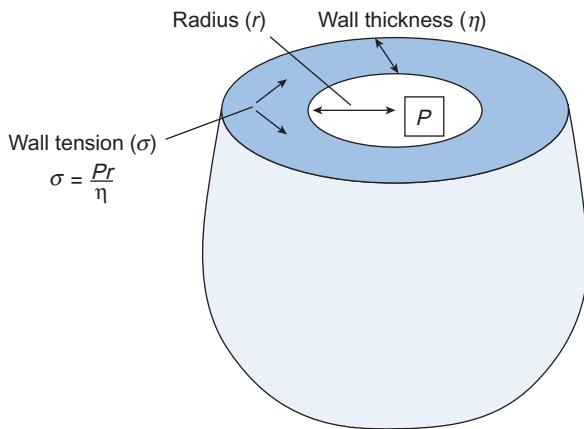
Fig. 18.5 Relation between pressure difference across a wall, the radius of the cavity and the thickness of the cavity wall follows the law of Laplace. The greater the pressure difference (P) or larger the radius (r), the more tension (σ) there will be in the wall; but tension is reduced the thicker the wall (η).

increases the filling time for the next regular ventricular contraction and so increases left ventricular end-diastolic volume. As dictated by the Frank–Starling law, the next ventricular contraction will be more forceful, causing the ejection of a larger than normal volume of blood, and brings the left ventricular end-diastolic volume back to baseline. A child may notice (and report) this sudden change. In contrast, a pericardial effusion would reduce myocardial compliance and decrease stroke volume.

The heart, however, is not two-dimensional but three-dimensional and the law of Laplace describes the relation between pressure difference across a wall, the radius of the cavity and the thickness of the cavity wall (Fig. 18.5). The greater the pressure difference (P) or larger the radius (r), the more tension (σ) there will be in the wall; but tension is reduced the thicker the wall (η).

In dilated cardiomyopathy, where the heart becomes distended and the radius of the ventricle increases, the heart must increase the cardiac tension produced by the cardiac muscle. The dilated heart therefore requires more energy to pump the same amount of blood compared to the heart of normal size.

Afterload

Afterload is the external load against which the ventricles must pump to eject blood. The total peripheral vascular resistance is determined by:

1. Vessel (resistance arterioles) diameter, pressure and tone
2. Aortic valve resistance
3. Ventricular cavity size
4. Haematocrit (blood viscosity)

Table 18.4 Factors affecting calibre of the arterioles

Constriction	Dilatation
Increased sympathetic activity	Decreased sympathetic activity
Circulating catecholamines	Increased PCO_2, decreased pH and PO_2
Circulating angiotensin II	
Locally released serotonin	Lactic acid, histamine and prostaglandins
Decreased local temperature	Increased local temperature

Factors affecting calibre of the arterioles are listed in Table 18.4.

Blood pressure (Fig. 18.6)

The control of blood pressure, hypertension and its treatment are considered in Chapter 19, Nephrology.

Heart failure

Question 18.3

A 4-week-old baby presents with signs and symptoms of heart failure. From the following list, which is the most likely cause? Select ONE answer only:

A. Cardiac arrhythmia
B. Cardiomyopathy
C. Fluid overload from overfeeding
D. Persistence of the arterial duct
E. Structural heart disease

Answer 18.3

E. Structural heart disease.

Heart failure occurs when the heart is unable to maintain adequate perfusion of the tissues for normal metabolism. Its causes can be divided into conditions of intrinsic cardiac muscle weakness and conditions that demand extra work of the heart (Table 18.5).

The most likely underlying cause is dependent on the age of the child. Neonates and infants younger than 2 months are most likely to present with heart failure secondary to structural heart disease. In older children, the causes of heart failure become broader and include the causes listed above but also chronic hypertension, renal failure, metabolic and endocrine disorders, anaemia, and illicit or accidental drug ingestion.
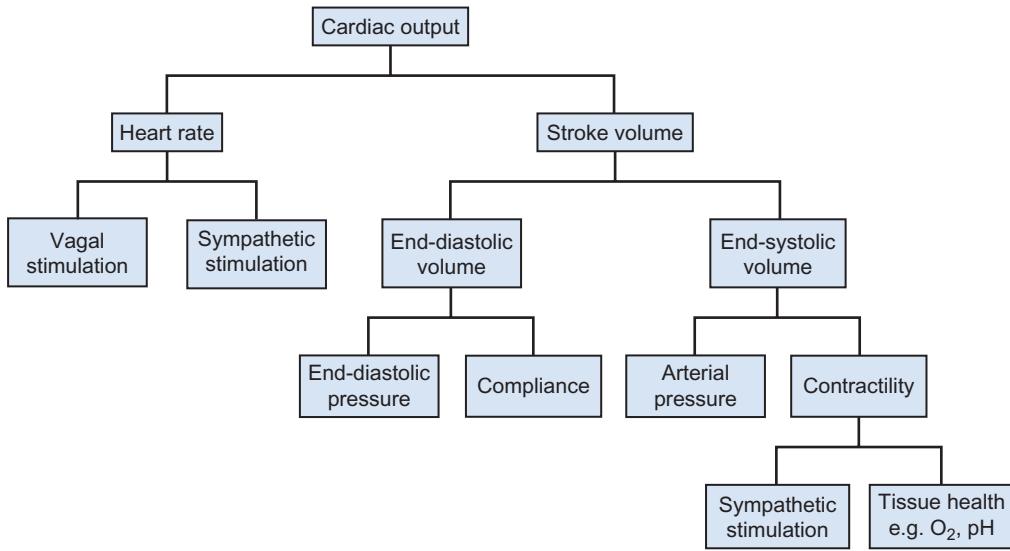
Fig. 18.6 Summary of the factors affecting cardiac output.

Table 18.5 Causes of heart failure

Volume overload	– Left-to-right shunts
	– Valvar regurgitation
	– Complex congenital cardiac lesions
	– Arteriovenous malformation, e.g. vein of Galen, haemangioma
Pressure overload	– Left heart obstruction, e.g. aortic stenosis, coarctation of the aorta, hypoplastic left heart
	– Acute hypertension, e.g. haemolytic uraemic syndrome, glomerulonephritis
	– Right heart obstruction, e.g. pulmonary stenosis
Cardiac arrhythmias	– Congenital complete heart block
	– Supraventricular tachycardia
	– Ventricular tachycardia
Ventricular dysfunction	– Myocarditis
	– Cardiomyopathy: dilated, hypertrophic, restrictive
	– Sepsis or anaemia
	– Pericardial effusion/cardiac tamponade
	– Ischaemia, e.g. birth asphyxia, anomalous left coronary artery

Pathophysiology of chronic heart failure

In chronic heart failure, there is a decrease in contractility of the affected heart muscle, shifting the Starling curve to the right (see Fig. 6.5). Increasing preload has a smaller effect on stroke volume than seen in the healthy heart. The resulting low cardiac output state triggers cardiac, autonomic and hormonal compensatory changes.

Cardiac compensatory changes

Attempts to increase stroke volume result in increased wall tension, which in turn increases oxygen consumption of the myocardium. In heart failure, cardiac hypertrophy or dilation develops in order to try and balance the increased pressure and keep the wall stress unchanged. This in turn may be counterproductive and a dilated heart may require treatment with diuretics to reduce the preload.

Autonomic compensatory changes

Baroreceptors increase sympathetic stimulation as an early compensatory mechanism in heart failure. Increased adrenal secretion of adrenaline and neural release of noradrenaline increases heart rate, cardiac contractility and augments blood pressure by increasing peripheral vasoconstriction. In the failing heart, this increase in the afterload increases cardiac demands and will eventually further depress cardiac output. Chronic adrenergic stimulation has other deleterious effects, including hypermetabolism, arrhythmogenesis and has direct myocardial toxicity causing apoptosis, hypertrophy and focal myocardial necrosis. Chronic exposure to high catecholamine levels decreases the density of the β-adrenergic receptors on the myocardial cell surface, resulting in functional loss of the catecholamine-mediated inotropic response. A reduction in heart rate variability is consistently observed in chronic heart failure due to the reduced sympathetic and vagal modulation at the sinus node and may be used as a prognostic marker.

Hormonal compensatory changes

Reduced blood flow to the kidneys results in a marked increase in renin production and subsequent

stimulation of the renin–angiotensin–aldosterone system. Angiotensin II is a potent vasoconstrictor of the renal efferent arterioles and systemic circulation, where it stimulates release of noradrenaline from the sympathetic nerve terminals and inhibits vagal tone and promotes the release of aldosterone. Aldosterone acts to increase sodium and water reabsorption and increase excretion of potassium in the renal tubules that increases blood volume and central venous pressure (preload) but also results in peripheral oedema. The effects of volume expansion and pressure overload result in the release of the natriuretic peptides antagonizing the effects of angiotensin II on vascular tone and sodium reabsorption, causing vasodilatation and natriuresis. Antidiuretic hormone acts on the renal collecting ducts to increase water permeability and reduce urine formation, increasing total blood volume and so preload and afterload. Endothelin is secreted by vascular endothelial cells and acts as a potent vasoconstrictor that has pronounced effects on the renal vasculature, promoting the retention of sodium. Plasma concentration of endothelin-1 is used as a prognostic indicator in heart failure.

A summary of compensatory changes in heart failure are shown in Figure 18.7. These compensatory changes only offer a limited improvement. Increased cardiac filling initially increases cardiac output, as expected by Starling's law, but prolonged excessive filling results in progressive dilatation of the heart, triggering it to hypertrophy and eventually fail.
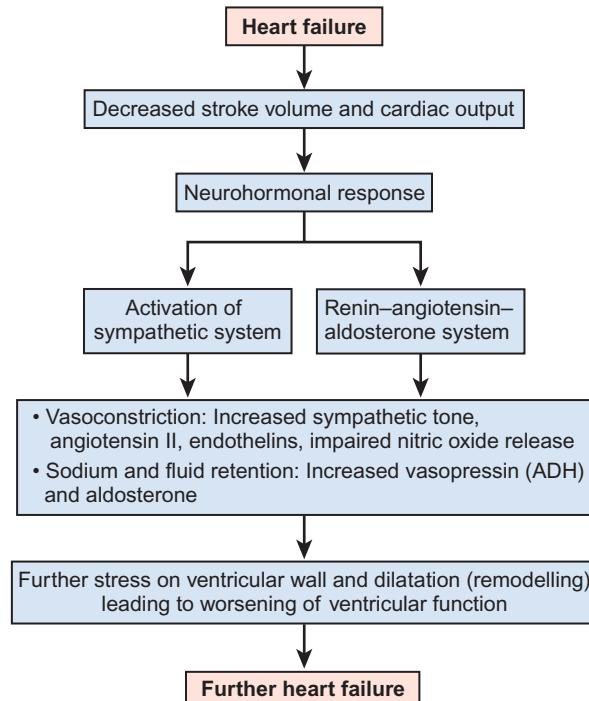
Fig. 18.7 Summary of compensatory changes in heart failure.

Question 18.4

The treatment of heart failure

The following (A–K) is a list of drugs commonly used to treat children with heart failure:

A. Adenosine
B. Adrenaline
C. Amiloride
D. Atenolol
E. Captopril
F. Digoxin
G. Dobutamine
H. Dopamine
I. Frusemide
J. Milrinone
K. Spironolactone

From the list (A–K), pick the drug that best matches the mechanism of action described. Each answer may be used once, more than once or not at all:

1. Sympathomimetic with stronger beta than alpha action. Increases contractility via β_1 stimulation and produces systemic vasodilation via β_2 receptors
2. Protects against deleterious effects of chronic sympathetic overactivity
3. Reduces preload via venous dilation and afterload by decreasing peripheral vascular resistance
4. A lusitrope (enhances myocardial relaxation)

Answer 18.4

1. G. Dobutamine
2. D. Atenolol
3. E. Captopril
4. J. Milrinone

The management of congestive heart failure (CHF) requires knowledge of the underlying cause. The goals of medical therapy for congestive heart failure include:

- Reducing the preload
- Enhancing cardiac contractility
- Reducing the afterload
- Improving oxygen delivery
- Enhancing nutrition

Treatment modalities are summarized in Table 18.6.

Cardiac conduction

The average human heart will contract approximately 100,000 times a day. The cardiac myocytes are the

Table 18.6 Pharmacological treatments for heart failure

Diuretics	Reduce preload – increased excretion of sodium and water.
ACE inhibitors – enalapril, captopril, lisinopril	Prevent conversion of angiotensin I to angiotensin II – increasing plasma renin levels and reducing aldosterone secretion. Reduce preload via venous dilatation and afterload by decreasing peripheral vascular resistance (angiotensin II is a potent vasoconstrictor).
Aldosterone antagonists – spironolactone	Competes with aldosterone for receptor sites in distal renal tubule, increasing water excretion whilst retaining potassium and hydrogen ions.
Beta-blockers – atenolol	Increase stroke volume and decrease contractility and left ventricular size. Long term administration blocks the damaging effects of overactive sympathetic activity.
Phosphodiesterase III inhibitor – milrinone	Positive inotrope and vasodilator with little chronotropic (increasing heart rate) activity. Also has lusitropic (myocardial relaxation) activity to help myocardium relax.
Digoxin	Cardiac glycoside inhibits Na/K ATPase that increases intracellular Na^+ and secondary increase in intracellular Ca^{++} increasing force of contraction.
Dopamine	Catecholamine that stimulates β_1, α_1 and dopaminergic receptors in a dose-dependent fashion. Lower doses cause vasodilation via dopaminergic receptors in renal and splanchnic vascular beds. Mid-range doses act on β-receptors to increase heart rate and contractility. High doses act on α-receptors to increase systemic vascular resistance and increase blood pressure.
Dobutamine	Sympathomimetic with stronger beta than alpha action. Increases contractility via β_1 stimulation and produces systemic vasodilation via β_2 receptors.
Adrenaline	α-agonist – increases peripheral vascular resistance. β_2-agonist – positive chronotrope and inotrope.
Nitroprusside	Vasodilation by relaxing vascular smooth muscle and increases the inotropic activity of the heart.

basic functional units of the heart. They are interconnected by electrical communication protein channels – gap junctions – which allow rapid spread of electrical signal through the cardiac muscle permitting co-ordinated electro-mechanical activity of the heart.

Cardiac cells have an electrical potential across the cell membrane determined by the distribution of ions across the membrane and the differential permeability of the cell membrane. Of the different ions present inside and outside of cells, the concentrations of Na^+,
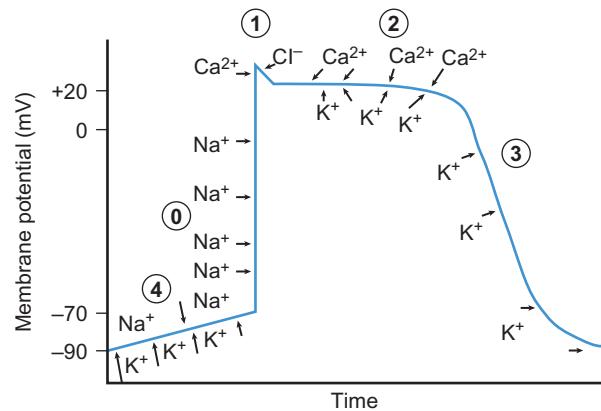
Fig. 18.8 Action potential showing the movement of sodium, potassium, chloride and calcium during the five phases. *(Adapted from http://slideplayer.com/slide/4232070/)*

K^+ and Ca^{++} are the most important in determining the membrane potential. The K^+ gradient is the major determinant of the resting membrane potential in cardiac myocytes. At rest, the concentration of K^+ is high inside and low outside the cell, forming a chemical gradient that favours diffusion outwards. The opposite is true for Na^+ and Ca^{++}, where their chemical gradient favours inward diffusion. The concentration differences across the cell membrane for these ions are determined by the activity of energy-dependent ionic pumps and the presence of impermeable, negatively charged proteins within the cell that affect the passive distribution of cations and anions.

Non-pacemaker action potential

The ionic mechanisms responsible for the generation of 'fast response' non-pacemaker action potentials, such as those found in atrial and ventricular myocytes and Purkinje fibres, are represented in Figure 18.8. By convention, the action potential is divided into five numbered phases (phases 0–4).

Non-pacemaker cells have a true resting membrane potential (phase 4) that remains near the equilibrium potential for K^+. When these cells are depolarized (from −90 mV to a threshold of −70 mV), a rapid depolarization (phase 0) is initiated by a transient increase in conductance of voltage-gated fast Na^+ channels. At the same time, the K^+ concentration falls. These changes move the membrane potential away from the potassium equilibrium potential and closer to the sodium equilibrium potential. Phase 1 represents an initial repolarization caused by the opening of K^+ channels allowing movement of potassium outwards and the inactivation of the Na^+ channels. However, due to the large increase in slow inward Ca^{++}, the repolarization is delayed and the action potential reaches a plateau (phase 2). The cardiac plateau phase

is much longer than that seen in nerves, lasting around 300 ms compared to 1 ms. The inward calcium movement is through long-lasting calcium channels that open when the membrane potential depolarizes to approximately −40 mV. It is these channels that are blocked by the classical calcium channel blockers verapamil and diltiazem. Repolarization (phase 3) occurs when K⁺ increases through delayed rectifier potassium channels and Ca⁺⁺ decreases. During phases 0, 1, 2 and part of 3, the cell is effectively refractory to the initiation of new action potentials where stimulation of the cell will not produce a new, propagated action potential. This is a protective mechanism allowing adequate time for the heart to fill and eject blood. The long effective refractory period also prevents the heart from developing sustained, tetanic contractions like those that can occur in skeletal muscle. At the end of the effective refractory period, the cell is in a relative refractory period where supra-threshold depolarization stimuli can elicit action potentials. Because not all the sodium channels have recovered to resting state by this time, the action potentials generated during the

relative refractory period have a decreased slope and lower amplitude. When the sodium channels are fully recovered, the cell becomes fully excitable and normal depolarization stimuli can elicit new, rapid action potentials.

Pacemaker cells

The heart is able to beat rhythmically in isolation, triggered by waves of electrical excitation initiated by the pacemaker cells of the sinu-atrial (SA) node. The cells within the SA node constitute the primary pacemaker site (Fig. 18.9). Factors influencing the SA node firing rate are listed in Table 18.7. Other, lower order

Answer 18.5

A. False; B. False; C. False; D. True; E. True. The heart rate is slowed by digoxin, hyperkalaemia and hypoxia. It is increased by many drugs (including salbutamol) and pyrexia (see Table 18.7).

Question 18.5

Sinu-atrial node

Which of the following will increase the firing rate of the sinu-atrial node? Answer with true (T) or false (F).

A. Digoxin
B. Hyperkalaemia
C. Hypoxia
D. Pyrexia
E. Salbutamol

Table 18.7 Factors influencing the SA node firing rate

Increasing	Decreasing
Sympathetic stimulation	Parasympathetic stimulation (digoxin)
Muscarinic receptor antagonist	Muscarinic receptor agonist
β-adrenoceptor agonists	Beta-blockers
Circulating catecholamines	Ischaemia/hypoxia
Hypokalaemia	Hyperkalaemia
Hyperthyroidism	Sodium and calcium channel blockers
Hyperthermia	Hypothermia
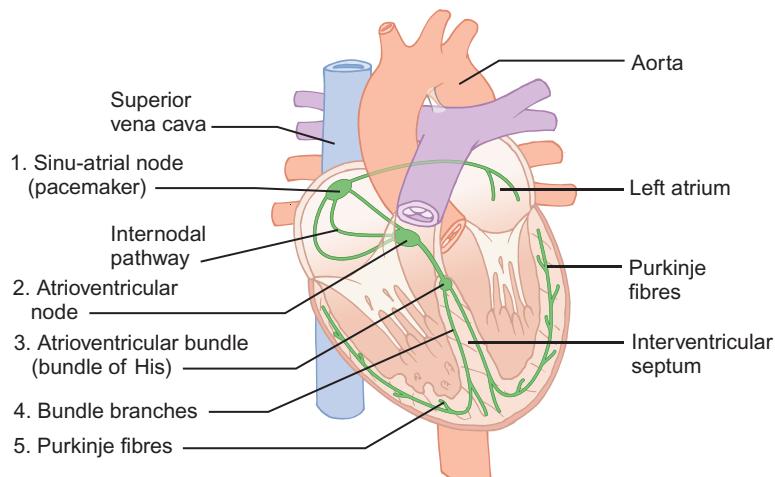
Fig. 18.9 Site of pacemaker cells.

pacemaker cells exist in the atrioventricular node, bundle of His and Purkinje fibres. These have slower intrinsic pacemaking rates than that of the SA node. Normally the intrinsic pacemaker activity of the lower order pacemakers is suppressed by 'overdrive suppression' and their firing rates are driven by the higher rate generated by the SA node. If the SA node becomes depressed, or its action potential fails to reach secondary pacemakers, overdrive suppression ceases, which permits a secondary site to take over as the pacemaker of the heart – an ectopic focus.

The atrioventricular node

The atrioventricular (AV) node is the sole pathway for AV conduction through the fibrous tissue layer that separates atria from ventricles. As conduction is slower than through the ventricular muscle (0.05 m/sec compared to 1.0 m/sec), the action potential transmission from atria to ventricles is delayed by about 0.1 seconds at resting heart rates and, as a consequence, atrial excitation finishes at about the time that ventricular excitation begins.

The lower order pacemaker centres are key to the fast and orderly spread of cardiac excitation to the ventricular myocardium. From the AV node, the action potential swiftly travels down the ventricular septum in the bundle of His and along the right and left bundle branches to enter the Purkinje network, which ramifies through the ventricles. The Purkinje network has a high conduction velocity (5 m/sec) and delivers excitation to the sub-endocardial layers of both ventricles with minimal delay. As excitation reaches both ventricles in a coordinated manner, this allows them to contract almost simultaneously.

An arrhythmia is the manifestation of disturbances in the initiation or propagation of one or more action potentials. Any heartbeat that is triggered by an action potential that arises outside the normal pacemaking tissue is called an ectopic beat. These are common and most have no adverse consequences. Arrhythmias arising from changed SA node pacemaking activity cause more sustained changes to the heart rate.

The electrocardiogram

The synchronized activity of cardiac chambers gives rise to electrical potential differences that can be recorded via electrodes placed at various points on the body surface. This signal can be amplified and recorded as an electrocardiogram (ECG). The ECG provides information on the state of the conduction system and myocardium through heart rate, rhythm, electrical conduction, cardiac position and anatomical changes secondary to abnormal haemodynamics.

The ECG of children normally changes with age. The greatest changes occur during the first year of life, reflecting the changes in the circulation system:

- At birth – ECG reflects right ventricular (RV) dominance. The QRS complex consists of a tall R wave in the right precordial leads (V1–V2) and an S wave in the left precordial leads (V5–V6). There is an upright T wave and a rightward QRS axis (90°–150°). The T wave in lead V1 inverts by day 7 and typically remains inverted until at least 7 years of age.
- At 2–4 years old – the QRS axis shifts from the right to the normal quadrant, as the child grows and the LV becomes dominant, the R wave diminishes over the right precordial leads and the S wave disappears from the left precordium.
- By school age – the ECG has a nearly adult pattern.

A reminder about ECG basics

The ECG is recorded onto standard paper travelling at a rate of 25 mm/second. The paper is divided into large squares, each measuring 5 mm wide (equivalent to 0.2 seconds). Each large square is five small squares in width and each small square is 1 mm wide (equivalent to 0.04 seconds). The electrical activity detected by the ECG machine is measured in millivolts. An amplitude of 1 mV = 10 mm, i.e. 1 small square/1 mm = 0.1 mV. The amplitude of the waveform recorded in any lead is influenced by the myocardial mass, the net vector of depolarization, the thickness and properties of the intervening tissues and the distance between the electrode and the myocardium. The direction of the deflection on the ECG depends on whether the electrical impulse is travelling towards or away from a detecting electrode. By convention, an electrical impulse travelling towards the electrode produces an upright (positive) deflection relative to the isoelectric baseline, whereas an impulse moving directly away from an electrode produces a downward or negative deflection relative to the isoelectric baseline. The six chest leads (V1–V6) view the heart in the horizontal plane; the information from the limb electrodes is combined to produce the six limb leads (I, II, III, aVR, aVL and aVF), which view the heart in the vertical plane. The information from these 12 leads is combined to form a standard ECG where leads II, III and aVF represent the inferior leads; V1–V4 the anterior surface of the heart; I, aVL, V5 and V6, the lateral surface; and V1 and aVR look through the right atrium directly into the cavity of the left ventricle.

Components of the ECG

These are shown in Figure 18.10.
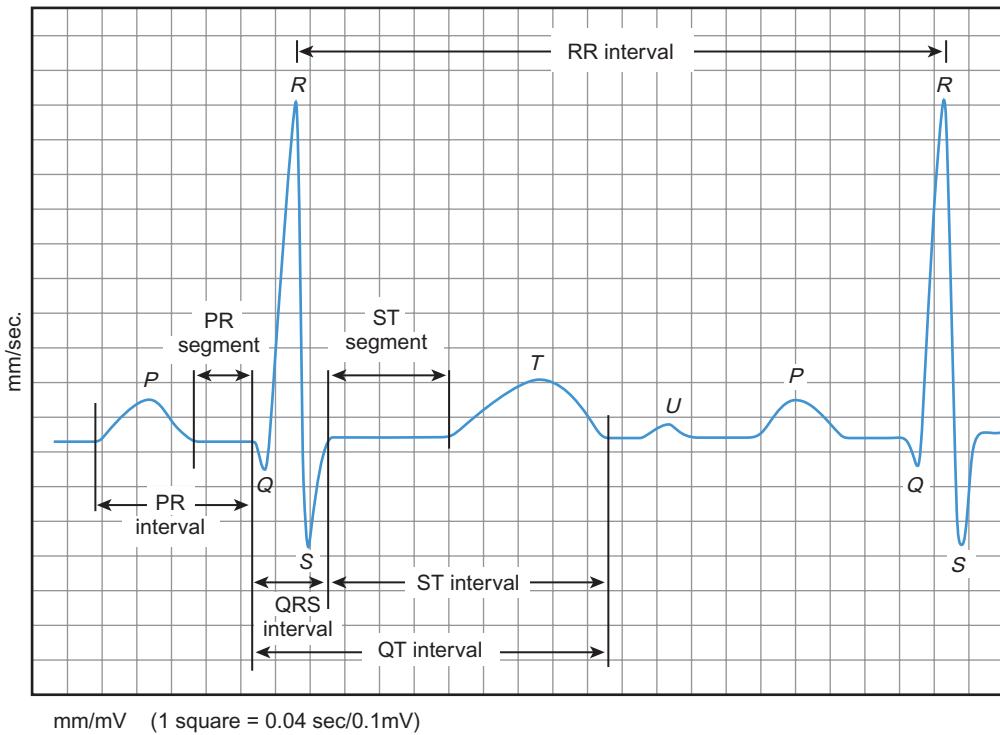
Fig. 18.10 Components of a normal ECG.

mm/mV   (1 square = 0.04 sec/0.1mV)

P wave

Formed by depolarization of the atria, initiated from the SA node, it generally proceeds inferiorly and left-ward toward the AV node located at the junction of the atrium and ventricle low in the right atrium (RA) and adjacent to the coronary sinus. As atrial depolarization begins in the RA, the initial portion of the P wave is formed primarily from RA depolarization, while the terminal portion is formed from left atrium (LA) depolarization. Electrically, the atria act almost as one.

1. P-wave axis – indicates net direction of atrial depolarization, normally +60, and therefore the largest P waves are usually in lead II. P waves are normally positive in leads I, II and aVF and always negative in lead aVR.
2. Amplitude – P waves should not exceed 3 mm in height. P waves taller than 3 mm indicate RA enlargement.
3. Duration – should be less than 120 ms in duration (three small squares); if longer, LA enlargement or intra-atrial block must be considered.
4. Bifid P waves – result from asynchrony between right and left atrial depolarization.

T wave axis

The T wave axis is normally upright in V1 at birth and negative by day 5–7. Persistent upright T wave suggests RV hypertension. The T wave normally remains negative for first 4–5 years and then becomes more anterior. T waves in V2–V6 should be upright by adulthood.

PR interval

After the P wave there is a brief return to the isoelectric line, resulting in the PR segment. During this time the electrical impulse is conducted through the AVN, the bundle of His, bundle branches and the Purkinje fibres. PR interval is the time between the onset of atrial depolarization and the onset of ventricular depolarization and is usually measured in lead II from onset of P wave to beginning of QRS. Varies with age and heart rate. Usually <0.2 seconds; abnormalities of the conducting system may lead to transmission delays, prolonging the PR interval.

Q waves

Normally present in leads II, III, aVF, V5 and V6. Q waves in other leads are rare and associated with disease, e.g. anomalous left coronary artery, or myocardial infarction secondary to Kawasaki disease.

QRS complexes

QRS complexes represent the electrical forces generated by ventricular depolarization. With normal intra-ventricular conduction, depolarization occurs in an efficient fashion. The duration should not exceed 3

Normal R wave progression

V₁ V₂ V₃ V₄ V₅ V₆

R wave height gradually increases to approximately V_4 and then decreases
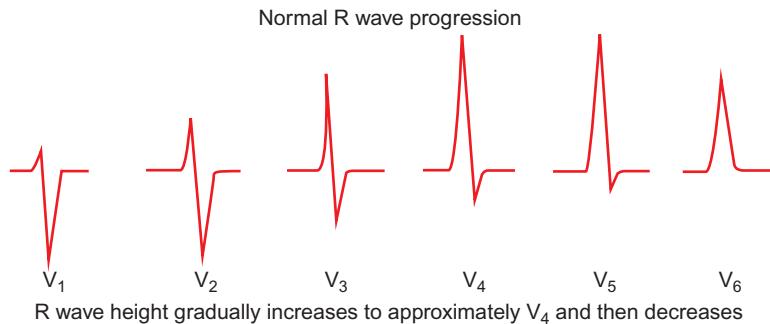
Fig. 18.11 This shows that the R wave height gradually increases to approximately V_4 and then decreases.

small squares (0.12 seconds). Prolongation may occur in left and right bundle branch blocks (WiLLiaM and MaRRoW) and Wolff–Parkinson–White with pre-excitation delta wave.

R wave progression (Fig. 18.11)

In the pre-cordial leads, QRS morphology changes depending on whether the depolarization forces are moving towards or away from a lead. The forces generated by the free wall of the left ventricle predominate, and therefore in lead V1 a small R wave is followed by a large S wave. The R wave in the precordial leads steadily increases in amplitude from lead V1 to V6 with a corresponding decrease in S wave depth, culminating in a predominantly positive complex in V5. Since the V6 electrode is further from the left ventricle, the R wave in V6 is slightly smaller than V5.

- Left ventricular hypertrophy – inverted T wave in V6, increased R voltages in leads I, II, aVL, aVF and sometimes III.
- Right ventricular hypertrophy – upright T wave in V1 at any age, from 1 week to 16 years of life, increased R voltages in leads aVR and III, increased S in lead I.

ST segment

The QRS complex terminates at the J point or ST junction. The ST segment lies between the J point and the beginning of the T wave and represents the period between the end of ventricular depolarization and the beginning of repolarization. The ST segment should be level with the subsequent TP segment and is normally fairly flat, although it may slow upwards slightly before merging with the T wave. In leads V1 to V3, the rapidly ascending S wave merges directly with the T wave, making the J point indistinct and the ST segment difficult to identify. This produces elevation of the ST segment, and this is known as 'high take-off'. Non-pathological elevation of the ST segment is also associated with benign early repolarization, which is particularly common in young men and athletes.

However, high J point and right bundle branch block pattern in V1 is a hall mark of Brugada syndrome.

QT interval

The QT interval normally varies with heart rate, lengthening as the heart rate slows and therefore the heart rate must be taken into account. Bazett's correction formula is used to calculate the QT interval corrected for heart rate.

$$QTc = QT/\sqrt{RR} \text{ (normal is 0.4 with an}$$
$$\text{upper limit of 0.44 seconds)}$$

QT prolongation may be seen in association with hypokalaemia, hypocalcaemia, hypothermia, drug treatment, cerebral injury and the congenital long QT syndrome. Other features of the long QT syndrome include notching of the T waves, abnormal U waves, relative bradycardia for age and T wave alternans. These children may be at risk of ventricular arrhythmia and sudden cardiac death.

T wave

The T wave is produced by ventricular repolarization. The normal T wave is asymmetrical, the first half having a more gradual slope than the second half. T wave orientation usually corresponds with that of the QRS complex, and thus is inverted in lead aVR and may be inverted in lead III. T wave inversion in lead V1 is normal in children up to 16 years, inversion in V2 is normal up to 12 years and T wave inversion in V3 is normal up to 8 years. T wave amplitude should be less than 2/3 of the amplitude of the corresponding R wave. T wave amplitude rarely exceeds 10 mm.

U wave

The U wave is a small deflection that follows the T wave. It is generally upright except in aVR and is often most prominent in leads V2–V4. U waves result from repolarization of the mid-myocardial cells (i.e. those between the endocardium and epicardium and the His–Purkinje system). Prominent U waves may be

found in athletes and are associated with hypokalae-mia and hypercalcaemia.

Arrhythmias

Narrow complex tachycardia (supraventricular tachycardia)

A narrow complex tachycardia refers to any arrhythmia that originates above or at the bundle of His. They are the most common tachycardia seen in children.

In supraventricular tachycardia (SVT) (Fig. 18.12), the heart rate is rapid, between 220 and 300 beats per minute. The clinical relevance in an individual patient is related to the ventricular rate, the presence of any underlying heart disease and the integrity of cardio-vascular reflexes. In the young infant or neonate, SVT typically presents with symptoms of heart failure. It is also a cause of hydrops fetalis and intrauterine demise.

In the paediatric population, it can be difficult on initial presentation to differentiate the different types of SVT from sinus tachycardia (Table 18.8). The

Table 18.8 Clinical and ECG features that can differentiate between supraventricular tachycardia and sinus tachycardia

Sinus tachycardia	Supraventricular tachycardia (SVT)
• Child may have systemic illness	• Previously well with no preceding systemic upset
• Heart rate rarely >200 bpm	• Heart rate generally >220 bpm
• P wave upright in leads II, III, aVF	• P waves may be absent or negative in leads II, III and aVF
• Beat-to-beat variability	• No beat-to-beat variability (fixed RR interval)
• Heart rate slows with treatment/fluid resuscitation	• Rate abruptly changes with adenosine
	• Sudden onset
	• May have had previous episodes
	• Little change in rate with activity, crying or breath-holding

probability of complete resolution of SVT is dependent on age of onset. In the majority of infants diagnosed at 1 year of age or less, SVT is likely to resolve in >90%, compared to only 33% of patients diagnosed after 1 year of age.

SVT may be divided into two distinct groups depending on whether they arise from the atria or the atrioventricular junction. Increasing the atrioventricular block by manoeuvres such as carotid sinus massage or administration of IV adenosine may be of diagnostic value, as slowing the ventricular rate allows for more accurate visualization of the atrial activity.

From the atria or sinu-atrial node

Atrial fibrillation or flutter

Atrial fibrillation is caused by multiple re-entrant circuits trigging waves of activation in the atria. It is seen on ECG as an irregular baseline made up of fibrillation waves with absent P waves. Conduction of atrial impulses to the ventricles is variable and unpredictable, manifesting as an irregular RR interval on ECG. Atrial flutter is due to a re-entry circuit in the right atrium with secondary activation of the left atrium. This produces atrial contractions at a rate of about 300 bpm seen on the ECG as saw-toothed flutter waves. The ventricular rate depends on the rate of conduction through the AV node and is typically 2:1 producing a ventricular rate of 150 bpm.

From the atrioventricular junction

AV re-entry tachycardia (AVRT), also known as accessory pathway-mediated tachycardia, is the most common type of SVT seen in children, representing over 80% of arrhythmias occurring during infancy. It involves an electrical re-entry circuit proceeding down the AV node and then up an accessory pathway outside the AV node, creating a narrow complex tachycardia. Some 50% of patients with AVRT have Wolff–Parkinson–White syndrome where, when in sinus rhythm, they manifest ventricular pre-excitation in the form of a delta wave on ECG. The remainder have a 'concealed' pathway, which is not evident on ECG during sinus rhythm. In Wolff–Parkinson–White

Fig. 18.12 Rhythm strip showing supraventricular tachycardia.

syndrome, as conduction through the accessory pathway can occur before the AV node is activated, a shortened PR interval, slurred QRS upstroke and widened QRS result. This also creates the potential for rapid ventricular response during atrial fibrillation, which can result in ventricular fibrillation and sudden death. Importantly, digoxin should not be given to children with Wolff–Parkinson–White syndrome, as it can enhance conduction through the bypass tract, whilst slowing down conduction through the AV node, and this may trigger descent into VF. Due to this increased risk of VF, although the acute management of SVT is the same for patients with concealed and manifest pathways, definitive ablative therapy in patients with WPW is recommended.

AV nodal re-entry tachycardia

AV nodal re-entry tachycardia (AVNRT; Fig. 18.13) is also due to a re-entry circuit but the pathway involves the AV node itself. There are two discrete conduction limbs, a slow (usually anterograde conduction) and a fast pathway (usually retrograde conduction). This accounts for approximately 15% of SVT in the paediatric population and its incidence increases with age and is rarely seen in infants.

Treatment of SVT

Many SVTs self-terminate. If treatment is required, then vagal manoeuvres – i.e. ice bag on the face (diving reflex), carotid sinus massage – may be effective in up to 80%. Intravenous adenosine is the drug of choice – negative chronotropic and inotropic actions, induces AV block and terminates the tachycardia by breaking the re-entry circuit that is set up between the AV node and the accessory pathway. This is mediated via the A_1 receptor, inhibiting adenylyl cyclase, reducing cAMP and causing cell hyperpolarization by increasing

outward K^+ flux. It is given via a rapid IV bolus; an initial low dose is administered via a large proximal vein and flushed with IV saline. Further higher doses may be administered if the arrhythmia is not terminated.

Synchronous electrical cardioversion may be carried out if the child is unstable (0.5–2 J/kg of body weight) or after failure of adenosine. Other medication may also be tried on advice from a paediatric cardiologist and may include propranolol, flecainide, amiodarone or digoxin. Propranolol, flecainide and sotalol may help to prevent recurrence. For those who relapse, electrophysiology study with catheter ablation may offer definitive treatment. It is commonly required in children who are symptomatic from WPW or AVNRT. All patients warrant echocardiography to look for evidence of an underlying congenital heart disease. However, the majority will have a structurally normal heart.

Heart block

AV block is a disturbance in conduction between the normal sinus impulse and the eventual ventricular response. There are three separate types, according to severity of conduction disturbances:

- First degree: Prolongation of PR interval due to abnormal delay in conduction through the AV node. Causes include infections, inflammatory conditions including acute rheumatic fever, CHD and drugs, e.g. calcium channel blockers.
- Second degree: Some but not all P waves are followed by QRS complexes (dropped beats).
  - Mobitz type 1 (Wenckebach): PR interval progressively prolongates until one beat is dropped. The block is at the level of the AV node. Normally caused by infections, cardiomyopathy, CHD, post cardiac surgery.
  - Mobitz type 2: All or no AV conduction. Two-to-one, or higher AV block. A QRS follows every second, third or fourth P wave resulting in 2:1, 3:1 or 4:1 block, respectively. Block is usually at bundle of His and therefore can progress to complete heart block.
- Third degree: Atrial and ventricular activities are entirely independent of one another. Congenital causes: maternal lupus, anti-Ro or anti-La maternal antibodies, isolated anomaly, or congenital heart disease. Acquired occasionally after cardiac surgery.

Ventricular tachycardia

Ventricular tachycardia (VT) is uncommon in children. VT is defined as a series of three or more premature ventricular contractions. Typically, this has a rate
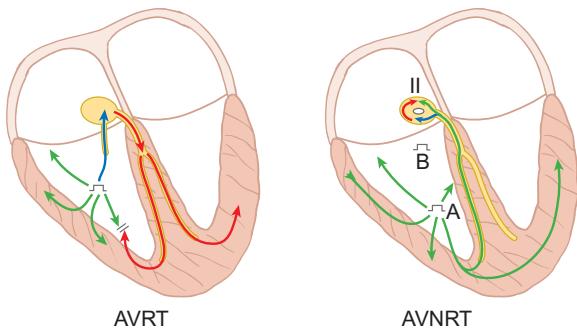
Fig. 18.13 Re-entry tachycardia. A. AV re-entry tachycardia (AVRT), in which the electrical re-entry circuit proceeds down the AV node and then up an accessory pathway. B. AV nodal re-entry tachycardia (AVNRT), in which the pathway involves the AV node itself. *(Redrawn from http://lifeinthefastlane.com/ecg-library/svt/)*

Table 18.9 Causes of acquired long QT syndrome

Electrolyte disturbance	Hypokalaemia, hypocalcaemia, hypomagnesaemia
Drugs	Range of antibiotics, antifungals, antidepressants, antiarrhythmic and other drugs
Medical conditions	Hypothermia Hyperparathyroidism, hypothyroidism Encephalitis, head injury Cardiac – complete AV block, sick sinus, congestive heart failure, myocarditis

of more than 120 beats per minute with wide QRS morphology. It may degenerate into ventricular fibrillation and is a medical emergency. If the child is not shocked then intravenous amiodarone may be administered. If a child is shocked then DC cardioversion under sedation should be performed.

Prolonged QT

Long QT syndrome (LQTS) is a disorder of ventricular repolarization, characterized by prolonged QT interval (QTc >0.45 seconds in lead II) on the ECG and ventricular arrhythmias, usually torsades de pointes (which is where there are gradually larger and smaller complexes; can lead to ventricular fibrillation and sudden death). It may be congenital or acquired and symptoms include a sudden loss of consciousness during exercise, stress or emotion, usually in later childhood. Treadmill (exercise) testing characteristically results in significant prolongation of QTc with maximal prolongation 1–2 minutes in recovery phase. Ventricular arrhythmias may develop during the test in up to 30%. There are now many recognized genetic causes of long QT syndrome; some acquired causes are listed in Table 18.9. The clinical features depend on the effect of gain-of-function or loss-of-function sodium, calcium and potassiumion channel genes. This will determine the management accordingly. Some will just require β-blocking medication, whereas others will require implantation of defibrillator devices.

Management of a child with prolonged QTc involves a beta blocker, a 24-hour ambulatory ECG and genetic screening. Avoidance of competitive level sport should be advised. All first-degree relatives should also receive an ECG and genetic testing. Similarly, there is also short QT syndrome, where the QTc is less than 320 ms. This can also predispose to sudden death.

Cardiac investigations

If congenital heart disease is suspected, a chest X-ray and ECG should be performed. Echocardiogram combined with Doppler enables almost all cases of congenital heart disease to be identified, with cardiac catheterization seldom required to make a diagnosis but reserved for haemodynamic measurements and interventions.

Chest X-ray

The plain chest film is an important part of the cardiac evaluation and can provide important information, including heart size and silhouette; enlargement of specific cardiac chambers; pulmonary blood flow or pulmonary vascular markings. It also provides information regarding lung parenchyma, spine, bony thorax, abdominal situs, etc.

Cardiac silhouette

In a newborn, a normal cardiac silhouette is often obscured by the large thymus and the films are often poorer quality, often being exposed during expiration. Characteristic shapes of the contact silhouettes are:

- Boot shaped – Fallot/tricuspid atresia
- Egg on side – transposition of great arteries
- Snowman/cottage loaf – total anomalous pulmonary venous connections.

Echocardiogram

Echocardiography is now the standard non-invasive cardiac investigation and is indicated:

- To detect cardiac defects or dysfunction
- To rule out cyanotic congenital heart disease in newborns with clinical findings of pulmonary hypertension
- To diagnose patent ductus arteriosus in a premature infant requiring respiratory support
- To follow up conditions that may change with time
- To evaluate a patient after cardiac surgery

Doppler is useful for detecting the presence and direction of cardiac shunts, studying stenosis or regurgitation of cardiac valves, assessing the haemodynamic severity of a lesion, estimating cardiac output or blood flow, and assessing diastolic function of the ventricle.

Cardiac catheterization

The improvement of two-dimensional and Doppler echocardiography has reduced but not supplanted the need for cardiac catheterization. Cardiac catheterization is usually performed under general anaesthesia in children. A femoral catheter is inserted and advanced to the heart. At each position in the heart and vessels, values of pressure and oxygen saturation of blood

Table 18.10 Normal values for oxygen saturations and pressures during cardiac catheterization

Right atrium	Left atrium
$SaO_2 = 65\%$	$SaO_2 = 99\%$
Pressure = 4 mmHg	Pressure = 6 mmHg
Right ventricle	Left ventricle
$SaO_2 = 65\%$	$SaO_2 = 98\%$
Pressure = 25/4	Pressure = 75/6
Pulmonary artery	Aorta
$SaO_2 = 65\%$	$SaO_2 = 97\%$
Pressure 25/15	Pressure 75/50 (age dependent)

(Table 18.10) are obtained. The oxygen saturation data provides information on the site and magnitude of a left-to-right or right-to-left shunt if present. The pressure data provides information on the site and severity of obstruction. Complications are rare but may relate to catheter insertion and manipulation, e.g. arrhythmias, heart block, cardiac perforation, hypoxic spells, arterial obstruction, haemorrhage and infection. They may also relate to contrast injection, exposure, sedation and medications.

Cardiac symptoms and conditions seen in children

Syncope

Up to 15% of children between the ages of 8 and 18 years are estimated to have a syncope event and most are benign. Factors that point to cardiac syncope include:

- Sudden onset without any prodromal period of dizziness or imminent awareness
- Syncope during exercise or exertion
- Complete loss of awareness and muscle tone so that fall results in injury
- Palpitations or abnormal heartbeat noted before the event
- Abnormal heart rate (fast or slow) after the event
- Family history of cardiovascular disease at an early age or sudden death.

Cardiac causes of sudden death in the young occur due to ventricular fibrillation in the setting of myocardial or coronary abnormalities or primary rhythm disorders. The main structural causes are hypertrophic cardiomyopathy, anomalies of the coronary artery, Marfan's syndrome, and arrhythmogenic right ventricular dysplasia. Abnormal coronary arteries as sequelae of Kawasaki disease may be a consideration. Prolonged QT syndrome and Wolff–Parkinson–White syndrome are sometimes implicated. Children with congenital heart disease are at a higher risk of sudden cardiac death.

Kawasaki disease

Kawasaki disease is a vasculitis of small to medium vessels of unknown aetiology and is a leading cause of acquired heart disease in children. It most commonly affects children 6 months to 4 years of age and has clinical features of fever for more than 5 days, associated with at least four of the following clinical features:

- Polymorphous rash
- Lymphadenopathy
- Conjunctivitis
- Mucositis
- Oedema of hands and feet with subsequent desquamation

Coronary arteritis can occur and result in aneurysm formation.

Infective endocarditis

Infective endocarditis is rare in childhood but important to diagnose and treat. Those at increased risk (NICE guidelines) are patients with:

- Acquired valvar heart disease with stenosis or regurgitation
- Valve replacement
- Structural congenital heart disease, including surgically corrected or palliated structural conditions, but excluding isolated ASD, fully repaired VSD or fully repaired PDA, and closure devices that are judged to be endothelialized
- Hypertrophic cardiomyopathy
- Previous infective endocarditis

The risk is highest in congenital heart disease where there is a turbulent jet of blood, artificial prosthetic material within or outside the heart or repetitive IV drug use. Antibiotic prophylaxis is no longer recommended in the UK as it has not been proven to be effective, but good dental hygiene and avoidance of invasive procedures, including body piercing and tattooing, is stressed.

Rheumatic fever

Rheumatic fever is rare in the UK but is the most important cause of acquired heart disease worldwide. An inflammatory disease involving the joints and heart and, less frequently, the central nervous system, skin and subcutaneous tissues, it is a complication of group A β-haemolytic streptococcus, and mainly

affects children aged 5–15 years of age (peak 8 years). There is a 2–6 week latent period between an upper respiratory tract infection and the onset of rheumatic fever. The incidence is higher in people living in overcrowded conditions and there may be a genetic influence, as family clustering occurs.

In the early stages there is acute inflammatory exudative reaction lasting 2–3 weeks and involves the myocardium, valves (mitral, most commonly, followed by aortic) and pericardium. This is followed by a proliferative phase, where Aschoff bodies form; this pathognomonic lesion consists of perivascular infiltrations of large cells with polymorphous nuclei and basophilic cytoplasm arranged in a rosette around an avascular centre of fibrinoid. Subsequently, fibrotic scarring occurs in the region of the Aschoff bodies. Valvar lesions begin as small verrucae composed of fibrin and blood cells along the borders of the valves. This may progress to loss of valve tissue with shortening and thickening of the chordae tendinae. With persistent inflammation, fibrosis and calcification occur. Chronic mitral regurgitation leads to left atrial dilatation, which may in turn lead to atrial fibrillation. There is also an increased risk of endocarditis.

Joint symptoms are the most common feature, occurring in 75% with a typical migratory polyarthritis. The joint symptoms usually disappear in 3–4 weeks. Carditis occurs in approximately 50% of initial attacks. Tachycardia disproportionate to fever is a typical finding. The most distinctive sign of rheumatic carditis is a new distinctive murmur, which is most commonly the blowing pansystolic apical murmur of mitral regurgitation. Other signs of carditis are a pericardial rub or evidence of congestive heart failure. Sydenham's chorea occurs in approximately 15% of patients. Subcutaneous nodules are found in 5–10% and erythema marginatum in less than 5%.

Cardiomyopathy

Cardiomyopathy is a disease of the myocardium, may be primary or secondary and is divided into three broad categories: dilated, hypertrophic or restrictive.

Myocarditis

Myocarditis is an inflammatory disorder of the myocardium leading to necrosis of the myocytes. It can occur at any age, including the newborn period, and is most commonly caused by viral infections such as Coxsackie B or adenovirus although multiple other infective agents have also been implicated. Rarely, myocarditis may be caused by drugs, toxins or autoimmune disease. It is supposed that a disordered autoimmune response to the initial viral insult may

play a part in disease progression and this may have a genetic basis.

Pulmonary hypertension

In children, pulmonary hypertension is defined as a mean pulmonary artery pressure greater than 25 mmHg at rest or when systolic pulmonary artery pressure is >50% of systemic systolic pressure. It may occur as a result of failure of pulmonary blood pressures to fall after birth (persistent pulmonary hypertension of the newborn; see Chapter 11, Neonatal medicine), rarely as a primary phenomenon or usually secondary to a number of respiratory causes. The term *cor pulmonale* describes right ventricular hypertrophy and/or dilatation secondary to pulmonary hypertension caused by pulmonary diseases.

Symptoms are often vague and include fatigue, exertional dyspnoea, syncope, chest pain and headaches. The diagnosis is usually made by a vigilant doctor who notices clubbing and/or unexpectedly low oxygen saturations with a loud second heart sound and right ventricular heave.

Question 18.6

Treatment of pulmonary hypertension

The following (A–J) is a list of drugs used in the treatment of pulmonary hypertension:

A. Bosentan
B. Calcium channel blocker
C. Digoxin
D. Furosemide
E. Inhaled nitric oxide
F. Magnesium sulphate
G. Oxygen
H. Prostacyclin analogue (epoprostenol)
I. Sildenafil
J. Spironolactone

From the list above, select the drug that best matches the mechanism of action described below. Each answer may be used once, more than once or not at all:

1. Results in elevation of cyclic GMP causing local vasodilation
2. Competitively inhibits the vasoconstrictive effects of endothelin-1 in the lung
3. Slows the ventricular rate in children with secondary tachyarrhythmia

Table 18.11 Management options for the treatment of pulmonary hypertension

Treatment	Effect
Oxygen	Provides symptomatic improvement
Calcium channel blockers, e.g. nifedipine or amiodipine	Systemic and pulmonary vasodilator
Inhaled nitric oxide	Potent and selective pulmonary vasodilator acts via cyclic GMP pathway
Sildenafil, Tadalafil	Oral or IV phosphodiesterase-5 inhibitor, increases GMP levels and endogenous nitric oxide effect
Riociguat	Oral soluble guanylate cyclase stimulator, increases GMP levels
Bosentan and Macitentan Ambrisentan	Endothelin receptor antagonist; competitively binds to endothelin-1 receptors reducing smooth muscle cell proliferation
Prostanoids	Pulmonary vasodilator and inhibitor of platelet aggregation; acts on cyclic AMP pathway Oral, subcutaneous, inhaled and IV preparations.

Table 18.12 Systemic diseases with frequent cardiac involvement

Muscular dystrophy	Dilated cardiomyopathy manifesting during adolescence. Secondary to fatty degeneration and lymphocytic infiltration. Dystrophic changes in the papillary muscles may be evident with mitral regurgitation or mitral valve prolapse.
Myotonic dystrophy	Fatty infiltration of the myocardium and degeneration of the sinus node and atrioventricular conduction pathway may result in arrhythmias and sudden death. Mitral valve prolapse may develop. Left ventricular dysfunction appears with advancing age.
Marfan's syndrome	Clinically evident cardiovascular involvement in over 50% occurs by age 21. Abnormalities including dilation of sinus of Valsalva, dilation of ascending aorta which may dissect or rupture, aortic regurgitation and mitral valve abnormalities. Microscopic examination of proximal aorta shows disruption of the elastic media with fragmentation and disorganization of elastic fibres.
Hyperthyroidism	Tachycardia, full bounding pulses, increased systolic and pulse pressures. Cardiac enlargement and cardiac failure may develop.
Hypothyroidism	Acquired hypothyroidism – slow heart rate with hypotension. Pericardial effusion and symmetrical septal hypertrophy. ECG – low QRS voltages, low T wave amplitudes, prolonged PR and QT intervals.
Sickle cell anaemia	Increased stroke volume secondary to anaemia, the heart gradually dilates and hypertrophies. Heart failure may develop.

Answer 18.6

1. I. Sildenafil
2. A. Bosentan
3. C. Digoxin (see above for explanation)

Management of secondary pulmonary hypertension is mainly targeted at the underlying cause, but treatment options are listed in Table 18.11.

Further reading

Anderson RH, Baker EJ, Penny D, et al., editors. Paediatric cardiology. 3rd ed. Philadelphia: Churchill Livingstone, Elsevier; 2010.

Lissauer T, Carroll W, editors. Illustrated textbook of paediatrics. 5th ed. Edinburgh: Mosby, Elsevier; 2015.

Opie LH, Gersh BJ, editors. Drugs for the heart. 7th ed. Philadelphia: Saunders, Elsevier; 2009.

Park MK. Pediatric cardiology for practitioners. 5th ed. Philadelphia: Mosby, Elsevier; 2008.

Cardiovascular involvement in systemic diseases

There are many systemic diseases that have important cardiovascular manifestations. Some examples are listed in Table 18.12.

Rajiv Sinha, Stephen D Marks

CHAPTER

Nephrology

19

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Understand the critical anatomy and embryology of the urinary tract
- Understand the relevant physiology of the kidney and understand how dysfunction relates to disease
- Know the commoner presentations of renal disease in children
- Have a logical rationale for the investigation of renal disease and disorders of the urinary tract
- Understand the principles of water balance and rehydration
- Know the causes of hypertension

Introduction

The kidneys and urinary tract are a critical organ system in enabling homeostasis. Their principle functions are those of water, electrolyte and acid–base balance. They also play an important role in hormone secretion, red cell production and the control of blood pressure. The functions of the renal tract are most clearly elucidated by examining the results of renal failure and renal disease (Fig. 19.1).

Anatomy and physiology of the kidney

Kidneys are retroperitoneal structures located in the paravertebral space; the right kidney is slightly lower than the left. At birth, average length of the kidney is 4.5–5.5 cm, whereas an adult kidney measures 10–11.5 cm in length and 5–7 cm in width. The anterior surface of the kidney lies in contact with the duodenum on the right side and the pancreas on the left side. Variable portions of colon may be in contact with the inferior pole of the anterior surface of the kidneys, and on the left side the spleen wraps the anterolateral aspects of the upper half of the kidney. The 12th rib and a portion of the 11th rib cover the upper third of the posterior surface of the left kidney, whereas the 12th rib may touch the upper pole of the right kidney.

The outer surface of the kidney is covered by a thin but firm capsule. The anatomical position of the kidney explains the retroperitoneal approach for renal biopsy and the choice of lower pole of the right kidney.

A longitudinal cut section of the kidney and its relationship to the other structures in the urinary tract is shown in Figure 19.2.

Nephrons (Fig. 19.3) are the ultrastructural units of the kidney, of which we have around a million in each kidney. The nephron comprises a glomerulus connected to a tubule which in turn drains into a collecting duct; ultimately, they join and drain into the calyces at the renal pyramids. The glomerulus generates filtrate through ultrafiltration of blood brought in by the afferent arterioles. The ultrafiltrate accumulates in the Bowman's space and thereafter traverses the tubules, where it is further modified into the final urine. During passage of tubular fluid down the renal tubule, solutes are reabsorbed by the highly selective transport mechanisms (Fig. 19.4). In general, most transport occurs in the proximal tubule, where the luminal membrane forms an elaborate 'brush border' of microvilli to provide extensive surface area for the reabsorptive processes. The brush borders are densely packed with mitochondria to supply the energy required for these active transports. Organic solutes such as low-molecular-weight proteins, sugars, and amino acids are avidly (>98%) reabsorbed in this

Healthy kidney
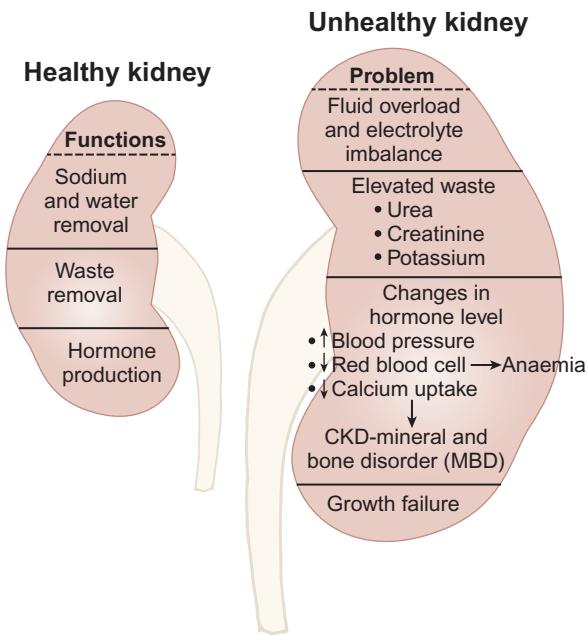
Unhealthy kidney

Fig. 19.1 Functions of the healthy kidney and consequences of renal dysfunction.

Table 19.1 Causes of renal tubular disorders

Segment	Function	Disorder
Proximal tubule*	Glucose transport Phosphate transport Amino acid transport	Renal glycosuria Hypophosphataemic rickets Isolated, generalized aminoaciduria
Ascending limb of Henle	Sodium, potassium, chloride transport	Bartter syndrome
Distal tubule	Proton (H$^+$) secretion Sodium chloride transport	Distal renal tubular acidosis Gitelman syndrome
Collecting duct	Water transport Sodium, potassium transport	Nephrogenic diabetes insipidus Pseudohypoaldosteronism Liddle syndrome

*Generalized dysfunction of the proximal tubule is called Fanconi syndrome.

segment. In addition, bulk transport of inorganic solutes and water is also accomplished in the proximal tubule. The subsequent tubules fine-tune the net re-absorption of these solutes and water. Dysfunction in the absorptive capacity of the tubules can give rise to various disorders of tubulopathy (see below). The glomerular filtration barrier consists of parietal epithelial cells with its foot process (podocytes), the glomerular basement membrane (GBM) and the capillary endothelial cells. Filtration of molecules across this structural barrier is limited by size, shape, and charge. Whereas charge selectivity is determined by negatively charged molecules present in the filtration barrier, size selectivity is determined by the GBM and by the slit diaphragm generated by interposing podocyte foot processes.

Tubular disorders

The adult kidneys filter on average 150 litres of plasma per day containing 22.5 mol of sodium; more than 99% of filtered sodium is reabsorbed by the tubules, so that the final excretion is <1% (see Fig. 19.4). Disorders in sodium handling affect blood pressure (BP); sodium-losing disorders lead to hypotension and sodium-retaining disorders to hypertension. The Na$^+$/K$^+$-ATPase, which is present in all cells, is the driving force which generates a favourable electrochemical gradient for Na entry into the cell. This gradient also enables cotransport of other substances (such as glucose, amino acids, phosphate) into the cell. As sodium is the main determinant of intravascular

volume, fractional excretion of sodium is normal in almost all renal salt-wasting disorders due to activation of renin–angiotensin–aldosterone system (RAAS). An overview of the different aetiologies of tubular disorder is given in Table 19.1.

Fanconi syndrome

This syndrome describes a generalized proximal tubular disorder with at least initially well-preserved glomerular function. There is a long list of potential causes and it is helpful to split these into congenital, acquired and renal causes. The cardinal clinical features are growth faltering, polyuria and rickets in association with a normal plasma anion gap, metabolic acidosis, hypophosphataemia, hypokalaemia and generalized aminoaciduria. Supportive therapy may be required, which includes salt, water and nutritional supplementation as well as bicarbonate, electrolyte and phosphate replacement.

Congenital causes include a familial idiopathic form, cystinosis (see below), tyrosinaemia and galactosaemia. Fanconi syndrome may also be acquired following treatment with aminoglycosides, sodium valproate, 6-mercaptopurine or ifosfamide or following poisoning with agents like toluene or paraquat. It occasionally occurs after renal transplantation, in the recovery phase of acute tubular necrosis or following tubulointerstitial nephritis or in focal and segmental glomerulosclerosis, a histopathological type of nephrotic syndrome.

Nephropathic cystinosis is the commonest cause of Fanconi syndrome in Europe and North America. It is a disorder of lysosomal cystine transport of autosomal recessive inheritance, resulting in excessive
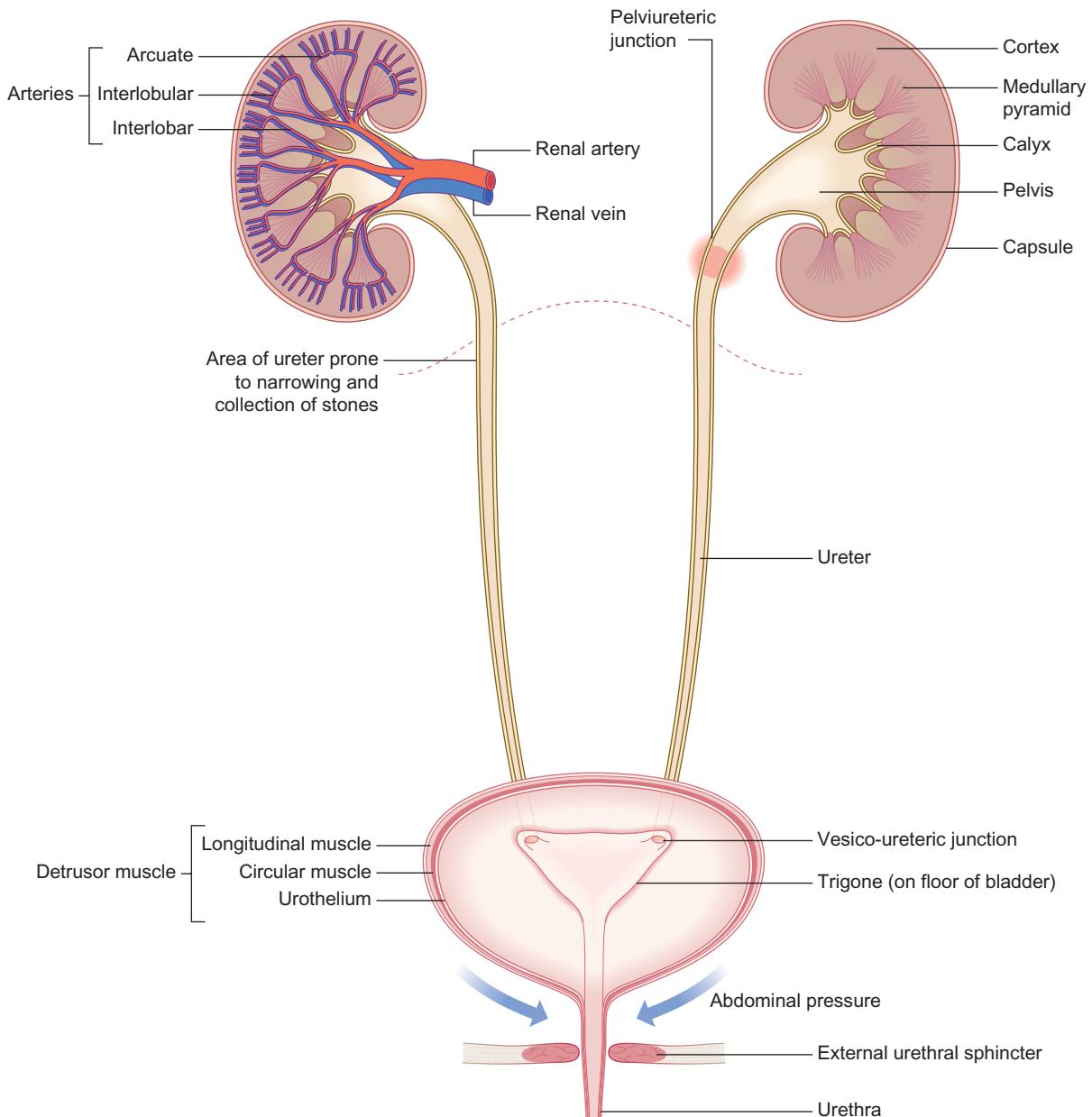
Fig. 19.2 The major components of the urinary tract and bladder. The ureter and renal vessels are placed in the medial side of the kidney, known as the hilum, which opens into a central space, the renal pelvis. The pelvis of the kidney extends out of the kidney to form the ureter, while the intrarenal portion divides into numerous calyces (6–10 in number), which drain the renal pyramids. The papillae of the renal pyramids open directly into the calyces. The pelvi-ureteric junction and vesico-ureteric junction are narrower points along the ureter and hence are most prone to obstruction. *(From Naish J, et al. Medical sciences, 2e. Saunders, 2014, with permission.)*
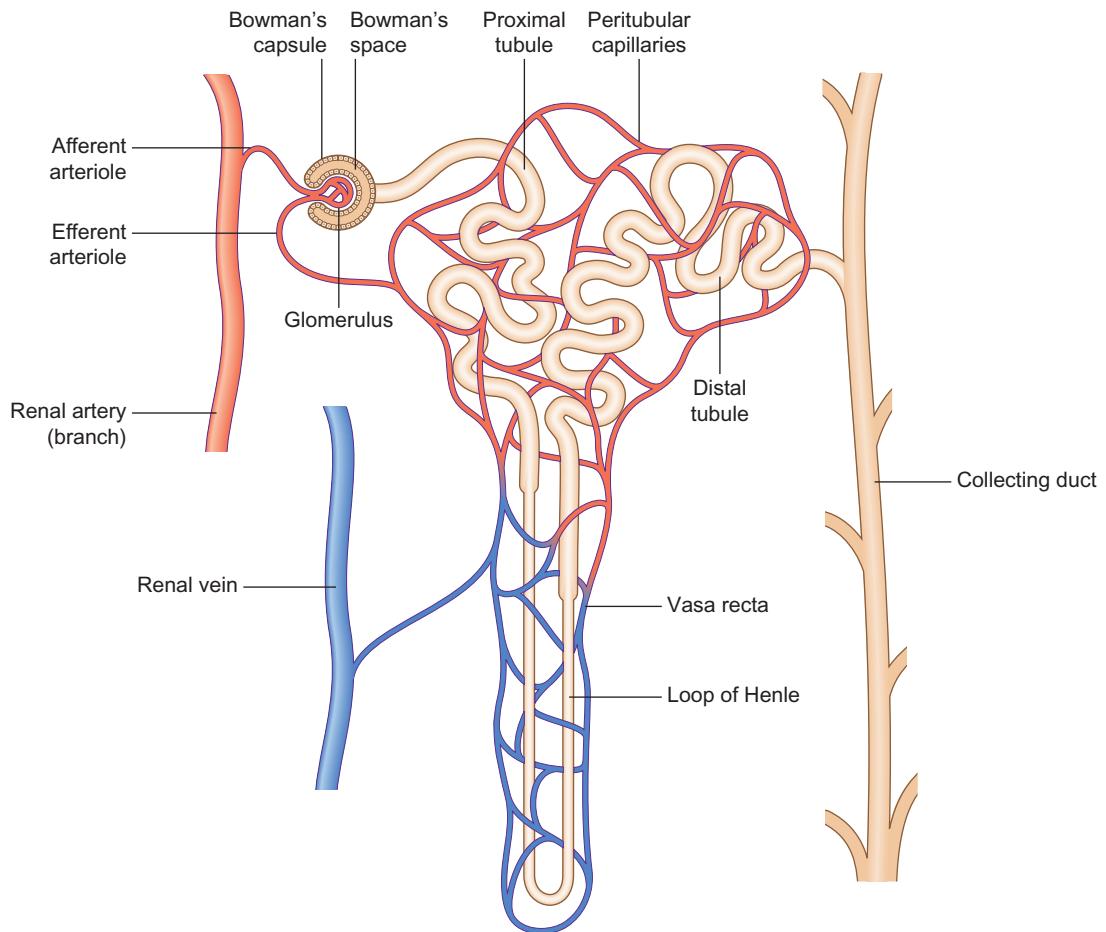
Fig. 19.3 Schematic diagram of a nephron. The blood supply originates from the renal artery (red) and leaves via the renal vein (blue). Blood passes through two capillary beds, the glomerular capillaries followed by the vasa recta. *(From Naish J, et al. Medical sciences, 2e. Saunders, 2014, with permission.)*

intracellular accumulation of free cystine in many organs including the kidney, eyes and thyroids. Management includes specific therapy with mercaptamine, which prevents accumulation of lysosomal cystine.

Bartter and Gitelman syndromes

These syndromes occur as a result of disturbances in the thick ascending limb of loop of Henle (Bartter) and distal convoluted tubule (Gitelman), respectively, and typically result in a hypokalaemic, hypochloraemic metabolic alkalosis with salt wasting. The main problem is tubular loss of sodium and chloride and secondarily excess loss of potassium in the distal tubule associated with hyperreninaemia and hyperaldosteronism. In this part of the nephron, sodium reabsorption is linked to chloride reabsorption through the furosemide-sensitive sodium–potassium–chloride channel (NKCC2) in the loop of Henle (disrupted in Bartter syndrome) or the structurally similar thiazide-sensitive sodium–chloride channel (NCCT)

in the early distal convoluted tubule (disrupted in Gitelman syndrome), respectively. Salt-wasting disorders from these parts of the nephron will always be associated with urinary chloride loss in excess of urine sodium loss because all chloride reabsorption is linked with sodium, with twice as much chloride as sodium reabsorbed via NKCC2. Moreover, sodium reabsorption but not chloride reabsorption can occur partly via the paracellular route and there is no capacity for chloride reabsorption more distally within the nephron.

Hypercalciuria occurs in Bartter syndrome because calcium reabsorption is a linked paracellular process. Hypomagnesaemia does not occur because of compensatory reabsorption in the early distal convoluted tubule (DCT). By contrast, Gitelman syndrome has hypocalciuria and hypomagnesaemia because of a compensatory mechanism in the early DCT which down-regulates cells expressing NCCT (and an apical magnesium channel) in favour of cells which reabsorb sodium and calcium. Gitelman syndrome generally
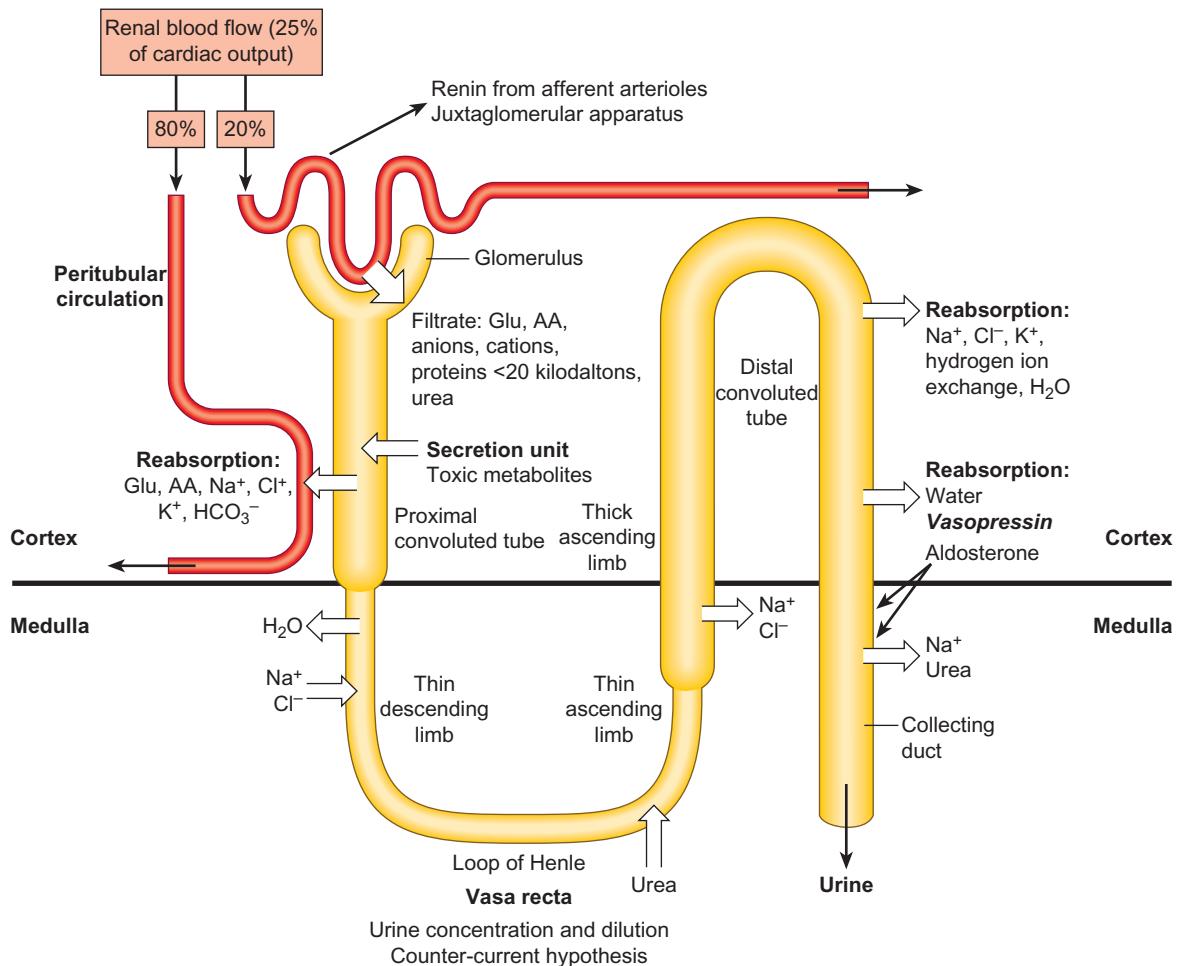
Fig. 19.4 Diagrammatic representation of the major transport sites across the nephron. Apart from macromolecules, the glomerular filtrate contains glucose, amino acids, electrolytes such as sodium, potassium, chloride, urea, bicarbonate and water. The PCT is the major site for reabsorption: 99% of the glucose is reabsorbed into the peritubular circulation, also essential nutrients and electrolytes. Bicarbonate reabsorption at the PCT affects renal acid–base homeostasis. Toxic metabolites, cations and anions are also secreted by the PCT. The loop of Henle is the major site for urine concentration according to the countercurrent hypothesis. Further sodium chloride and water reabsorption takes place in the DCT and CT, controlled by vasopressin and aldosterone. AA, amino acid; CT, collecting tubule; DCT, distal convoluted tubule; Glu, glucose; HCO_3^-, bicarbonate; PCT, proximal convoluted tubule. *(From Naish J, et al. Medical sciences, 2e. Saunders, 2014, with permission.)*

presents in older children or even adults with muscle weakness and cramps, and short stature. It is not uncommonly diagnosed following investigation of growth, constipation or enuresis. Classical Bartter syndrome is generally a more severe disorder, presenting in early childhood with growth faltering, dehydration, hypotonia and lethargy. There is often a history of maternal polyhydramnios with the classical form.

Renal tubular acidosis

The kidney achieves acid–base balance through bicarbonate reabsorption and acid secretion. Kidneys normally reabsorb up to 90% of filtered bicarbonate in the proximal tubules. The distal collecting tubules are principally responsible for acid secretion. Buffers in the tubular lumen bind free hydrogen ions, allowing excretion of the daily acid load within limits of the minimal achievable urine pH of 4.5 to 5. Ammonia and, to a lesser extent, phosphate are the main urinary buffers. Ammonia (NH_3), which is formed from amino acid metabolism, can freely diffuse across tubular membranes, where it combines with protons to form ammonium (NH_4^+), which becomes trapped in the tubular lumen.

Renal tubular acidosis (RTA) occurs in several ways: bicarbonate wasting in the proximal tubule (historically known as type 2 RTA), which almost always occurs as part of Fanconi syndrome; impairment in formation of ammonia results in type 4 RTA and in renal failure, where the acidosis is associated with hyperkalaemia; and failure to adequately secrete

hydrogen ions is the primary defect in distal RTA (associated with hypokalaemia).

In childhood distal RTA, most cases are genetic. Autosomal recessive forms can be associated with (*ATP6V1B1*) or without (*ATP6V0A4*) sensorineural deafness. Both mutations code for subunits of the H-ATPase apical hydrogen ion transporter. An auto-somal dominant form is caused by mutations of the *SLC4A1* gene which encodes the chloride–bicarbonate exchanger on the basolateral membrane. Urine pH in distal RTA is always >5.5, in contrast to proximal RTA where it varies according to the plasma bicarbonate.

Initial correction of acidosis needs to take into account potassium and calcium, which will both decrease in response to alkali treatment. Maintenance treatment consists of sodium bicarbonate or citrate (sodium and/or potassium). Generally the doses of base required are less than for proximal acidosis. Chil-dren require lifelong follow-up and are at risk of nephrolithiasis and long-term deterioration in renal function from the nephrocalcinosis.

Embryology of the urinary tract (Fig. 19.5)

In higher forms of vertebrates, including man, kidneys evolve through three stages: pronephros, mesoneph-ros and metanephros. Pronephric and mesonephric kidneys are temporary and metanephros persist as permanent kidneys. Whereas the urinary tract devel-ops from the cloaca and the intermediate mesoderm, the definitive functional kidney develops from the metanephros through involution of pronephros and mesonephros.

- The pronephros is thought to be the primitive kidney, which is non-functional in the humans. The pronephros degenerates by the fifth week; its duct becomes the mesonephric duct.
- The mesonephric duct ultimately becomes the ureteric bud, which is essential for the development of metanephros. The ureteric bud subsequently branches to form the ureter, pelvis, calyces and the collecting system.
- The metanephros forms the glomeruli and upper part of the nephrons. Interaction between the ureteric bud and the metanephros is essential for the development of the kidneys. Defective communication between them leads to various congenital anomalies of the kidney and urinary tract (CAKUT) ranging from renal dysplasia to renal agenesis.
- Nephrons start to develop from the eighth post-conceptual week and continue until 34 weeks post conception.
- The upper portion of the bladder is derived from the allantois and the lower portion from the cloaca, which is also involved in the development of the rectum. As a result of this link, anorectal malformations are often associated with nephro-urological problems. The fibrous cord, the urachus, is formed from the remainder of the allantois and connects the bladder to the umbilicus.
- During fetal life, the kidneys are lobulated, and a lobular appearance is present even at birth, which
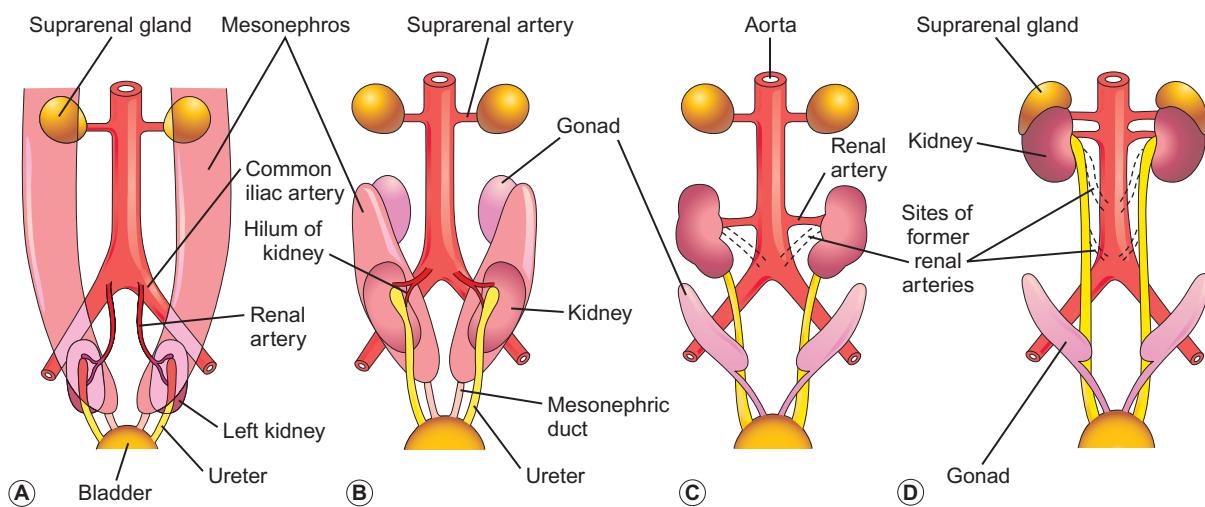
Fig. 19.5 Embryology of the kidneys between the critical sixth and ninth weeks of gestation. Ventral views of the abdominopelvic region of embryos and fetuses (sixth to ninth weeks) showing medial rotation and 'ascent' of the kidneys from the pelvis to the abdomen. A,B. Observe also the decrease in size of the mesonephroi. C,D. Note that as the kidneys 'ascend', they are supplied by arteries at successively higher levels, and that the hilum of the kidney (where the vessels and nerves enter) is eventually directed anteromedially. *(From Moore K L, Persaud TVN, Torchia MG. Before we are born, 8th edition. Saunders, 2013, with permission.)*

affects the appearance of the kidneys on ultrasound in newborns.

Question 19.1

Changes on ultrasound screening

The parents of a newborn term infant ask to speak to a paediatrician. They are concerned that their new baby had some 'changes' identified on antenatal scanning at 28 weeks and would like to discuss these with you. Which of the following represent changes that are likely to adversely affect the baby's health and/or renal function? Answer with true (T) or false (F).

A. An anterior–posterior diameter of 5 mm of the right renal pelvis
B. Lobulated appearance of kidneys
C. Multicystic dysplastic kidneys
D. Oligohydramnios
E. Visible bladder with a 5 mL volume

Answer 19.1

A. False; B. False; C. True; D. True; E. False.

Improvements in second and third trimester ultrasound (USS) screening have resulted in an increased number of antenatally-detected urinary tract abnormalities (AUTA). If a child has unilateral multicystic dysplastic kidney with normal contralateral kidney which develops normally with compensatory hypertrophy with normal ureter and bladder, then the child has an excellent prognosis. This is very different from children with bilateral renal anomalies. Abnormalities fall into two main categories:

• Abnormalities of renal parenchymal texture
• Abnormalities of drainage system

Congenital anomalies of the kidney and urinary tract are the most common abnormality detected on antenatal ultrasound scans, with an incidence of 1–4.5% of all pregnancies (Table 19.2). One of the most frequently detected abnormalities is dilatation of the renal tract. An anterior–posterior diameter (APD) of ≥7 mm at 18–20 weeks is considered significant. Early diagnosis improves the outcome because of early recognition and treatment of critical obstructions and urinary tract infections, preventing further renal damage and loss of renal function.

The fetal bladder is approximately 1 mL in volume by 20 weeks and increases to 35–50 mL by 40 weeks. It can be seen emptying every 30 minutes by 20 weeks' gestation and it empties approximately once per hour by term. A typical fetus at term produces approximately 50 mL of urine per hour.

Table 19.2 Congenital anomalies of the kidney and urinary tract

Transient hydronephrosis (normal postnatal scan)	50%
Hydronephrosis with no evidence of obstruction or external pelvis	15%
Pelvi-ureteric junction obstruction (PUJO)	11%
Vesico-ureteric reflux (VUR)	9%
Megaureter (obstructed, refluxing, non-refluxing and non-obstructed or both refluxing and obstructed)	4%
Renal dysplasia	3%
Multicystic dysplastic kidney (MCDK)	2%
Duplex kidney ± ureterocoele	2%
Posterior urethral valves	1%
Others	5%

Hydronephrosis

Hydronephrosis is dilatation of the collecting system of the kidney, and hydroureter is dilatation of the ureter. Neither term implies obstruction. There is no clear definition or test for obstruction; its diagnosis requires a mixture of clinical and functional assessment including nuclear medicine imaging with DTPA/MAG3 scans (see section on imaging below). Hydronephrosis secondary to pelvi-ureteric junction obstruction (PUJO) is the commonest abnormality of the upper urinary tract. Renal ultrasound would show a dilated renal pelvis (isolated renal pelvis diameter >20 mm is highly suggestive of PUJO) with usually non-dilated ureter. It is more common in boys with overall incidence of 1 in 1000. Older children may present with acute loin or abdominal pain (Dietl's crisis), haematuria, a palpable flank mass, infection (including pyonephrosis), nausea/vomiting, or pelvic rupture following minor trauma.

As there can be progressive renal damage, early diagnosis and assessment of the degree of renal dysfunction is important. Dynamic renogram such as DTPA or MAG3 will aid in this as they give split renal function which can be monitored. As only around 25% develop clinical problems, the need for surgical intervention has to be carefully evaluated. Surgery is considered if there is deterioration of renal function or increasing dilatation of the renal pelvis with thinning of renal cortex.

Functional development

In fetal life, excretion is performed primarily by the placenta, which receives 50% of fetal cardiac output whereas the fetal kidney accounts for only 2–4%. Hence, creatinine at birth reflects maternal creatinine level. The glomerular filtration rate (GFR) is 10–15 mL/min/1.73m² in the premature infant and 15–20 mL/min/1.73m² in the term infant. These values double

over the first two weeks after birth and reach adult values of 80–120 mL/min/1.73m² by one year of age. The increase in GFR is achieved by recruitment of more glomeruli and not by new glomerulus generation.

Urine formation starts by the end of the first trimester. Fetal urinary concentrating activity is poor and fetal urinary sodium and phosphate levels decrease while the creatinine increases with increasing gestation, reflecting increasing maturation. The maximum urine concentrating capacity is low even at birth (up to 600 mOsm/kg) which explains the higher susceptibility of newborns and infants to dehydration. Adult capacity is achieved only by 1–2 years. In contrast, the diluting capacity of newborns is equivalent to that of adults and the urine osmolality can be lowered to 30–50 mOsm/kg.

For common developmental anomalies of the kidneys, see Box 19.1 and Figure 19.6.

Investigating renal function

Urine examination

Question 19.2

Urine examination

The following (A–J) is a list of diagnoses:

A. Acute glomerulonephritis
B. Acute intermittent porphyria
C. Alport's syndrome
D. Benign familial haematuria
E. Diabetic ketoacidosis
F. Myoglobinuria
G. Nephrotic syndrome
H. Primary hyperoxaluria
I. Urinary tract infection
J. Zellweger's syndrome

Select the diagnosis from the list that BEST fits with the following urine findings. Each answer may be used once, more than once or not at all:

1. Macroscopic appearance: red/brown; urine dipstick: positive for blood (3+) and protein (2+), negative for leukocytes, nitrites, glucose and ketones; urine microscopy: no cells

2. Macroscopic appearance: brown/red; urine dipstick: positive for blood (3+), protein (2+), leukocytes (2+), negative for glucose and ketones; urine microscopy: granular casts

3. Macroscopic appearance: cloudy; urine dipstick: positive for leukocytes (2+), protein (+), ketones (+), negative for nitrites and glucose; urine microscopy: 70 white cells per high-powered field, occasional rod

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Answer 19.2

1. F. Myoglobinuria
2. A. Acute glomerulonephritis
3. I. Urinary tract infection
   See below for explanation.

Urine examination is an important but simple and non-invasive aid to diagnosis. It should ideally start with visual inspection, which may provide clues to haematuria (red urine) or pyuria (cloudy urine). However, as other conditions can mimic them, suspected haematuria or pyuria on inspection

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Box 19.1 Common developmental anomalies of the kidneys (see also Fig. 19.6)

- Agenesis of the kidneys – usually due to failure of development of the ureteric bud.
- Renal hypoplasia – renal architecture is maintained, but fewer nephrons. Unless bilateral, is usually asymptomatic. May predispose to hypertension in later life.
- Multicystic dysplastic kidneys (Fig. 19.6A) – if the secreting and collecting parts fail to communicate, the kidney may become non-functional and transformed into multiple non-communicating cysts.
- Renal dysplasia – malformed and rudimentary tissues such as cartilage, or even calcified tissue within normal kidney. Chronic kidney disease (CKD) may develop in severe bilateral cases.
- Multiple kidneys – due to early splitting of the ureteric bud.
- Pelvic kidney – failure of ascent of the kidney due to persistence of sickle-shaped fold of peritoneum which projects from the lateral pelvic wall containing umbilical arteries.
- Fused kidney – lower poles of both kidneys united by an isthmus of kidney tissue. Horse-shoe kidney (Fig. 19.6B) lies in a lower level as its ascent is arrested by inferior mesenteric artery.
- Duplex kidney (Fig. 19.6C) – embryologically, duplication occurs when two separate ureteric buds arise from a single Wolffian duct. Duplication is variable. At one end of the spectrum, there is merely duplication of the renal pelvis, draining via a single ureter. At the other extreme, two separate collecting systems drain independently into the bladder or ectopically.
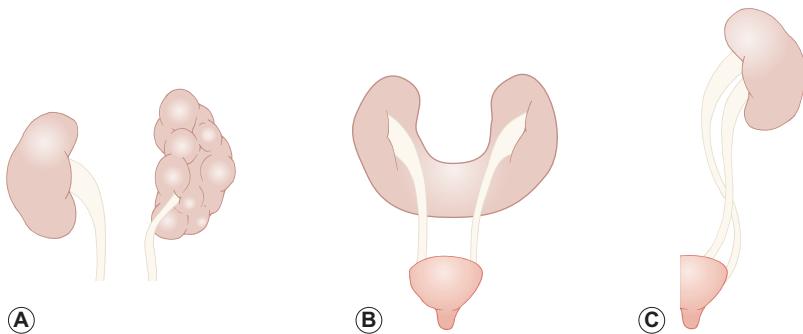
Fig. 19.6 Developmental anomalies of the kidneys. A. Multicystic dysplastic kidneys. B. Horse-shoe kidney. C. Duplex.

needs to be confirmed by urine microscopy. Testing urine by dipstick is a useful bedside test. It can be used for:

- Glucose, urobilinogen, bilirubin, ketones, pH and specific gravity.
- Haemoglobin – if dipstick positive, this usually indicates blood in the urine. Haematuria is confirmed by red blood cells on urine microscopy, and absence of red blood cells in the urine in presence of positive dipstick suggests either haemoglobinuria or myoglobinuria.
- Protein – can be detected but urine dipstick does not give an accurate quantitative estimation. Quantifying it requires spot urine albumin or protein : creatinine ratio or 24-hour urine protein estimation in an older child. A morning sample is preferable for testing, as this helps to exclude the false positives seen in children with orthostatic proteinuria. If significant proteinuria is seen on dipstick but insignificant albumin on quantitative estimation, leak of tubular proteins indicating tubular damage should be suspected.
- Leukocytes and nitrites – leukocytes are suggestive of urinary tract infection (UTI) but not diagnostic, as they can be secondary to fever. Most pathogenic bacteria produce nitrite, which has a high specificity but low sensitivity for diagnosing UTI. Nitrites may be negative in infants and younger children with UTI, as their increased urinary frequency does not allow sufficient time for nitrites to be produced. Urine cultures are therefore advisable to determine the bacteriological cause and antibiotic sensitivities in complicated UTI, as well as to confidently rule out UTI in children younger than three years. Urine microscopy can identify red and white blood cells and also RBC casts, which is considered to be diagnostic of glomerular involvement.

Glomerular filtration rate

Glomerular filtration rate (GFR) is a measure of renal function. Although inulin remains the reference solute for GFR estimation, it is mainly used as a research tool. In clinical practice, GFR is measured using radiopharmaceuticals, such as ^{99m}Tc-DTPA, 125I-iothalamate and ^{51}Cr-EDTA. Isotopic methods have the advantage that they do not require timed urine collection. In older children and adults, 24-hour urine collections are possible and can also be used. As these methods are too complex for routine clinical use, serum creatinine is used as a surrogate marker for renal function. However, this is not ideal as it is not an early indicator of renal damage. It also varies with age, muscle mass and nutritional status. Therefore, it can be inappropriately low in malnourished children or those with major amputation even in a stage of advanced renal failure.

Formulas for calculating GFR (estimated GFR) have been devised to correct for body size, such as the modified Schwartz formula:

$$\frac{K \times \text{height (cm)}}{\text{Plasma creatinine } (\mu\text{mol/L})}$$

where K is a constant (varying between 33 and 40).

When testing for renal function, serum electrolytes are usually measured. They not only tell us about life-threatening complications (e.g. hyperkalaemia), but are useful in assessing the tubular function and volume status. For interpreting urinary loss of any electrolytes, a calculation of the fractional excretion is better than spot urinary value.

Imaging of the urinary tract

Ultrasound

Ultrasound scan (USS) is the most frequently used imaging modality in paediatric nephrology, as it is

non-invasive and provides very good anatomical detail. Colour Doppler USS is useful for ascertaining renal blood flow, such as graft perfusion after renal transplantation, suspected renal vein or venous thrombosis or renal artery stenosis.

Micturating cystourethrogram

Micturating cystourethrogram (MCUG) requires bladder catheterization. Once the catheter is in place, a small amount of contrast medium is injected through the catheter to fill up the bladder. It allows very good images to be obtained of the anatomy of the lower urinary tract and is the 'gold standard' test for documenting and grading vesico-ureteric reflux (see below). It is also useful in documenting any bladder outlet obstruction, such as posterior urethral valves.

Its disadvantages are the small risk of infection, the requirement for radiation and the need for urethral catheterization that can be psychologically traumatic, particularly in the toddler age group.

Nuclear medicine

Dynamic scanning (99mTc-DTPA/MAG3)

Dynamic scanning (MAG3 or DTPA scans) is useful for showing obstruction, such as pelvi-ureteric junction (PUJ) obstruction and is most often used after USS has shown dilated collecting system (hydronephrosis). It also gives an estimate of split differential function of both kidneys. MAG3 nuclear scan is supposed to be superior to 99mTc-DTPA scan and can even be used to document reflux in older children who are continent and can control urination on demand.

Static scanning (99mTc-DMSA)

Static scanning provides information about the renal parenchyma, most frequently used to identify renal scars. However, the radiation dose is higher than that in dynamic scanning.

Fluid and electrolyte homeostasis

Basic principles

Fluid within the body is distributed between the intracellular fluid (ICF) and extracellular fluid (ECF) compartments (Fig. 19.7). Solute composition differs between the two components and this is maintained by cell membrane pump activity, and solute size and electrical charge.

BODY COMPARTMENTS
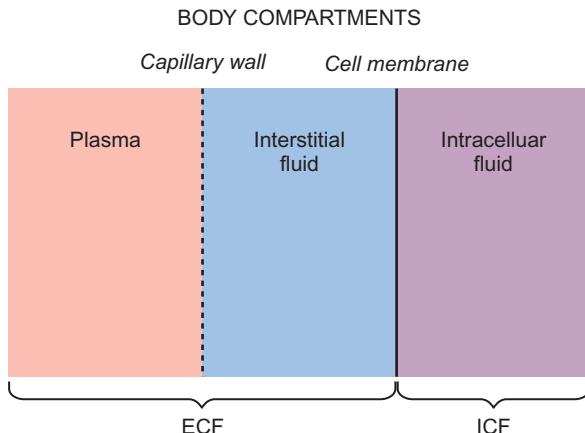
Fig. 19.7 **Body fluid distribution.**

Question 19.3

Intravascular volume

A 6-year-old boy presents with a relapse of his nephrotic syndrome. He has had heavy proteinuria for 5 days and is very oedematous. He has been taking oral prednisolone for two days. Which one of the following measurements will give the BEST indication of intravascular volume? Select ONE answer only.

A. Blood pressure
B. Capillary refill time
C. Heart rate
D. Respiratory rate
E. Weight

Answer 19.3

C. Heart rate.

Volume assessment of the individual compartments can be very tricky in clinical practice and involves clinical assessment of all of the above parameters. For example, in a situation like nephrotic syndrome, there may be weight gain and oedema on examination. However, since there is hypoalbuminaemia and albumin is the primary intravascular osmotic component, the intravascular fluid volume may be low but the total ECF volume high. Conversely, in acute kidney injury, there can be weight gain and oedema in a situation where both the total ECF and the intravascular volume are high. Oedema can therefore occur with high or low intravascular fluid volume. In nephrotic syndrome, intravascular hypovolaemia is easy to miss as the child is oedematous. Pulmonary oedema may result in tachypnoea and significant

Sodium (Na) and water homeostasis are intimately intertwined. A decrease in plasma water of 10% will lead to an increase in the plasma Na concentration from 140 to 154 mmol/L and dilution of plasma by 10% will decrease Na to 126 mmol/L. For the kidney, volume preservation (rather than serum Na concentration) is the most important stimulus. There are no bodily receptors that can detect serum Na levels directly, however changes in plasma *tonicity* are sensed by osmoreceptors in the brain which affect renal water handling via antidiuretic hormone (vasopressin). When there is conflicting information, the most important principle is preservation or restoration of a normal plasma volume, rather than Na concentration. This is the reason, even in the presence of hypernatraemic dehydration, urine Na may be low and urine Na is usually elevated in SIADH (syndrome of inappropriate antidiuretic hormone) or in acute water intoxication despite profound hyponatraemia. Nonetheless, biochemical parameters like fractional excretion of Na can assist in determining plasma volume status.

Abnormalities of serum sodium

Hyponatraemia (plasma Na <135 mmol/L) occurs when there is either water gain in excess of sodium gain or sodium loss in excess of water loss. Factitious hyponatraemia occurs due to the presence of abnormal solutes in the ECF such as mannitol, sorbitol or excessive glucose. This extra molecule results in a fluid shift which alters the Na measurement. High measured osmolality in contrast to calculated osmolality (i.e. $2 \times [Na + K] + [urea] + [glucose]$) despite low serum Na provides an important clue when it is suspected.

Genuine hyponatraemia can be managed using the following principles:

- Rapid correction is only given if symptomatic (coma/seizures), is rarely used and only recommended by specialists; 2–3 mL/kg of 3% NaCl may be used.
- Rapid correction should stop once symptoms improve. Plasma Na should not increase by more than 8–12 mmol per 24 hours.
- As most cases are due to excess water, fluid restriction is often helpful. Furosemide can also be useful in severe cases by increasing free water

clearance. Both these measures are often used in SIADH. Tolvaptan, a vasopressin receptor 2 antagonist is being explored as a possible drug for refractory SIADH. Replacement of the volume deficit and ongoing losses with normal saline will be needed in cases of hyponatraemia where salt loss is in excess of water loss.

Hypernatraemia (plasma Na >145 mmol/L) may be due to sodium gain in excess of water gain or water loss in excess of sodium loss. As sodium is the principle ECF osmole, the ECF volume is relatively well maintained and signs of dehydration and hypovolaemia are less apparent in cases of hypernatraemic dehydration, making assessment of degree of dehydration difficult. Severe hypernatraemia may be associated with brain damage because brain tissue shrinks as a result of intracellular dehydration and blood becomes hypercoagulable. This may result in encephalopathy, cerebral haemorrhage or thrombosis.

Management of hypernatraemic dehydration includes:

- Avoidance of rapid correction as it may result in cerebral oedema
- Sodium chloride 0.45% or 0.9% is used but boluses of normal saline are given only in presence of shock.

If acute, hypernatraemia can be corrected over 24–48 hours. If chronic, sodium correction should be performed even more slowly. If the correction is done rapidly, fluid will rapidly pass into the cells and catastrophic cerebral oedema may develop. The plasma Na should be reduced by no more than 0.5 mmol/hr. Normal hydration should be achieved over 36–48 hours and perhaps even 72 hours if the initial plasma Na is >170 mmol/L.

Abnormalities of serum potassium

In contrast to Na, potassium (K) is primarily intracellular (98%), so plasma K is a poor representation of total body K. The ratio of extra- and intracellular K is the major determinant for the membrane potential of excitable cells, such as in the heart or the neuromuscular system and acute changes can be life-threatening. The known effects of K on physiology are summarized in Box 19.2.

Hyperkalaemia (K >5.5 mmol/L)

It is imperative to be sure that the reported potassium level is not an artefact. There are several possible common causes including:

1. Haemolysed blood sample
2. Improper collection, e.g. EDTA contamination or squeezed sample

ECG changes

The pattern of the T wave on ECG reflects K concentration. In hypokalaemia, there is ST depression, a flat T wave and emergence of a U wave, whereas hyperkalaemia will show peaked T waves.

Acid–base changes

Acidosis results in hyperkalaemia as hydrogen ions displace potassium as the intracellular cation and potassium shifts from the intracellular to the extracellular compartment.

Drugs and hormones

As the distribution of K between ICF and ECF is controlled by Na/K ATPase channel, compounds that enhance the activity of this pump, such as insulin or adrenergics (salbutamol), can be used for treatment of hyperkalaemia.

The normal kidney

Most important K regulation is done at the collecting duct, where, under the influences of aldosterone, K is exchanged for Na. Absence of aldosterone activity or insufficient sodium delivery (as in hypovolaemia) will impair K excretion.

Transtubular potassium gradient (TTKG) can be used to assess aldosterone activity:

$$TTKG = \frac{K \text{ in urine} \times \text{serum osmolality}}{K \text{ in blood} \times \text{urine osmolality}}$$

In presence of normal aldosterone activity, TTKG is usually >5 and decreases to <3 in its absence. For interpreting TTKG, one has to ensure that urinary Na is >20 mmol/L (confirming sodium delivery) and the urine osmolality is equal to or greater than plasma.

Box 19.3 Treatment of hyperkalaemia

1. Correction of acidosis with bicarbonate ⎫
2. Insulin glucose infusion ⎬ Internalizes the potassium from extracellular to intracellular
3. Beta 2 agonist (e.g. salbutamol) ⎭
4. Potassium binder (e.g. calcium resonium resin: decreases body potassium store)
5. Intravenous calcium gluconate: stabilizes the myocardium

Table 19.3 Causes of hyperkalaemia and hypokalaemia

Hyperkalaemia (serum potassium >5.0 mmol/L)	Hypokalaemia (serum potassium <3.5 mmol/L)
Renal failure	Diarrhoea
Acidosis	Alkalosis
Adrenal insufficiency	Volume depletion
Cell lysis	Primary hyperaldosteronism
Excessive potassium intake	Diuretic abuse
In the critically ill neonate, inadequate cardiac output must always be excluded as a cause	

Hyperkalaemia in the presence of a normal glomerular filtration rate is usually due to either failure of delivery of sodium to the distal tubules (as in hypovolaemia) or to aldosterone deficiency/resistance (congenital adrenal hyperplasia or primary hypoaldosteronism). As discussed later, transtubular potassium gradient (TTKG) is a useful test in such situations.

Hypokalaemia (K <3.5 mmol/L)

Hypokalaemia has a variable clinical presentation and can present as lethargy, confusion, muscle weakness (paralysis in severe cases), intestinal ileus. It is either due to decrease in total body potassium or shift of potassium to the intracellular space (Table 19.3). A fractional excretion of >10% suggests renal loss. In presence of volume excess, hypokalaemia may be due to aldosterone excess such as hyperaldosteronism (Conn's syndrome), and renal artery stenosis. Hypokalaemia with acidosis should prompt a diagnosis of renal tubular acidosis. Low urinary potassium signifies an extrarenal loss of potassium such as diarrhoea.

Emergency intravenous treatment is rarely required. It is required urgently if cardiac arrhythmias or respiratory insufficiency secondary to paralysis are encountered. Very rapid infusion should be avoided as it has the potential to cause major adverse effects and, as very concentrated potassium solutions (>40 mmol/L of additional potassium) are damaging to peripheral veins, there is often a practical limit to how fast hypokalaemia can be corrected. If needed, it should

3. Delay in processing the blood sample
4. Markedly raised platelets, leukocytes or erythrocytes.

Severe hyperkalaemia can precipitate cardiac arrhythmia. In the presence of ECG changes, treatment has to be initiated as soon as possible (Box 19.3).

The first step in identifying the underlying aetiology is assessment of renal function, as renal failure from any cause will lead to hyperkalaemia. It is often aggravated by other coincidental factors such as use of angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta blockers, trimethoprim or increased K load secondary to tumour lysis, intravascular haemolysis, or rhabdomyolysis.

be performed under ECG monitoring and in paediatric intensive care. Many children will also have low serum magnesium levels and if untreated this will increase the risk of cardiac arrhythmia.

Question 19.4

Treatment of hyperkalaemia

Concerning the treatment of hyperkalaemia of a child in acute kidney injury, which of the following treatments is most likely to reduce the TOTAL body potassium level? Select ONE answer only.

A. Calcium gluconate intravenously

B. Correction of acidosis with bicarbonate

C. Insulin : glucose infusion

D. Potassium binder (e.g. calcium resonium)

E. Salbutamol via nebulizer

Answer 19.4

D. Potassium binder (e.g. calcium resonium).

Once renal failure has occurred, then either dialysis or calcium resonium will be required to eliminate potassium from the body. Other treatments will reduce serum potassium levels by driving the potassium intracellularly. Calcium gluconate prevents arrhythmias but does not alter serum potassium.

Urinary tract infection

Urinary tract infection (UTI) is the commonest bacterial disease in childhood, affecting 8% of all girls and 1% of all boys within the first 10 years of life. Apart from early infancy, when boys get UTI more often than girls, there is a marked female predominance. The recurrence rate is 50% in girls and 15% in boys.

Diagnosis is based on urine microbiology. Collection is very important and a clean catch midstream urine sample is usually the best. NICE also advocates absorbent urine collection pads but does not recommend adhesive plastic bags. Catheter sample or suprapubic aspiration (SPA) can be used in the severely ill infant under one year of age, where an urgent diagnosis and early start of antibiotic is indicated.

Whereas *any* growth is significant on suprapubic aspiration, for catheter and clean catch samples, bacterial growth rates of 50,000 colony forming units (CFU)/mL and 100,000 CFU/mL, respectively, are considered significant. Presence or absence of urinary WBC alone is not a reliable feature, as they may be present in febrile children as well as with balanitis or vulvovaginitis. Similarly, white cells in urine may be absent due to lysis during storage. Positive testing of the urine with dipstick testing for leukocyte esterase and nitrite is also suggestive of infection, but there may be both false positive and false negative results.

The most common organism in community-acquired UTI is *Escherichia coli*, which accounts for up to 75% of cases in childhood. Other important organisms include enterococci, *Klebsiella*, *Proteus*, and *Serratia*. The most important underlying contributing factor is urinary stasis, which can be secondary to anatomical obstruction, vesico-ureteric reflux, incomplete or inefficient voiding habits, low fluid intake or constipation. Other factors are periurethral colonization as in phimosis, as well as impaired host defence. Empiric treatment with antibiotics should be based on local knowledge of the prevalent strains and their sensitivity until the child's sensitivity report is available. If there is no clinical response within 24–48 hours, a review of culture report and change in antibiotic should be considered.

Investigation in UTI remains a controversial topic with the focus shifting from extensive investigation for all children to a more selective approach. The NICE guideline (CG54, 2007) for investigating children with UTI advises only abdominal ultrasound scan (USS) for children less than 6 months old with typical UTI and none for the first episode of UTI in children greater than 6 months. In its effort to reduce unnecessary investigation without increasing the risk of missing significant lesions, NICE has depended heavily on distinguishing between typical and atypical UTI as well as recurrent UTI (Box 19.4).

USS has the benefit of being a non-invasive test with no radiation risk and can identify serious structural abnormalities as well as urinary obstruction, such as posterior urethral valve or pelvi-ureteric junction obstruction. It can miss renal scars for which DMSA scan is considered the gold standard. DMSA should be delayed until 4–6 months after the acute UTI in order to avoid a false positive result secondary to acute renal parenchyma inflammation in pyelonephritis. USS can also miss significant vesico-ureteric reflux (VUR), for which MCUG is considered the gold standard investigation.

Long-term management

Recurrence is a major concern and some simple steps, such as adequate fluid intake, avoiding constipation and proper toilet hygiene, are important. Antibiotic prophylaxis remains controversial. Although some trials (e.g. PRIVENT and RIVUR) have shown some reduction in recurrence, NICE does not recommend routine antibiotic prophylaxis. It is still sometimes considered for recurrent UTI as well as those with significant VUR (grade 3 and above). Trimethoprim is

used most often, but nitrofurantoin may also be given. Broad spectrum antibiotics, such as amoxicillin should be avoided. Whether or not an antibiotic is used, early detection and prompt treatment should always remain the focus.

Follow-up

Repeat urine culture to check resolution is not advised if symptoms have resolved; neither is routine urine culture in asymptomatic children who have had recurrent UTI. Children who do not qualify for routine investigation do not require follow-up, according to the NICE guideline. Currently, there is no evidence regarding when to stop antibiotic prophylaxis (if used); generally this is considered once the child becomes toilet trained. Any child with renal scarring requires lifelong annual blood pressure measurements. Although hypertension has been reported in up to 10% of children with scars, such a high incidence has also been questioned. Bilateral renal defects place the child at increased risk for chronic kidney disease (CKD) progression and requires regular reviews for hypertension, proteinuria and renal dysfunction. Circumcision may benefit boys with recurrent UTI. It has been estimated that around 100 circumcisions are required to prevent one UTI in normal children. The number needed to treat is lower for children with recurrent UTI (11) and with high-grade vesico-ureteric reflux (4).

In those with recurrent UTI and progression of renal scars, surgical correction may be considered in the presence of vesico-ureteric reflux, although the outcome has not been shown to be better than antibiotic prophylaxis alone.

Vesico-ureteric reflux (VUR)

This is the retrograde flow of urine from the bladder into the upper urinary tract. It is usually congenital, with accumulating evidence of genetic predisposition. The incidence is about 1% in infants. It is likely that the inheritance of VUR is autosomal dominant with variable penetrance. Approximately one third of siblings of children with VUR also have it, usually of a mild degree, although most (75%) do not have a history of UTI. There is no consensus on screening, but if a child has significant VUR, selective imaging of siblings or offspring should be discussed and a low threshold for investigation of febrile illness highlighted. VUR has been linked with recurrent UTI, which has been thought to result in reduced renal function, renal failure, hypertension and increased incidence of pregnancy-related hypertension. Although rare, in cases of severe hypertension or recurrent UTI secondary to a poorly functioning refluxing scarred kidney, unilateral nephrectomy may be considered.

Management of VUR

Resolution of VUR over time with medical treatment is related to the grade of VUR and the age of the child. The lower the grade of vesico-ureteric reflux, the more likely it will resolve spontaneously. Grade I or II vesico-ureteric reflux resolves in about 80–90% after 5 years. Bilateral grades IV and V vesico-ureteric reflux have the lowest chance, less than 20% after 5 years. Although use of prophylactic antibiotics is still debated, it may be required for recurrent UTI with higher grade vesico-ureteric reflux. Surgical intervention is reserved for rarer cases of severe vesico-ureteric reflux, recurrent UTI and documented progressive scarring. Anti-reflux surgery can be either by open re-implantation or by periureteric injection of bulking agents (Deflux procedure). However, the success rate is lower for this procedure than re-implantation of the ureters, and it often needs to be repeated.

Hypertension

Hypertension is a risk factor for cardiac failure, cardiovascular and cerebrovascular disease in adult life. There is increasing evidence that 'essential' hypertension has its origin in childhood. The kidney has an important role in hypertension, both as the 'villain', as in primary renal disease, and as the 'victim', with

damage of the kidney in malignant hypertension and chronic kidney disease from poorly controlled hypertension.

Measurement of blood pressure

Question 19.5

Assessment of blood pressure

Concerning the assessment of blood pressure in children, which of the following statements are true (T) and which are false (F)?

A. Aneroid sphygmomanometers need regular calibration

B. The cuff should cover no less than two thirds and no more than 85% of the upper arm

C. Giving an infant a bottle of formula is helpful as it prevents spuriously high readings

D. Blood pressure is normally slightly higher in the lower limbs than the upper limbs

E. 24-hour monitoring is not useful in children, as reference ranges do not exist

Answer 19.5

A. True; B. False; C. False; D. True; E. False.

Accurate measurement of BP is essential but problematic. Mercury sphygmomanometers are no longer used because of environmental concerns. Aneroid sphygmomanometers need regular calibration and, whilst automated methods are easy and rapid to use, not all have been validated for children and often devices are not maintained and calibrated. The widest cuff that can be applied to the arm should be used, covering at least two thirds of the upper arm, and preferably 90–100%. The child should rest beforehand for at least 3 minutes in a warm room. The blood pressure reading may be elevated during eating, sucking, or crying.

Blood pressure measurement in patients with suspected cardiac disease should ideally be measured in both arms and legs. Doing this aids in the diagnosis of conditions causing outflow obstruction (e.g. coarctation of the aorta), recognition of conditions with 'aortic runoff', such as patent ductus arteriosus (PDA), and identification of reduced cardiac output states. Ordinarily the blood pressure in the lower limbs is approximately 10 mmHg higher than in the arms. This is due to the direct transmission of pressure from the aorta to the larger descending aorta. The pressure is transmitted from aorta to the upper

limb through a comparatively narrow vessel. Coarctation of the aorta is suspected when the systolic pressure is 20 mmHg lower in the legs than in the arms. Abnormal measurements should always be checked with a more reliable method. Twenty-four hour ambulatory BP monitoring or home BP monitoring may be useful for borderline cases or to monitor therapy.

In contrast to adults, where the definition of hypertension is based on epidemiological studies and the risk of adverse events, in children it has a statistical definition, namely a systolic and/or diastolic pressure greater than the 95th percentile for age, gender and height on at least three occasions. It is classified into two types: essential (where no specific cause can be identified) and secondary, of which >90% are caused by three conditions: renal parenchymal disease, renovascular disease and coarctation of the aorta. Other causes to be considered are raised intracranial pressure, phaeochromocytoma and congenital adrenal hyperplasia. Obesity is associated with hypertension and, as more children are becoming obese, the incidence of hypertension is increasing. Hypertension in children usually presents as an incidental finding. Uncommon presentations are headache or facial palsy, or as an acute emergency (congestive cardiac failure, cerebrovascular accident or hypertensive encephalopathy).

Pathophysiology of control of blood pressure

Haemodynamics are the physical factors that govern blood flow. Blood flow (F) is determined by difference in the pressure difference or gradient (ΔP), resistance (R) provided by the blood vessel and viscosity of the blood:

$$F = \Delta P/R = (P_A - P_V)/R$$

where P_A is arterial pressure and P_V is venous pressure.

Due to the constant tension in the walls of the arteries, secondary to the muscle and elastic tissue, and the resistance offered to the passage of blood as it passes into smaller and smaller vessels (peripheral resistance), the blood inside the arteries and their smaller branches is under pressure, even when the left ventricle is not contracting. As the ventricle contracts, there is a surge of pressure that causes the larger arteries to distend momentarily and then recoil due to their own elasticity, and so causing a pulsation which helps keep the blood moving onto the smaller branches. The greater the stroke volume, the greater the change in arterial pressure during ejection. The maximal change in aortic pressure during systole represents the aortic pulse pressure that is defined as the systolic minus the diastolic pressure. Cardiac output and total peripheral

resistance broadly determine the systolic and diastolic pressures.

The rise in aortic pressure from diastolic to systolic is determined by the compliance of the aorta as well as the ventricular stroke volume. In the arterial system, the aorta has the greatest compliance, which dampens down the pulsatile output of the left ventricle. If the aorta were rigid, the pulse pressure would be very high, but as it expands, the pressure change is reduced. As the circulatory system is elastic, and has resistance and other impediments to flow, the energy from ventricular contraction is not transferred instantaneously around the circulation after each heartbeat, as would occur in a rigid system. Instead, the energy of venous flow is several heartbeats behind that of ventricular ejection.

Question 19.6

Meningococcal septicaemia

A 3-year-old girl is admitted with meningococcal septicaemia. Following resuscitation with intravenous fluids and mechanical ventilation, her heart rate is 180 beats per minute, her capillary refill is 1 second and she has a blood pressure of 85/30 mmHg. You note the wide pulse pressure. These findings are most likely to suggest which of the following? Select ONE answer only.

A. Exogenously administered catecholamines would reduce cardiac output
B. Mean blood pressure is adequate
C. Peripheral vascular resistance is low
D. Preload is adequate and further fluid is not required
E. Stroke volume is inadequate due to lack of filling time

Answer 19.6

C. Peripheral vascular resistance is low.
Here the wide pulse pressure suggests a good stroke volume. However, the low mean BP and fast heart rate suggest that this is because pulmonary vascular resistance is inadequate. She is currently in 'warm shock'. Here, adrenaline or noradrenaline infusion will 'tighten up' the peripheral circulation and should be used in conjunction with fluid.

As blood pressure (BP) is determined by cardiac output and peripheral vascular resistance, clinical disorders which increase either cardiac output or peripheral vascular resistance can raise BP. Cardiac output is determined by stroke volume and heart rate with alteration in either of the two resulting in elevated BP, although stroke volume is the most commonly affected factor. Stroke volume can rise if there is a rise in the intravascular volume, which can be from excessive fluid retention. Excessive fluid retention can be due to decreased output, as is seen with oliguric renal failure or from salt retention either due to excessive salt intake, or activation of the renin–angiotensin–aldosterone system (RAAS), one of the most important determinants of BP control (Fig. 19.8).

If blood pressure falls, there is a reduction in concentration of sodium and chloride in the distal tubule, which is sensed by specialized cells in the macula densa, resulting in release of renin by the juxtaglomerular apparatus. A fall in blood pressure can also be detected by baroreceptors in the aortic arch, carotid sinus and the afferent renal arteriole, all of which can also stimulate renin release by the juxtaglomerular apparatus. Renin cleaves angiotensinogen into angiotensin I, which in turn is cleaved by angiotensin converting enzyme (ACE) into angiotensin II. Angiotensin II is a potent vasoconstrictor and also stimulates the release of aldosterone, which acts on distal tubules and collecting ducts in the kidney causing retention of sodium and water and further increasing the BP. Increased sympathetic tone also increases cardiac output by stimulating renin release, as well as by increasing cardiac contractility and heart rate.

Peripheral vascular resistance can be influenced by multiple factors. Increased angiotensin II, elevated sympathetic activity, increased endothelins (prostaglandin H2; PGH2), decreased endothelial relaxation factors (e.g. nitric oxide), and genetic abnormalities in vascular cell receptors are all associated with increased vascular smooth muscle contractility, and raise peripheral vascular resistance. These may also interact with each other. For example, a sustained rise in cardiac output can result in a compensatory rise in peripheral vascular resistance, further worsening BP control. In this situation, BP may remain elevated even if the cardiac output normalizes. Uric acid has recently been suggested to influence peripheral arteriolar resistance and implicated in causing hypertension. Chronically, these changes in vascular compliance and associated inflammation lead to endothelial dysfunction and vascular remodelling – a state that may be reversible initially but when prolonged can become irreversible.

A stepwise approach is advocated in a child being investigated for hypertension. First-line investigations are listed in Box 19.5. Subsequent investigations will depend on the suspected aetiology.

Management of hypertension

Understanding the pathophysiology of hypertension influences the selection of antihypertensive medications (Table 19.4). ACE inhibitors (e.g. enalapril) or
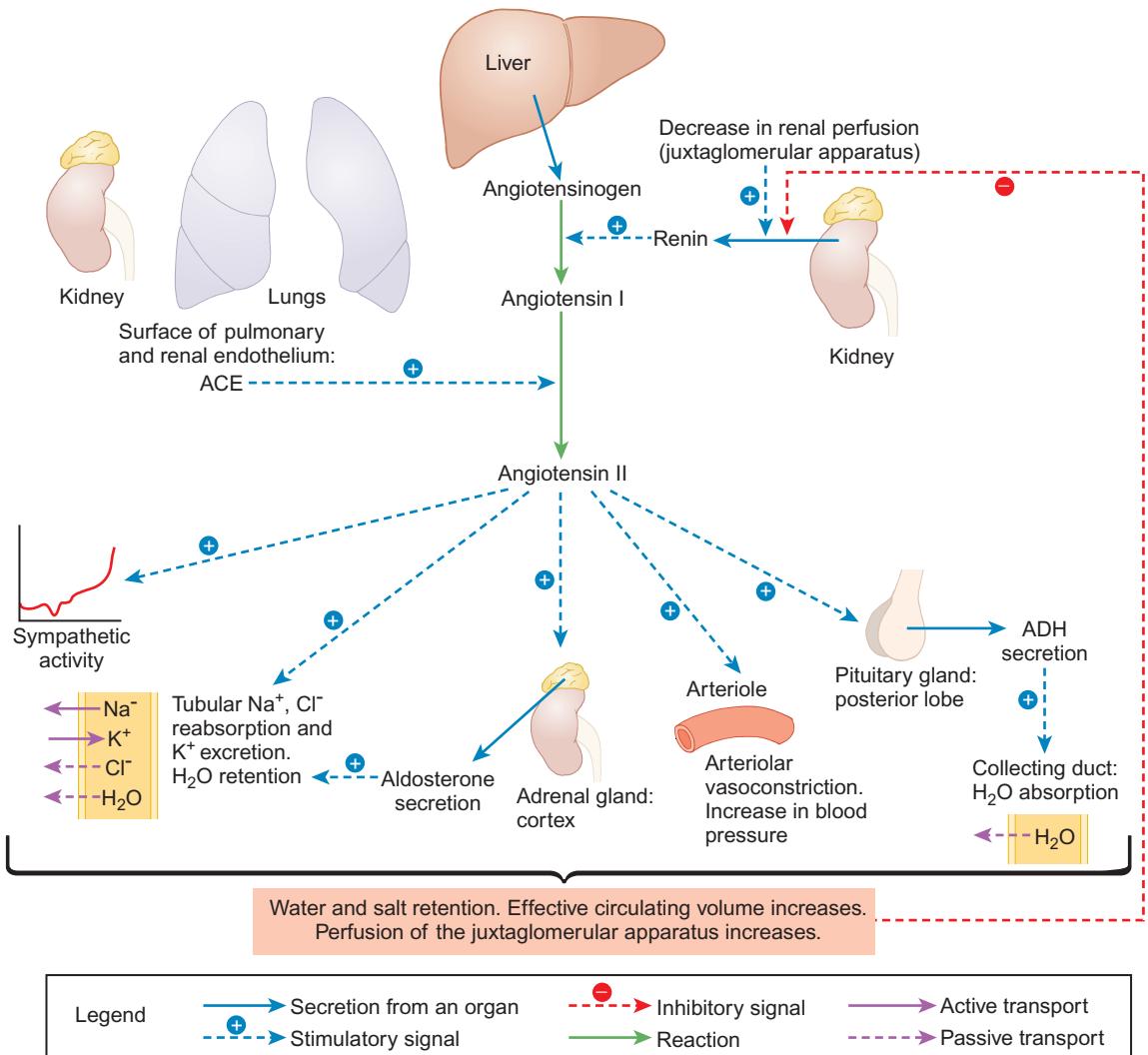
Fig. 19.8 Renin–angiotensin–aldosterone system. *(© Ari Rad 2006, http://en.wikipedia.org/wiki/Renin%E2%80%93angiotensin_ system#/media/File:Renin-angiotensin-aldosterone_system.png, with permission.)*

Box 19.5 First-line investigations to be considered in all children with hypertension

- Full blood count
- Urea and electrolytes (U & E), creatinine, albumin, bicarbonate, Ca, PO_4, liver and thyroid function tests, ± urine electrolytes
- Fasting glucose, cholesterol and triglycerides
- Plasma aldosterone
- Plasma renin activity
- Plasma/urine catecholamines
- Urine albumin : creatinine ratio
- Urine microscopy (to check for red cell casts)
- Electrocardiogram (ECG)/echocardiography
- Chest X-ray (CXR)
- Renal ultrasound (US) with Doppler flow studies of renal vessels

angiotensin receptor blockers (e.g. losartan) are used in childhood hypertension because of the important role of RAAS in renal-mediated hypertension. For hypervolaemia (e.g. post infectious glomerulonephritis), diuretics are often used. Calcium channel blockers, like nifedipine, are also frequently used, as increased peripheral vascular resistance is often a contributing factor to the hypertension. Similarly, children with primary hypertension are treated by medications that act by either reducing central venous pressure, by reducing systemic vascular resistance, or by reducing cardiac output (by reducing heart rate and stroke volume).

Severe acute hypertension

Severe, symptomatic hypertension (seizures, cardiac failure) with decompensation is very rare but is a

Table 19.4 Antihypertensive drugs

Drug	Types	Modes of action
Diuretics	Loop: furosemide	Reduce extracellular and plasma volume by increasing sodium and water excretion by the kidney.
	Thiazide: chlorothiazide	Inhibit sodium–potassium–chloride cotransporter in the thick ascending limb of the loop of Henle.
		Inhibit the sodium–chloride transporter in distal convoluted tubule. Also decrease peripheral vascular resistance with long-term use.
	Potassium sparing: spironolactone	Aldosterone receptor antagonists in the distal convoluted tubule.
Adrenergic inhibitors	Beta blockers: propranolol	Bind to beta-adrenoceptors in cardiac nodal tissue, conducting system and myocytes preventing the action of adrenaline or noradrenaline at these sites (reduce sympathetic tone). They also inhibit the release of renin, decreasing angiotensin II and aldosterone – enhancing renal loss of sodium and water.
Angiotensin-converting enzyme inhibitors	Captopril, enalapril	Inhibit formation of angiotensin II. Block the breakdown of bradykinin causing vasodilation. Down regulate sympathetic adrenergic activity. Inhibit cardiac and vascular remodelling associated with chronic hypertension and cardiac failure.
Angiotensin receptor blockers	Candesartan, losartan	Displace angiotensin II from its receptor, antagonizing its effect.
Calcium channel blocker	Nifedipine, amlodipine	Bind to L-type calcium channels in cardiac myocytes, reducing conduction velocity and myocardial contractility. Cause smooth muscle relaxation decreasing PVR.
Vasodilator	Hydralazine	Smooth muscle relaxation.

medical emergency and should be treated with intravenous antihypertensive agents (e.g. sodium nitroprusside or labetalol infusions). Hydralazine as a slow intravenous injection may be used if PICU facilities are not available. The child must have two large bore intravenous cannulae inserted so that intravenous 0.9% sodium chloride can be given if the BP is reduced too quickly. Sublingual nifedipine may cause a precipitous drop in BP and should be avoided. In long standing hypertension, a gradual reduction of BP is advised. A third of the reduction towards the target BP should be done in the first 8 hours and the rest over 48 hours.

Proteinuria and haematuria

Proteinuria and haematuria can be glomerular or tubular in origin (Boxes 19.6–19.7). Glomerular disease usually presents with generalized oedema and proteinuria with or without haematuria, hypertension and azotaemia (raised blood urea).

Nephrotic syndrome

Idiopathic nephrotic syndrome in childhood is a disease of unknown aetiology, characterized by the onset of proteinuria, oedema and hypoalbuminaemia together with hyperlipidaemia. It is more common in boys and is usually secondary to minimal change pathology, the likelihood of which varies with age of presentation. Although most children with nephrotic syndrome (85–90%) will respond to corticosteroids,

> **Box 19.6 Commoner causes of haematuria in children**
>
> **Glomerular**
> - Post-infectious glomerulonephritis
> - Glomerulonephritis secondary to systemic disease
> - Hereditary/familial nephropathies
>
> **Non-glomerular**
> - UTI
> - Tumour
> - Nephrolithiasis and/or hypercalciuria
> - Trauma
> - Structural disease (e.g. obstructive uropathy)
> - Drugs (e.g. cyclophosphamide)

a significant percentage of them (70%) will relapse. Definitions of the terms used in relation to nephrotic syndrome are listed in Table 19.5.

Postulated hypothesis for proteinuria in nephrotic syndrome

Glomerular filtrate is formed by ultrafiltration of plasma across the glomerular capillary wall, which is negatively charged. This wall has three layers: the endothelium, the basement membrane and an outer epithelium consisting of podocytes with interdigitating foot

Table 19.5 Definition of relapse/dependence/resistance for nephrotic syndrome

Remission	Urine albumin nil or trace (or proteinuria <4 mg/m^2/hour) in three consecutive early morning urine specimens
Relapse	Urine albumin 3+ or 4+ (or proteinuria >4 mg/m^2/h) in three consecutive early morning specimens having been in remission previously
Frequent relapses	Two or more relapses in initial six months or more than three relapses in any twelve months
Steroid dependence	Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation
Steroid resistance	Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg/day for 4 weeks

processes. Plasma albumin is negatively charged and there is evidence of a barrier to passage of albumin by electrical charge, as well as a sieve-like size-specific barrier. On renal biopsy in minimal change, whilst there are minimal histological changes on light microscopy, electron microscopy shows effacement of the foot processes. Extensive research has being undertaken on the filtration barrier in nephrotic syndrome. A number of proteins on the podocytes have been identified; disruption of which has been shown to destabilize the podocyte cytoskeleton resulting in proteinuria. Mutations in some of these proteins have been linked with various forms of steroid resistant nephrotic syndrome (e.g. podocin, the commonest mutation resulting in steroid resistant nephrotic syndrome beyond infancy, and nephrin, the commonest mutation causing congenital nephrotic syndrome).

Oedema results from the movement of water and small solutes between the intravascular and extravascular compartments, either from an increase in capillary intravascular hydrostatic pressure or from decrease in capillary oncotic pressure. Since plasma protein (mainly albumin) is the main contributor to intravascular oncotic pressure, loss of urinary albumin, causing hypoalbuminaemia, will lead to a shift of fluid from the plasma to the interstitium. This will result in contraction of the circulating volume leading to physiological responses (reduction in GFR; activation of the RAAS; release of arginine vasopressin (AVP); inhibition of atrial natriuretic peptide (ANP); increased proximal tubular salt and water reabsorption), resulting in salt and water retention and increasing oedema.

Acute management of nephrotic syndrome

Initial management includes prednisolone (60 mg/m^2/day for four weeks followed by 40 mg/m^2 for at least another four weeks with further wean over four weeks to reduce chances of subsequent relapses). Protein loss includes the loss of immunoglobulins and complement which hampers the normal immune response. Penicillin prophylaxis is required to prevent pneumococcal infections, especially peritonitis. A no added salt diet is advised.

Monitoring for potential complications is required. Hypovolaemia is a major concern (see Question 19.3 above), particularly as it can be deceptive. Following antibody loss in the urine, infection can be a significant problem, with children being prone to peritonitis, cellulitis and pneumonia. Chickenpox may be severe in the presence of nephrotic syndrome and corticosteroid usage and unimmunized or previously unexposed children should receive varicella zoster immunoglobulin within 96 hours of exposure to chickenpox. If a child with nephrotic syndrome develops chickenpox, they should receive treatment with intravenous aciclovir.

Nephrotic syndrome results in a procoagulant state as there is loss of anticoagulant protein in the urine. Reduced intravascular volume, immobilization, indwelling vascular catheter, and aggressive diuresis aggravate this tendency to coagulate. If thrombosis occurs, treatment is primarily correction of hypovolaemia and use of heparin (including low molecular

analogues). The role for prophylactic anticoagulants is controversial.

As most young children with nephrotic syndrome will have 'minimal change' on renal biopsy, renal biopsy is only indicated in those with atypical features, such as steroid resistance or older or younger age at presentation. Most children with steroid sensitive nephrotic syndrome (SSNS) will have more than one episode and some will go on to become frequent relapsers. For initial relapses, prednisolone is started at high dose (60 mg/m^2/day) until remission and thereafter at a lower dose (40 mg/m^2 alternate days) for four weeks. Those having repeated courses of high-dose steroids or requiring long-term continuous steroids (>0.5 mg/kg/day) or with clinical evidence of corticosteroid toxicity should be considered for second-line therapy using agents such as levamisole, cyclophosphamide or calcineurin inhibitors (CNI) such as ciclosporin/tacrolimus.

Acute glomerulonephritis

Acute glomerular injury can present with various features including: haematuria (microscopic or macroscopic) with red cell casts on microscopy; oliguria, uraemia, elevated creatinine indicating acute kidney injury; hypertension; oedema or proteinuria. The common childhood causes are listed in Box 19.8.

Post-infectious glomerulonephritis

Post-infectious glomerulonephritis (PIGN) is the commonest of acute glomerulonephritis. It usually follows a couple of weeks after a streptococcal throat

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Box 19.8 Causes of acute glomerulonephritis

1. Immune complex glomerulonephritis
   - Post-infectious, usually post streptococcal
   - Other post-infectious causes – bacterial, viruses, rickettsiae, fungal, parasites
   - Henoch–Schönlein purpura (HSP)/IgA vasculitis
   - Systemic lupus erythematosus (SLE)
   - IgA nephropathy (IgAN)
   - Membranoproliferative glomerulonephritis (MPGN)/C3 glomerulopathy
2. Pauci-immune glomerulonephritis
3. Anti-glomerular basement membrane antibody-mediated glomerulonephritis (Goodpasture syndrome)
4. Miscellaneous
   - Haemolytic uraemic syndrome
   - Ventriculoperitoneal shunt
   - Thrombotic thrombocytopenic purpura

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infection or up to six weeks after a skin infection with group A haemolytic *Streptococcus*. Haematuria (cola-coloured urine) is the most striking presentation along with hypertension, decreased urine output and oedema. Laboratory biomarkers include a low complement C3. However, this is not a specific finding of PIGN. Antistreptolysin O titre (ASOT) is raised in the majority of pharyngeal infections, but is often not raised post skin infection and may also be positive in up to 20% of healthy children. The streptozyme assay also detects antibodies to other Streptococcal antigens (e.g. DNAse B), improving the chance of detecting streptococcal infection.

Percutaneous renal biopsy is not normally undertaken unless atypical features, such as rapidly progressive glomerulonephritis (which may be associated with crescentic glomerulonephritis), are present. When a renal biopsy is undertaken it usually shows proliferative changes on light microscopy with immunofluorescence showing discrete granular deposits of IgG and C3 in a capillary loop and mesangial distribution. Electron microscopy shows humps in the sub-epithelium. It is indicated in persisting azotaemia or persisting nephrotic range proteinuria with an unclear diagnosis. Treatment with penicillin prevents spread to contacts but will not help the nephritis. Hypertension is usually secondary to fluid retention and responds to furosemide. Based on the overall excellent prognosis of children (less than 1% will develop CKD), treatment is supportive.

IgA nephropathy

IgA nephropathy usually presents with macroscopic haematuria following an upper respiratory tract infection. There is a male preponderance and it is a relatively common cause of gross haematuria worldwide. It may also present with asymptomatic microscopic haematuria with or without proteinuria. Although increased levels of circulating IgA immune complexes is sometimes documented (<20%), it does not correlate with disease activity. The diagnosis is confirmed by renal biopsy, which shows deposits of IgA in the glomerular mesangium on immunofluorescence. C3 is also usually present and IgG and IgM are seen in approximately half of biopsies.

About 20% progress to CKD, but the rate of progression is usually very slow. Persistent proteinuria, hypertension and biopsy findings such as crescents or interstitial fibrosis are associated with greater risk of progression. The management depends on the severity of the disease and its likelihood of progression. *Microscopic haematuria and/or recurrent macroscopic haematuria* are usually not of clinical significance in the absence of proteinuria. Tonsillectomy has been recommended by some investigators. In the presence of *proteinuria,*

ACE inhibition or angiotensin receptor blockers (ARB) can be tried. Immunosuppressive agents are sometimes indicated. Omega 3 fatty acids may be of benefit but adherence is difficult in view of the bad fish odour on the breath.

Membranoproliferative (mesangiocapillary) glomerulonephritis

Membranoproliferative (mesangiocapillary) glomerulonephritis (MPGN) is a comparatively rare disorder which occurs predominately in older children and young adults. It usually presents with nephrotic/nephritic features, and causes about 5% of childhood nephrotic syndrome. It may be primary or secondary to infections (e.g. streptococcal, hepatitis B and C, and HIV). Diagnosis is confirmed by percutaneous renal biopsy.

Anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis

This is a part of pauci-immune vasculitis, characterized by absence of any significant immunofluorescence findings. The most common is granulomatosis with polyangiitis (GPA, previously called Wegener's granulomatosis (WG)), characterized by granulomatous inflammation affecting the small to medium-sized vessels and frequently involving the respiratory tract and the kidneys. Whereas cytoplasmic ANCA (proteinase 3) is usually positive in GPA, perinuclear ANCA (myeloperoxidase) is positive in microscopic polyangiitis. Although ANCA has been shown to be pathogenic, the exact mechanism is yet to be fully described.

From a clinical perspective, GPA has two forms, which may coexist or present sequentially in an individual patient: a predominantly granulomatous form with mainly localized disease, or a more florid form characterized by severe pulmonary haemorrhage from granulomatous pulmonary nodules with or without central cavitations and/or rapidly progressive vasculitis. The localized form may affect the upper respiratory tract, including nasal septal involvement with cartilaginous collapse and chronic sinusitis. Renal presentation is usually with features of acute glomerulonephritis, including hypertension, proteinuria and renal failure. They can also have ocular manifestations including unilateral or bilateral proptosis caused by granulomatous inflammation of the orbit (pseudotumour). Vasculitis can result into peripheral gangrene with tissue loss as well as features of mononeuritis multiplex.

Diagnosis is based on a combination of clinical features along with ANCA positivity and tissue biopsy.

The key to successful treatment is early diagnosis and initiation of treatment, which may involve immunosuppressive agents and plasma exchange. Mortality is as high as 12% with almost 40% progressing to chronic kidney disease.

Urolithiasis

Urolithiasis is the presence of solid deposits (calculi) in the urinary tract, whereas nephrocalcinosis (Fig. 19.9) is an increase in the calcium content of the kidney. The incidence and composition of stones vary with geographical region. In the UK, the incidence is around 2 children per million population, which is lower than in the adult population (2 per thousand). It is much higher in other parts of the world, for example in the Middle and Far East and North Africa. Factors such as socio-economic status, climate, race, diet, fluid intake, dehydration and infections may be important. Predisposing factors include recurrent urinary tract infection or an underlying metabolic condition (Box 19.9). It is much more common to identify a predisposing cause in children than in adults. In European children, more than half of cases

Fig. 19.9 **Renal ultrasound showing nephrocalcinosis.**

Box 19.9 Metabolic disorders that cause calculi

- Hypercalciuria (commonest cause)
- Idiopathic hypercalcaemia associated with renal tubular dysfunction (e.g. distal renal tubular acidosis)
- Hyperoxaluria
- Cystinuria
- Disorders of purine metabolism
- Uric acid overproduction (e.g. following chemotherapy)
- Familial juvenile hyperuricaemic nephropathy
- Xanthuria

are infective in origin, frequently related to *Proteus* urinary tract infections, with hypercalciuria the most common metabolic cause.

About half affected children present with abdominal, flank or back pain. A few will pass a stone; if possible, they should be retrieved and undergo physicochemical analysis. Microscopic haematuria is usually present and renal stones should be part of the differential diagnosis of any child with haematuria. Detailed investigation (Box 19.10) is often required to ensure that an underlying cause is not missed.

Management

Acute management usually requires appropriate analgesia and encouragement to drink or intravenous fluids. The specific treatment is likely to depend upon any underlying cause. For those with hypercalciuria, it is important to ensure increased fluid and potassium intake with decreased salt intake (reduces urinary calcium excretion). Small stones usually pass spontaneously, however in acute obstruction, percutaneous nephrostomy may be required as a temporary measure.

Polyuria and polydipsia

The definition of polyuria is somewhat arbitrary, since normal urine volumes in childhood are ill-defined and the factors influencing urine volume vary with maturity. However, a working definition is a urine volume >2 litres/m^2/day. Polyuria should be distinguished from increased frequency and a frequency/volume chart may be useful in differentiating between them. Polyuria is often accompanied by polydipsia (increased oral fluid intake) and, therefore, a history of fluid intake is required.

Primary polydipsia is a relatively common problem in the young child beyond infancy. The polydipsia may be selective for maybe only juice, and if this happens, substituting water for all or part of the daily fluid intake resolves the polydipsia! Habitual water drinking or psychogenic polydipsia is found mainly in older children and adolescents. It may require a water deprivation test. A history of the child drinking at inappropriate times as well as from inappropriate sources, such as the toilet, is suggestive of significant pathology. There may be a history of salt craving, as children with a tubular disorder also lose salt in the urine. Other factors pointing towards a pathological cause include faltering growth, constipation and vitamin D-resistant rickets and investigations showing electrolyte abnormalities.

Diabetes insipidus

The hallmark of diabetes insipidus (DI) is polyuria and polydipsia in the absence of osmotic diuresis. This can be primary (nephrogenic or central DI) or can be secondary to other causes (see Chapter 26, Diabetes and endocrinology). Polyuria/polydipsia may not be immediately obvious in infants, who may present with irritability, need for frequent feeds, unexplained fever, constipation, faltering growth and/or delayed development. Young children are at high risk of hypernatraemic dehydration, as they are dependent on their carers to provide them with fluid.

Central diabetes insipidus (CDI) results from a defect in antidiuretic hormone (ADH) secretion, whereas nephrogenic diabetes insipidus (NDI) results from failure of ADH to produce the desirable result. This is usually due to a receptor (aquaporin) defect and is inherited in an X-linked dominant manner. In both central as well as nephrogenic DI, urine osmolality (Uosm) will not change significantly despite water deprivation, whereas plasma osmolality will usually exceed 300 mOsm/kg. Following DDAVP, the urine osmolality will increase in central DI (beyond 800 mOsm/kg) but will remain unchanged in nephrogenic DI. In partial DI, the urine osmolality will be 300–800 mOsm/kg but will show an adequate response to DDAVP.

Cystic renal disease

Cystic renal diseases occur in isolation or as part of syndromes. They include ciliopathies and juvenile nephronophthisis, which are usually normal-sized kidneys with poor corticomedullary differentiation, increased echogenicity, along with cysts at the corticomedullary junction.

Cystic renal disease can be:

- *Multicystic* – a wide spectrum of conditions ranging from simple cysts to cystic renal dysplasia
- *Polycystic* – includes autosomal dominant polycystic kidney disease (ADPKD), including the

contiguous gene syndrome with tuberous sclerosis and autosomal recessive polycystic kidney disease (ARPKD)

A multicystic dysplastic kidney is the extreme end of the dysplasia spectrum and implies a non-functioning kidney with atretic ureter so no connection to the bladder. Dysfunction of primary cilia has been identified as the unifying aetiology for cystic renal diseases. Primary cilia are sensory organelles involved in cell polarity and proliferation. They are ubiquitous in various organs, explaining the wide spectrum of associated symptoms in many cystic renal diseases.

Polycystic kidney disease

This is an inherited disorder of two main types, autosomal recessive kidney disease (ARPKD) or autosomal dominant kidney disease (ADPKD).

Autosomal recessive kidney disease

ARPKD has an incidence of approximately 1 : 20,000 live births, due to autosomal recessive mutations (*PKHD1*, 6p21–12*)*. The kidneys are large and are often easily palpated. It is usually present antenatally and in its severe form may be associated with pulmonary hypoplasia secondary to oligohydramnios. The kidneys have innumerable microcysts, giving it enlarged hyperechogenic appearance on USS. Children usually progress to renal failure in early childhood. Hypertension is frequently present and can be difficult to control. Congenital hepatic fibrosis is invariably present but may initially not be detectable clinically or on ultrasound. Hypersplenism and oesophageal varices may develop secondary to hepatic fibrosis. Cholangitis can be a major concern, presenting with recurrent septicaemia. Management is supportive, with aggressive control of hypertension and management of renal failure. Renal transplantation with or without liver transplantation is usually required in childhood.

Autosomal dominant kidney disease

ADPKD is the commonest inherited renal disease, with an incidence of 1 : 500 live births, secondary to a gene mutation (in either *PKD1* (16p13) or *PKD2* (4q21–23)). A positive family history is not always present, as about 10% are *de novo* mutations. It may be detected antenatally, during the neonatal period or early childhood, but is more likely to present in later childhood or adulthood. In contrast to ARPKD, the cysts are macrocysts and easily seen on USS. Those presenting early in life have more severe disease and may progress to renal failure in childhood. Others preserve renal function for many decades, although they are likely to eventually progress to end-stage kidney disease.

Proteinuria and hypertension may develop even in childhood, so regular follow-up is required even if the renal function is normal. Control of hypertension is a major factor influencing progression of disease, as well as cardiovascular morbidity and mortality. Extrarenal manifestations include cystic liver disease, pancreatic cysts and intracranial aneurysms (the latter are rarely seen in childhood).

Diagnostic screening for families remains controversial, as no therapy is available to stop or delay disease progression (although there are current clinical trials) and early diagnosis may raise problems in later life regarding life insurance, mortgages and occupation. Currently, the most common modality for diagnostic screening is a renal USS. However, the first cysts may not appear until the fourth decade of life, so ADPKD cannot be excluded until then. The presence of any cyst in an at-risk child is highly suggestive of the disease; the presence of two or more cysts is considered diagnostic. Genetic testing enhances diagnosis.

Acute kidney injury

The term 'acute renal failure' has been replaced by acute kidney injury (AKI), aiming at prevention, earlier detection of deterioration in renal function and dispels the negativity of the term 'failure'. Although there is ongoing debate about the definition, the currently accepted ones are any of:

- Increase in serum creatinine by 26.5 μmol/L within 48 hours
- Increase in serum creatinine to 1.5 times baseline, which is known or presumed to have occurred within the previous 7 days
- Urine volume <0.5 mL/kg/hour for six hours.

In children, particularly newborns, it may be non-oliguric, so may be missed if concentrating on urine output alone. Causes can be divided into pre-renal (hypovolaemia), renal (intrinsic renal failure) and post-renal (obstructive) (Table 19.6). It may occur in isolation (for example, in intrinsic renal disease like glomerulonephritis), or coexist with other disorders (e.g. multi-organ failure in intensive care).

Management of AKI

Assessment of volume status is critical to treatment strategies. In pre-renal failure, restoration of intravascular volume is required, whereas in intrinsic renal failure repeated fluid boluses will be counterproductive, and in obstructive renal failure relieving the obstruction is the priority. USS usually identifies an

Table 19.6 Causes of acute kidney injury

Pre-renal	Intrinsic	Post-renal
Dehydration/fluid losses	Acute tubular necrosis	Posterior urethral valves
Blood loss	Congenital renal disease	Obstructed solitary kidney
Third space (sepsis)	Bilateral renal vein thrombosis	Bilateral ureteric obstruction (mass)
Heart failure		Bladder dysfunction

obstruction when present; clinical and biochemical parameters can help distinguish between pre-renal and intrinsic AKI.

In clinical practice, it is often difficult to determine if the AKI is an acute process of previously normal kidneys or secondary to an acute insult on a chronically damaged kidney. A small echogenic kidney with loss of corticomedullary distinction on USS suggests chronically damaged kidneys. Percutaneous renal biopsy is indicated if renal function is deteriorating and the aetiology is uncertain or in presence of persistent azotaemia (uraemia) with nephritic/nephrotic presentation in normal-sized or large kidneys.

Treatment is initially focused on managing acute life-threatening complications, such as hyperkalaemia and fluid overload. Once the volume status has been restored to normal, a furosemide challenge (2–4 mg/kg) is often given. If it fails to improve, urine output continuation of furosemide will not be beneficial. If there is persistent oliguria or anuria, fluid balance is maintained by restricting fluid intake to insensible water loss and output. Low-dose dopamine has not been shown to improve outcome.

Acidosis is often present and needs to be corrected, but only after hypocalcaemia has been corrected, otherwise correction of acidosis may further decrease the ionized calcium. Most cases respond to conservative management, but dialysis is sometimes required. Recent evidence has underlined the danger of fluid overload, where fluid excess >15% increases mortality. This has resulted in early initiation of fluid removal either by diuretics and, if necessary, by haemofiltration. Nutrition should not be ignored, as it has been shown to improve outcome. Once recovery starts, children can become polyuric and proper fluid balance remains essential, as otherwise the recovering kidney may be subjected to further insult from hypovolaemia.

Haemolytic uraemic syndrome (HUS)

Haemolytic uraemic syndrome (HUS) is the most common cause of childhood AKI in Europe and North America. Most cases are associated with a diarrhoea prodrome (so-called typical). HUS without diarrhoea (atypical HUS) can still be infective, such as after pneumococcal infection or can have non-infective aetiology, such as genetic mutation. In the UK, most typical HUS cases are associated with infection with verocytotoxin-producing *Escherichia coli*, whereas worldwide Shigella toxin-producing *E. coli* is more common. The risk of developing HUS in patients with intestinal *E. coli* 0157:H7 infection is 10%.

Typical HUS occurs primarily in pre-school children (and the elderly). The clinical features include bloody diarrhoea followed by reduced urine output, pallor and malaise. Central nervous system disturbance can affect up to 20% and carries a bad prognosis. Diabetes mellitus can develop due to necrotizing pancreatitis.

Investigation reveals microangiopathic haemolytic anaemia (with fragmented red blood cells, i.e. schistocytes), thrombocytopenia and renal failure. If HUS is suspected but the initial blood film does not support the diagnosis, a blood smear should be repeatedly examined over the next hours and days.

Management

The mainstay is supportive management with control of fluid and electrolyte disturbance, dialysis and blood transfusion. Packed red cell transfusion may be required for anaemia, but platelet transfusion is rarely indicated unless surgical intervention is planned or there is suspicion of intracranial haemorrhage. Antibiotics should probably be avoided for typical HUS (and have been reported to increase mortality), but are indicated for pneumococcal infection-induced HUS. Most children with typical HUS recover, but there still is significant mortality (2–10%) and up to one third of survivors have some long-term renal sequel in the form of ongoing renal impairment, proteinuria or hypertension.

Plasma infusion/plasmapheresis is often helpful for genetically-mediated atypical HUS. A newly available monoclonal antibody that inhibits complement (eculizumab) may be the drug of choice in some cases, particularly in complement-mediated atypical HUS.

Chronic kidney disease

In a similar way to the term 'acute kidney injury' replacing the term 'acute renal failure', the term 'chronic renal failure' (CRF) has been replaced by chronic kidney disease (CKD). In children, it can present in various ways ranging from subtle findings such as faltering growth, increased tiredness with pallor, to overt signs such as oliguria, oedema and hypertension. The commoner causes, which are often different from adults, are listed in Table 19.7.

Table 19.7 Causes of chronic kidney disease in children

Congenital	Urinary tract malformations Obstructive nephropathy Renal dysplasia/hypoplasia Reflux nephropathy	Congenital anomaly of kidney and urinary tract (CAKUT)
Hereditary/metabolic	Nephronophthisis Cystinosis Oxalosis Alport syndrome Polycystic kidney disease (autosomal recessive and dominant types)	
Glomerulonephritis	Focal segmental glomerulosclerosis Membranoproliferative glomerulonephritis (types I, II and III) Congenital nephrotic syndrome Finnish type, diffuse mesangial sclerosis IgA nephropathy (Berger's disease) Goodpasture (antiglomerular basement membrane) disease Haemolytic uraemic syndrome Henoch–Schönlein purpura Systemic lupus erythematosus	
Others	Bilateral Wilms' tumour (requiring bilateral nephrectomy)	

Investigations are aimed at identifying an underlying cause and differentiating it from AKI, as well as identifying the complications of CKD. Presence of non-haemolytic anaemia, small or dysplastic kidneys on ultrasound, X-ray evidence of rickets and end-organ damage from hypertension suggest chronic kidney disease.

Management

The overall aim of management is to treat any underlying disorder and associated conditions and support kidney function. Often it is not possible to reverse the renal damage and focus is on preventing further renal damage by maintaining nutrition and growth, controlling hypertension, reducing proteinuria, treating anaemia and fluid, electrolyte and acid–base imbalance (acidosis), relieving any obstruction and controlling renal osteodystrophy (keeping calcium, phosphate, alkaline phosphatase and parathyroid hormone in normal range for age).

End-stage renal failure and transplantation

Renal failure is a continuum from mild renal impairment through pre-terminal renal failure to the severe irreversible form of end-stage kidney disease when renal replacement therapy (RRT) is required. The indications for RRT are complex and depend on a holistic view of the child rather than specific biochemical values. In general, it is started when the child becomes symptomatic from renal failure, with tiredness, anorexia and vomiting, or when blood biochemistry approaches hazardous levels despite therapy and dietary restrictions. The ultimate aim of therapy is pre-emptive renal transplantation, because it places far less restriction on normal life and is associated with lower morbidity and mortality. Transplantation before dialysis can be considered, but some children are not suitable for pre-emptive transplantation (such as those requiring bilateral native nephrectomies for focal and segmental glomerulosclerosis). The choice of dialysis modality is individualized to the child and family. Haemodialysis for children is based in a few specialist centres and therefore travel to and from the centre for a 3–5-hour session three times a week may be problematic. Home haemodialysis is available in only a few paediatric centres throughout the world.

Fluid restriction is normally more severe when on haemodialysis, but the family is relieved of some stresses and responsibilities of peritoneal dialysis and the child retains some independence. Home peritoneal dialysis is usually performed by machine overnight. This enables normal school attendance. There is a huge burden on the caregivers and the child is very dependent on them on a regular basis. Its advantage includes avoidance of sudden fluid and electrolyte shifts and less severe fluid and dietary restrictions. It is particularly suited to younger patients.

Successful renal transplantation offers the nearest to a normal lifestyle and is the preferred form of treatment for end-stage kidney disease. Currently, 5 year graft survival is over 95% and living donor kidneys do give some survival advantage. Immunosuppression medication needs to continue and non-compliance with medication is a significant cause of renal allograft failure in teenagers and young adults.

Further reading

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Daniel Carroll, Charlotte Slaney
With contributions by
John W Gregory

CHAPTER

20

Genital disorders

Genital anomalies in children are common, and are the cause of much anxiety for children and their parents. The first question often asked of new parents after delivery is what sex their baby is, and this clearly demonstrates the importance within our society of normal genitalia and sexual identity. The development of the genitalia is complex, and as there are multiple steps in development there are many opportunities for congenital or acquired abnormalities to develop. Although most are detected at birth, they are increasingly recognized antenatally. However, congenital problems, particularly in the development of the internal genitalia, may not be detected until later in life.

An understanding of the normal embryology of sexual differentiation is fundamental to understanding urogenital abnormalities.

Genetic aspects of genital development

Genetic sex is established at conception by the chromosome complement of the egg (23 X) and the sperm that fertilizes it (23 X or 23 Y). The presence of at least one X chromosome appears to be necessary for the survival of individual cells.

Major chromosomal abnormalities can occur during gametogenesis, or during the first few cell divisions (which results in mosaicism). Failure of sex chromosomes to separate fully during gametogenesis may result in Turner's syndrome (45 XO) and Klinefelter's syndrome (47 XXY).

Abnormalities of the sex chromosomes may occur in two distinct cell lines derived from the same zygote (sex chromosome mosaicism). The genetic imbalance arising from chromosomal abnormalities is expressed as profound disturbances of embryogenesis across a number of systems, including the genitourinary tract.

The majority of congenital anomalies do not have such a clearly defined genetic basis. Most are either sporadic or, if genetic, have variable expression and penetrance and are likely to involve the interaction of multiple genes rather than a single gene mutation.

Embryology of the genital tracts

The internal and external genitalia of both sexes are genetically programmed to differentiate as female. The presence of an active *SRY* gene on the Y chromosome causes development to move towards the male phenotype (Fig. 20.1). Until the 6th week of gestation, the embryonic precursors of the genitalia of both genetically male and genetically female embryos share identical embryonic precursors.

Differentiation of the gonads and the genital tracts is initiated by the migration of primordial germ cells from the yolk sac to the lumbar regions of the embryo. This occurs at around the 6th week of gestation (Fig. 20.2). The germ cells and the surrounding mesenchyme coalesce to form the primitive sex cords. At the same time the paired paramesonephric ducts appear. From this stage onwards, the pathways of development of the genetically male and the genetically
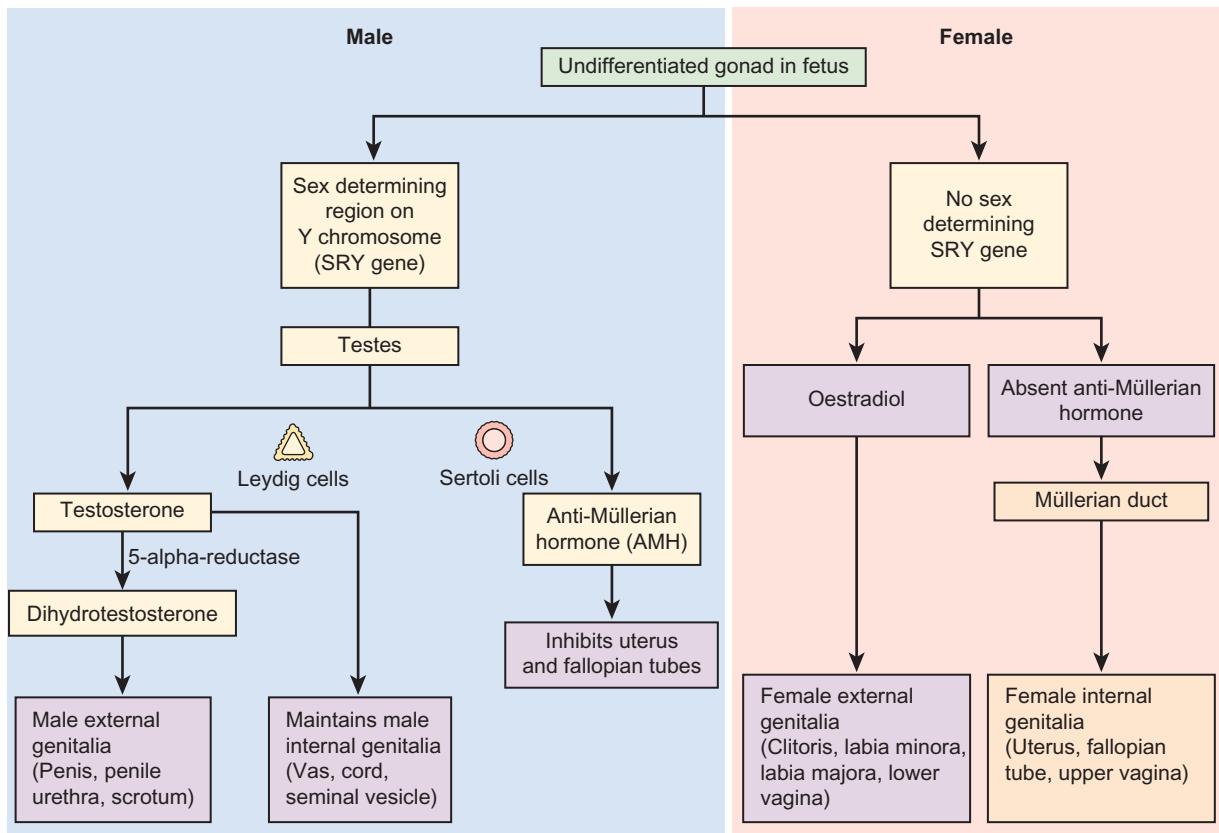
Fig. 20.1 Sexual differentiation in the fetus.
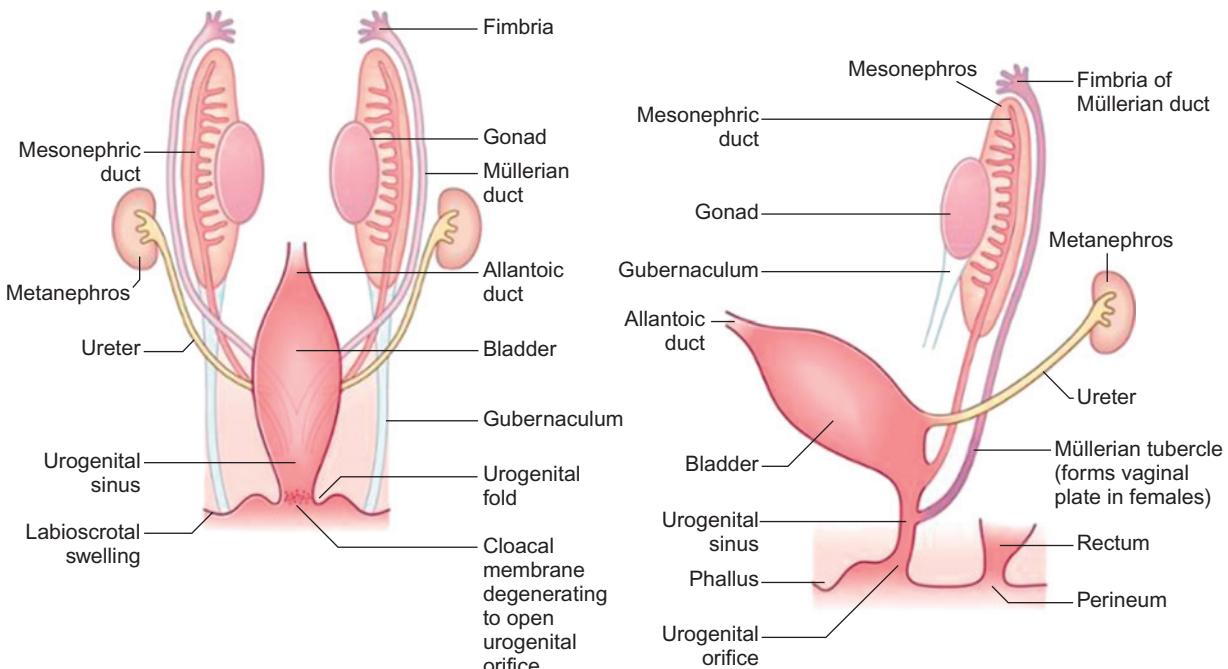
Fig. 20.2 Undifferentiated human embryo (week 7). Frontal and lateral views. *(Modified from Naish J, et al. Medical sciences 2/e. Saunders, 2014, with permission.)*

female embryo begin to diverge as sexual differentiation begins to be phenotypically expressed.

Female development

Internal genitalia

The primitive sex cords degenerate and secondary sex cords develop from the mesoderm of the genital ridge enfolding the primordial germ cells to form primitive ovarian follicles. Differentiation of the genitalia down a female pathway is not entirely passive, as the normal development of the ovary requires two normal X chromosomes (females with Turner's syndrome (XO) typically have streak ovaries). In the absence of testosterone, the mesonephric ducts regress leaving only vestigial remnants. The paramesonephric ducts persist as the fallopian tubes. The fused distal portions of the paramesonephric ducts give rise to the uterus and upper two thirds of the vagina (Fig. 20.3).

Distally, the paired paramesonephric ducts fuse with the urogenital sinus. Between the 10th and 20th week of gestation, displacement of the sinuvaginal bulb towards the perineum separates the opening of the vagina from the perineum. The upper two thirds of the vagina forms from the paramesonephric ducts, whereas the distal third has its origins in the urogenital sinus. The introitus and external genitalia are derived from ectoderm.

External genitalia

In the absence of androgens or effective androgen receptors, the external genitalia progress down a pathway of female development. The genital tubercle becomes the clitoris, the urogenital sinus becomes the vestibule of the vagina, the urogenital folds persist as the labia minora and the labioscrotal folds persist as the labia majora.

Fig. 20.3 **Female development at approximately 12 weeks' gestation.** *(Modified from Naish J, et al. Medical sciences 2/e. Saunders, 2014, with permission.)*

Questions 20.1 and 20.2

An infant with lumps in the groin

A two-week-old infant with normal external female genitalia is found to have lumps in both groins. The infant is found to have a 46XY karyotype. An HCG stimulation test shows an increase in serum androstenedione concentrations from <0.7 to 2.4 nmol/L and an increase in testosterone from <0.7 to 16 nmol/L (normal response).

Question 20.1
What is the most likely diagnosis? Select ONE answer only.

A. 21-hydroxylase deficient congenital adrenal hyperplasia (CAH)

B. Biosynthetic defect in testosterone production

C. Complete androgen insensitivity syndrome

D. Gonadal dysgenesis

E. Partial 5α-reductase deficiency

Question 20.2
Which action is correct? Select ONE answer only.

A. Advise that gonadectomy will be required at some point in the future

B. Assign a male gender

C. Start hydrocortisone therapy

D. Start sodium chloride supplementation

E. Start testosterone therapy

Answers 20.1 and 20.2

Question 20.1: What is the most likely diagnosis?

C. Complete androgen insensitivity syndrome.

The infant is genotypically male but phenotypically female. The presence of lumps in the groin of an infant with externally female genitalia raises the possibility that these lumps are testes and that there is a defect in either androgen synthesis or action. The testes have descended to the inguinal ring under the influence of anti-Müllerian hormone (AMH), but the second phase of descent into the scrotum requires the action of testosterone on the gubernaculum and has not occurred. The HCG stimulation test demonstrates normal production of testosterone, suggesting normal testicular function consistent with complete androgen insensitivity syndrome, and excludes gonadal dysgenesis and biosynthetic defects of

testosterone production. Therefore, the most likely diagnosis is androgen insensitivity.

Question 20.2: Which action is correct?

A. Advise that gonadectomy will be required at some point in the future.

Children with complete androgen insensitivity cannot respond to testosterone therapy. As CAH is not the correct diagnosis, the child will neither require nor benefit from either hydrocortisone or salt supplementation, which is appropriate therapy for salt-losing variants of CAH. At some point in the future, gonadectomy will be advised to avoid a risk of malignancy in later adult life, which may be up to 33%.

Male development

The differentiation of the development of the male sexual phenotype is initiated by the *SRY* gene located on the Y chromosome, mediated by multiple other Y chromosome and autosomal 'downstream' genes. The gene products expressed by the *SRY* gene stimulate the medullary sex cords to differentiate into secretory pre-Sertoli cells. From the seventh week of gestation, these cells secrete anti-Müllerian hormone (AMH) – a glycoprotein that plays a central role in subsequent differentiation of the male genital tract.

In the male, the paramesonephric ducts disappear leaving behind only the vestigial remnants (the appendix testis and utriculus). From the seventh week of gestation, the urogenital sinus advances onto the developing phallus as the urethral groove. Ingrowth of the urethral groove is associated with the appearance of urethral plate tissue, which subsequently canalizes to form the anterior urethra (Fig. 20.4). Closure of the urethra should be complete from around 15 weeks' gestation.
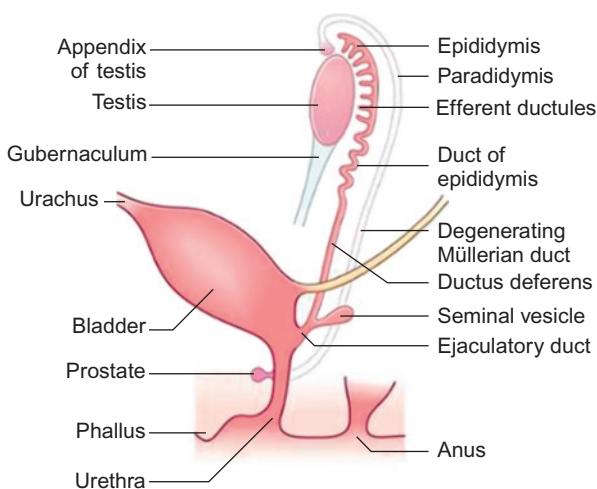
Fig. 20.4 Male sexual development at 12 weeks' gestation. *(Modified from Naish J, et al. Medical sciences 2/e. Saunders, 2014, with permission.)*

Question 20.3

The hormonal control of gonadogenesis

The following (A–G) is a list of hormones:

A. Anti-Müllerian hormone (AMH)
B. Dihydrotestosterone
C. Follicle-stimulating hormone
D. Human chorionic gonadotropin
E. Oestrogen
F. Luteinizing hormone
G. Testosterone

Each answer may be used more than once. Which hormone is MOST responsible for the following actions:

1. Abdominal phase of testicular descent
2. Scrotal phase of testicular descent
3. Virilization of the newborn infant

Answer 20.3

1. A. AMH
2. G. Testosterone.
3. B. Dihydrotestosterone.
   See below for discussion.

The testis

Testicular descent occurs in two distinct phases. The first phase (abdominal phase) is initiated by the presence of anti-Müllerian hormone (AMH). Thus, the testis may descend to the internal ring from the lumbar region without active Leydig cells.

The gubernaculum (Latin for rudder) extends down to the labioscrotal folds and a second more active phase of testicular descent begins between 25 and 30 weeks' gestation. Under the influence of testosterone, the gubernaculum contracts, pulling the testis into its definitive scrotal position. Abnormal positioning of the gubernaculum leads to ectopically positioned testes; a failure in testosterone production or testosterone recognition results in non-descent or incomplete descent. In summary:

- Anti-Müllerian hormone (AMH) (also called Müllerian-inhibiting substance; MIS) causes regression of the mesonephric ducts.
- AMH stimulates testosterone production by Leydig cells of the embryonic testis from the 9th week of gestation. The male fetus is exposed to very high levels of androgen stimulation at the start of the second trimester.
- The intra-abdominal stage of testicular descent is initiated by the action of AMH on the gubernaculum.

In response to testosterone, the mesonephric (Wolffian) duct differentiates between the 8th and 12th week of gestation, giving rise to the epididymis, rete testes, vas deferens, ejaculatory ducts and seminal vesicles.

External genitalia

The complete and adequate differentiation of the male external genitalia is dependent upon a number of different factors. Firstly, the production of testosterone by the primitive Leydig cells of the embryonic testis. This is converted into the more physiologically active dihydrotestosterone by the enzyme 5α-reductase. Active androgen receptors within target cells are required to complete the androgenic stimulation of the male external genitalia. Under the influence of dihydrotestosterone, the genital tubercle develops into the male phallus.

Male genitalia

At birth, it is straightforward to identify a phenotypically normal male infant. Abnormalities of the external genitalia are seen in around 2% of male infants at birth. The penis should be straight and sit cranial to the scrotum, the prepuce should be completely formed (although there are a wide variation of normal variants), and the external urethral meatus should be hidden behind the prepuce and located centrally at the tip of the penis (i.e. distal). It is painful to retract the prepuce as male infants are typically born with a physiological phimosis and so retraction to visualize the external urethral meatus should not be attempted. If the urethral meatus and glans is visible at birth, it should prompt more detailed examination, as an incomplete or hooded foreskin is almost always present in infants with hypospadias.

In the term male infant, the testes should be present bilaterally and be easily drawn to the base of the scrotum. The scrotum should be well-developed to accommodate the testes. In the prepubertal male, the size of the testis should be roughly the same size as the glans penis and symmetrical. The stretched length of the penis from the pubic tubercle should be greater than 2.5 cm. A penis smaller than this should prompt more detailed examination and investigation for ambiguous genitalia.

Disorders of sexual development (DSD)

The pathway of normal sexual differentiation explains the problems that occur. There are a large number of ways to classify pathology of sexual differentiation, but it is simplest to think of the pathogenesis of abnormal sexual differentiation at three different levels:

- Chromosomal abnormalities
- Endocrine abnormalities
- Insensitivity of target tissues

As the underlying problems can be very complicated for individual patients, it is helpful to simplify the topic by describing patients in one of four main categories:

1. A virilized 46 XX female
2. Inadequate virilization for a 46 XY male
3. Gonadal dysgenesis
4. True hermaphroditism

Assessment of an infant with disordered sexual development

History

Details should be sought about:

- Consanguinity, given the genetic basis of many DSDs
- Maternal medication during pregnancy

Examination

In a child presenting with a DSD, the following should be assessed:

- Presence of general dysmorphic signs or congenital abnormalities
- Abdomen and inguinal region for gonads
- Detailed description of the genital abnormalities
- Anus
- Blood pressure, which may be elevated in 11β-hydroxylase deficient CAH.

Investigations

The following should be performed:

- Karyotype
- Abdominal ultrasound to define the internal reproductive anatomy: depending on findings and likely diagnosis, an MRI or laparoscopy may be required for later clarification
- Plasma 17-hydroxyprogesterone and electrolytes to exclude 21-hydroxylase-deficient CAH, testosterone, gonadotrophins and AMH. Further investigation may require HCG stimulation tests for precise assessment of testosterone biosynthesis and ACTH stimulation tests and collection of urine for steroid metabolite profiling for more detailed examination of steroid biosynthetic pathways
- Genitogram before genitoplasty to confirm the location of the external urethral orifice.

Causes of virilization of the 46XX female

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is a consequence of autosomal recessively-inherited mutations of genes encoding enzymes involved in steroid hormone biosynthesis. It is the most common disorder of sexual differentiation, accounting for 85% of all cases of neonates with ambiguous genitalia. The incidence in the UK is approximately 1 in 15,000 births and 95% of cases are due to mutations (of the *CYP21B* gene on chromosome 6) encoding 21-hydroxylase. The normal pathway of aldosterone and cortisol production is dependent upon three major enzymes in the adrenal gland. Reduced function of any of them leads to virilization due to failure of feedback inhibition of ACTH secretion from reduced cortisol levels and preservation of the androgen synthetic pathway (Fig. 20.5).

21-hydroxylase deficiency is the most common form. Virilization may be so severe that affected females are born with apparently normal male genitalia, albeit absent testes. In affected males with no genital abnormalities and virilized females, presentation may be with a severe salt-losing crisis, which may be life-threatening. This is due to impaired mineralocorticoid as well as glucocorticoid synthesis from the child inheriting two severe mutations leading to near complete (<1%) loss of enzyme function. When one of the two inherited mutations is relatively mild, there is preservation of 1–5% of 21-hydroxylase activity, significant salt loss does not occur and the simple virilizing form develops. In the presence of a mild mutation, a non-classical late onset form occurs, affecting girls in adolescence onwards.

Diagnosis is made from elevation of plasma 17 alpha-hydroxyprogesterone.

Treatment requires hydrocortisone at a dose that ensures suppression of ACTH and adrenal androgen production. The first dose needs to be given immediately on waking to counteract the early morning surge in ACTH secretion. Because of the relatively short half-life of hydrocortisone, there is no value in administering large doses of hydrocortisone at bedtime, as this results in grossly unphysiological nocturnal profiles, which may predispose to adverse metabolic health consequences in the long term.

CONGENITAL ADRENAL HYPERPLASIA
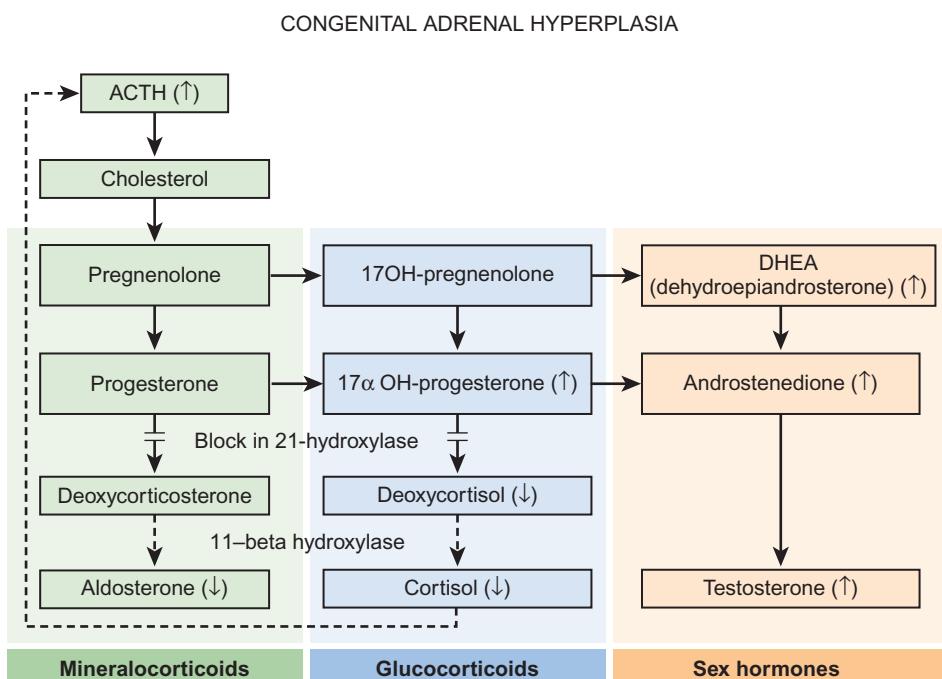
Fig. 20.5 Sites of the two commonest forms of enzyme deficiency causing congenital adrenal hyperplasia. The consequences of the commonest enzyme deficiency, 21-hydroxylase deficiency, are shown; the decreased cortisol results in increased ACTH and increased testosterone, resulting in virilization. Impaired mineralocorticoid and glucocorticoid synthesis may result in a salt-losing crisis.

Adequacy of therapy is monitored by measurement of 17-hydroxyprogesterone profiles and androgen concentrations. In salt-wasting forms, fludrocortisone is also needed. Because of the presence of functional resistance to mineralocorticoid activity in infancy, it is usual to need to administer large doses of sodium chloride during the first year, monitored by measurement of plasma renin activity. Monitoring of growth and pubertal development are the most sensitive markers of adequate treatment; excess height velocity usually indicates excess androgenic activity and undertreatment, whereas excessive glucocorticoid therapy may slow growth. In females, subsequent surgery (feminizing genitoplasty) may be required.

Antenatal treatment with maternal dexamethasone to prevent virilization of female infants at risk of CAH is possible, but needs to be started by six to eight weeks' gestation. This is necessary because from eight weeks onwards, dihydrotestosterone formed from testosterone stimulates the genital tubercle to form the penis, and the urethral folds and genital folds to form the scrotum and ventral part of the penis.

> **Key point – congenital adrenal hyperplasia**
>
> Rapid diagnosis of congenital adrenal hyperplasia is crucial, as salt-losing crises may be life-threatening.

11β-hydroxylase deficiency is the second most common cause of CAH. It is associated with severe virilization, salt retention and potassium loss and in some instances impaired stress response and hypoglycaemia. This is detected by elevated plasma levels of 11-deoxycortisol.

Other causes of 46 XX virilization

The oestrogen synthase enzyme is normally present in high concentrations in the placenta. Deficiency of this enzyme (aromatase deficiency) results in an accumulation of androgen precursors and subsequent fetal virilization.

More rarely, androgen-secreting natural tumours of the adrenal or ovary or maternal treatment with progestational agents can also result in abnormal virilization of the 46 XX infant.

Inadequate virilization of the 46 XY male

Causes

Genetic male infants should develop testes. The pre-Sertoli cells and Leydig cells in the developing gonad then produce anti-Müllerian hormone (AMH) and testosterone as previously described. A small number of male infants exhibit varying degrees of incomplete virilization (this was previously termed male pseudohermaphroditism, a term no longer used because of its negative linguistic connotations). Incomplete virilization can be broadly ascribed either to defects in androgen production or metabolism or to abnormalities of receptor sensitivity in the target tissues.

Failure of testosterone production

Rarely, the primitive testis may be morphologically abnormal resulting in testicular dysgenesis or Leydig cell aplasia. In these patients, absence of Leydig cells results in a failure of production of testosterone. Alternatively, the testis may be morphologically normal, but the production of testosterone is impaired by a failure of the normal biosynthetic pathways.

Defects of testosterone metabolism

Testosterone is converted to the physiologically more potent androgen dihydrosterone by the action of 5α-reductase on testosterone in the developing male infant. 5α-reductase activity may be wholly or partially deficient, resulting in a characteristic pattern of virilization defects seen in some small communities with a limited gene pool (e.g. in the Dominican Republic).

Androgen receptor defects

Virilization may be incomplete in the presence of normal or supranormal levels of circulating androgens if the target tissues are insensitive to androgens. Androgen insensitivity syndrome is an inherited X-linked recessive disorder. In the complete form, the external genitalia are entirely female, however, the internal genitalia have differentiated down a male pathway in response to the AMH secreted by the pre-Sertoli cells in the developing testis. Classically, this condition is discovered when a phenotypically female infant undergoes inguinal hernia surgery (the incidence of complete androgen insensitivity in girls with inguinal herniae has been calculated as 1:1000) or later following investigation for primary amenorrhoea. Partial or incomplete androgen insensitivity has a broad phenotypic spectrum.

Abnormalities of AMH activity

Deficiency of AMH or insensitivity of target tissues by virtue of abnormal AMH receptors in a 46 XY male may result in normal male external genital development with abnormal internal genitalia due to the persistence of Müllerian structures (the uterus, fallopian tubes and upper two thirds of the vagina). This condition typically presents during surgery for undescended testes or inguinal herniotomy. The diagnosis

is confirmed by measuring plasma AMH levels, which are abnormally low in cases of AMH gene mutation but are elevated in patients with AMH-receptor defects.

Idiopathic incomplete virilization

In around half of all cases of incomplete virilization, no specific genetic or hormonal abnormality is readily identifiable.

Gonadal dysgenesis

In this condition, a degenerate ovary or testis persists as a 'streak' gonad. In a 46 XY fetus with completely dysgenetic testes, a failure of production of both testosterone and anti-Müllerian hormone (AMH) results in an entirely female phenotype. Partial gonadal dysgenesis may occur on one or both sides and gives rise to varying degrees of incomplete sexual differentiation.

In *mixed gonadal dysgenesis*, a mixed phenotype occurs. In 45 XO/46 XY mosaicism, varying degrees of incomplete virilization and persistence of Müllerian structures occur. Streak or dysgenetic gonads are at a much increased risk of subsequent malignant transformation. Although much controversy surrounding the management of such patients exists, it is usual to remove gonads that are inappropriate to the sex of rearing of the child at some point in childhood. The involvement of the wider multi-disciplinary team and complex discussions with the family are important in determining the appropriate timing of such surgery.

True hermaphroditism

True hermaphroditism is a rare form of gonadal dysgenesis in which the affected individual possesses both testicular and ovarian tissue. The genitalia are invariably ambiguous. The choice of sex of rearing is very difficult in such cases.

Abnormalities of the male external genitalia

A number of conditions may present at birth or develop later in childhood giving rise to abnormalities of the male external genitalia (Box 20.1).

Cryptorchidism

The most common problem of the male genitalia is cryptorchidism or abnormalities of testicular descent. This is seen in around 1 : 60 of all male infants at one year of age. The risk is considerably higher in premature infants. Further testicular descent is unusual after 3 months of age, as circulating levels of androgens typically fall dramatically at this age and do not rise

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> **Box 20.1 Abnormalities of the male external genitalia**
>
> Congenital:
> - Cryptorchidism
> - Hypospadias
>
> Acquired:
> - Phimosis
> - Meatal stenosis
> - Balanitis xerotica obliterans (BXO)

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again until puberty. Around 1 : 30 boys in the UK undergo operations for inadequately descended testes (a figure somewhat at odds with the figure of 1 : 60 who have undescended testes at 1 year of age). The reason for the apparent discrepancy is purported to be that in some boys the testis, although adequately descended in infancy, comes to occupy an increasingly inadequate scrotal position as boys grow (the ascending testis).

There is some evidence that in these boys the testis is 'tethered' close to the external ring by an inguinal hernia, a patent processus vaginalis or fibrous band left as a remnant of the involuting patent processus vaginalis. Perhaps a more satisfactory term for such testes would be a 'stationary testis', as it is the growth of the scrotum away from the fixed position of the testis that is the fundamental problem.

Failure of testicular descent can result from a wide variety of different mechanisms, which have been investigated in animal models and provide further understanding to the different stages. In the first stage, the gubernaculum tethers the developing gonad to the region of the internal ring, resulting in its migration to this location in the developing fetus during the second trimester. This *abdominal phase* of testicular descent is dependent upon AMH and functioning AMH receptors, but is independent of testosterone. The second phase is characterized by the movement of the testis through the inguinal canal to come to lie within the scrotum. This is typically seen from around 20 weeks of gestation and is *androgen-dependent*.

One proposed mechanism by which failure of testicular descent occurs is seen in the rat animal model. Virilization of the genitofemoral nerve by the production of testosterone causes it to release calcitonin gene-related peptide (CGRP). This subsequently stimulates the gubernaculum, which responds by rhythmically contracting and drawing the testis into the scrotum. Therefore, abnormal positioning of the gubernaculum may result in an ectopic location of the testis (i.e. outside the scrotum). Abnormalities of testosterone production may limit the virilization of the genitofemoral nerve, resulting in less production of CGRP and

incomplete testicular descent. There is evidence that testes that fail to descend normally are intrinsically abnormal (both macroscopically and microscopically). Histological studies of undescended testes have repeatedly demonstrated that dysplastic elements are common. These abnormalities, in combination with the abnormal environment outside the scrotum, contribute to the increased risk of malignant transformation in the child with undescended testicles. The aim of surgery for the correction of abnormally positioned testes is to allow adequate testicular self-examination later in life because of the greatly increased relative risk of the development of testicular cancer.

Classification of abnormally descended testes

Abnormally descended testes should be classified as palpable (80%) or impalpable (20%). Palpable undescended testes are more common, and are further categorized as to their position. The majority are in the superficial inguinal pouch (a position above the scrotum and slightly superior and lateral to the external inguinal ring).

Rarely, palpable testes may be found ectopically in the perineum or thigh, or even in the contralateral hemiscrotum. Impalpable testes are either absent (50%), intra-abdominal (40%) or canalicular (10%).

Children with impalpable gonads may be suffering from a more complex disorder of sexual differentiation. The combination of abnormalities of the penis and impalpable testes (either unilateral or bilateral) should prompt further investigations to confirm genetic sex and investigate failure of normal development. This process is usually undertaken in concert with specialist advice from paediatric endocrinologists and/or paediatric urologists.

Inguinal hernias

Inguinal hernias are common in boys, with a reported incidence of 1–5% for full-term babies. The majority are on the right (60%) as the right testis usually descends second, meaning that failure of closure of

the processus vaginalis is more likely on the right than the left. Premature infants are known to have an increased incidence, from 7–30% in males and 2% in females. Boys are between 4 and 8 times more likely than girls to have an inguinal hernia.

Pathophysiology

The processus vaginalis is an outpouching of peritoneum that is pulled down into the scrotum as the testis in the male; the round ligament in the female descends through the inguinal canal during the third trimester. Ordinarily, the processus vaginalis undergoes a process of obliteration resulting in closure of the patent processus and no connection between the peritoneal cavity and the tunica vaginalis (Fig. 20.6).

Incomplete obliteration of the processus vaginalis can result in either an indirect inguinal hernia, an inguinoscrotal hernia, a hydrocoele of the cord or a communicating or non-communicating hydrocoele. The mechanism by which the processus vaginalis closes is uncertain, but some studies indicate that CGRP released from the genitofemoral nerve may play a role in initiating its obliteration.

Most hernias in children occur spontaneously, but a number of conditions predispose to their development (Box 20.2).

Presentation and management

Inguinal hernia usually presents as a lump in the groin, occasionally extending into the scrotum. Management is surgical. It is one of the commonest surgical procedures in childhood.

Congenital abnormalities of the penis

Hypospadias

The most frequent abnormality of the penis at birth is hypospadias. It consists of an abnormal position of the urethra with an opening on the ventral surface of the shaft of the penis. It is a complex entity with a
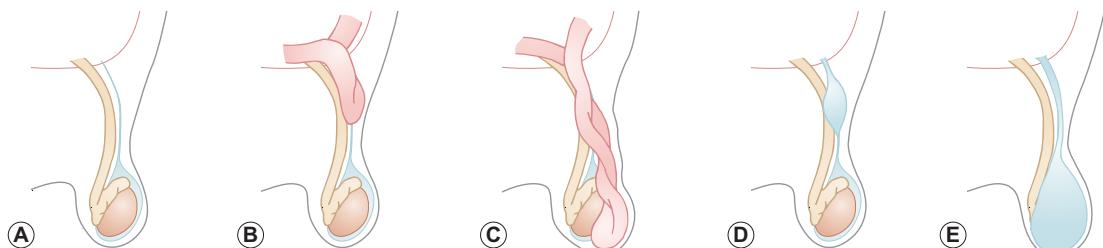
Fig. 20.6 Diagrammatic representation of herniae and hydrocoeles. A. Normal. B. Inguinal hernia. C. Inguinoscrotal hernia. D. Hydrocoele of the cord. E. Communicating hydrocoele.

broad phenotype and is usually seen in combination with a number of other abnormalities:

- A hooded foreskin (the foreskin is incomplete ventrally)
- Chordee (the penis curves downwards due to the presence of scar tissue in the site of the absent corpus spongiosum)
- An abnormally sited urethral orifice with a hypoplastic urethra
- A degree of penoscrotal transposition is common.

Box 20.2 Conditions that predispose to inguinal hernias

- Prematurity
- Intrauterine growth restriction (IUGR)
- Causes of raised intra-abdominal pressure
  - Hydrops fetalis
  - Ascites
  - Ventriculoperitoneal shunts
  - Peritoneal dialysis
- Systemic disorders
  - Mucopolysaccharidosis
  - Connective tissue disorders, e.g. Ehlers–Danlos
  - Marfan's syndome
  - Cystic fibrosis
- Abdominal wall defects
  - Gastroschisis
  - Omphalocoele
- Urogenital developmental abnormalities
  - Cryptorchidism
  - Hypospadias
  - Epispadias
  - Bladder exstrophy
  - Ambiguous genitalia

Its incidence varies widely between populations; it is about 1 : 200–300 in the UK. It appears to be increasing in frequency, although the reason for this is unknown.

Classification

It is usually classified on the basis of the site of the abnormal external urethral meatus. Perhaps more usefully for the non-surgeon, it can be divided into either *distal* (subcoronal and glanular (85%)) or *proximal* (midshaft, proximal shaft, penoscrotal or perineal) hypospadias (15%) (Fig. 20.7). The reason for this distinction is that proximal hypospadias is associated with disorders of sexual differentiation.

Acquired abnormalities of the male external genitalia

The foreskin (prepuce)

The prepuce has a role to protect the fragile tissues of the external urethral meatus in the male infant. A discussion as to the relative merits of the prepuce lies outside the scope of this chapter, however there are a number of pathologies that may develop later in childhood.

The prepuce is usually non-retractile at birth, but typically becomes retractile without medical intervention in 99% of boys by the age of 16. The vast majority of young boys demonstrate *physiological phimosis*, which does not require intervention. On attempted retraction of the preputial orifice, the inner layer of the prepuce becomes visible akin to the blooming of a rose-bud – this appearance is termed 'flowering'. Developmental non-retractability of the foreskin is called phimosis (Greek for 'muzzling'). In boys who develop a phimosis or in whom the foreskin looks abnormal on attempted retraction, there may be a *pathological phimosis*. In this condition, the preputial orifice becomes cicatrized, leading to a 'shark's mouth' appearance, almost always in boys over the age of 5 years. They present with difficulty or pain on voiding. There is usually a characteristic pallor, scarring and
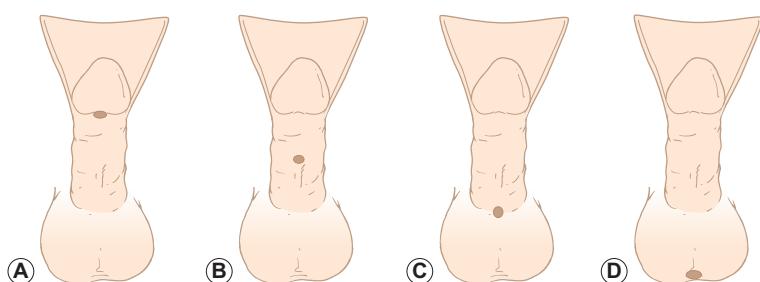
Fig. 20.7 Diagrammatic representation of hypospadias. A. Subcoronal hypospadias. B. Midshaft hypospadias. C. Proximal hypospadias (penoscrotal). D. Proximal hypospadias (perineal).

stenosis of the prepuce. The histological appearances of this condition are termed balanitis xerotica obliterans (or, more conveniently, BXO). This condition is progressive, ultimately leading to potentially irreversible scarring of the glans and urethra and most surgeons would agree that boys with this condition should undergo circumcision. BXO remains relatively uncommon, affecting around only 1:200 boys under the age of 15 years.

Abnormalities of the female external genitalia

As with male external genitalia, it is helpful to split abnormalities broadly into congenital and acquired causes (Box 20.3).

Congenital abnormalities

Imperforate hymen

A small number of girls are born with an imperforate hymen. Clinically, this presents as a bulging introital mass as a neonate, or less commonly as primary amenorrhoea or urinary retention in post-pubertal girls. It is possible to detect vaginal distention antenatally during routine antenatal scans and this is an increasingly frequent mode of presentation to paediatricians and paediatric urologists. The treatment is surgical incision of the imperforate hymen to allow the physiological flow of menses to be established.

Vaginal agenesis (Mayer–Rokitansky syndrome)

This may occur as an isolated congenital abnormality but is most commonly seen as part of a spectrum of abnormalities resulting from a failure of organogenesis of the mesonephric and paramesonephric duct structures. Classically, the upper two thirds of the vagina is absent, but the vagina may be completely absent or manifest as a dimple in the perineum. This condition is the most common cause of primary amenorrhoea.

Box 20.3 Abnormalities of the female external genitalia

Congenital:
- CAH (see above)
- Imperforate hymen
- Vaginal anomalies

Acquired
- Vaginal discharge
- Labial adhesions

Acquired abnormalities

Problems with the female external genitalia of girls are common.

Labial adhesions

Parents often present with concerns surrounding an abnormal appearance of the external genitalia. This may be due to the wide range of normal appearances of the external genitalia. However, the most frequent problem is labial adhesions, where the labia minora become fused together giving a 'blank' appearance to the perineum. They usually occur in girls between the ages of 2 and 6 years and are thought to be a response to inflammation (vulvovaginitis). They rarely cause problems, but occasionally can cause obstruction or deviation in the normal urinary stream. This can even result in girls finding it difficult to keep the flow of urine diverted into the toilet or potty during toilet training or voiding, as the stream from the urethra may be directed upwards by dense labial adhesions; in these cases surgical division is recommended. In most cases it is asymptomatic.

The natural history of labial adhesions is that they resolve spontaneously and they can be managed conservatively. Surgical separation or therapy with oestrogen creams have been tried, but in prepubertal girls the lack of circulating oestrogens means that they often reform on stopping the topical oestrogen. Reassurance and patient watchful waiting is usually successful.

Vaginal discharge

Vulvovaginitis is common in prepubertal girls, but vaginal discharge is uncommon. There is a wide differential diagnosis, but if persistent or severe, a potentially serious underlying pathology needs to be identified. It may be due to a vaginal foreign body from a small item, such as a Lego brick, placed in the vagina and forgotten about, though this is rare. Other pathologies include bacterial infections (including sexually transmitted infections), sexual abuse and genitourinary malignancies (rhabdomyosarcoma), but these are rare. If sexual abuse is considered, the child protection team should be consulted.

A pelvic ultrasound scan can be a useful first-line investigation after a detailed history and clinical examination. Microbiology swabs taken for microscopy culture and sensitivity may identify causative organisms, which may include *Neisseria gonorrhoeae* in the case of sexual abuse. Examination under anaesthesia, including cystoscopy and vaginoscopy, may ultimately be necessary and may also be therapeutic in the case of vaginal foreign bodies.

Vaginal bleeding

Vulvovaginitis may be associated with occasional 'spotting' of blood on the undergarments, but frank vaginal bleeding is rare and serious in prepubertal girls. Rhabdomyosarcoma of the vagina, although rare, is the most important potential diagnosis to exclude. It is much less common than trauma and foreign bodies. Other causes include vascular malformations, precocious puberty and sexual abuse. An ultrasound of the pelvis may be helpful, but an examination under anaesthesia may be required.

Abnormalities of the female internal genitalia

Ovarian cystic lesions

Antenatally diagnosed ovarian cystic lesions are increasingly detected on ultrasound screening. They are usually simple cysts, which are benign follicular cysts. Small to medium-sized simple cysts (<5 cm in diameter) are managed conservatively (although there

may be a risk of torsion). In general, larger and more complex cysts should be referred for specialist management.

The standard surgical treatment of large simple cysts is now laparoscopic deroofing and marsupialization with ovarian and fallopian tube preservation. Prior to surgery, patients should undergo thorough assessment to ensure there is little risk of malignancy (ovarian teratomas). In more complex masses (i.e. characterized by septation or incorporating solid elements), tumour markers are sent preoperatively and the patients are usually managed in concert with paediatric oncology. Removal of the lesion is often a satisfactory and complete treatment, as benign teratomas are the most common lesions seen in infants.

Further reading

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Deirdre Kelly, Nicola Ruth

Hepatology

LEARNING OUTCOMES

By the end of this chapter the reader should:

- Know the anatomy and embryology of the liver and biliary tract and how variation relates to specific disorders, e.g. biliary atresia
- Know the basic histopathology and cellular dysfunction of important disorders, e.g. autoimmune hepatitis, Wilson's disease
- Understand the anatomical, physiological and hormonal changes in the liver that occur throughout childhood
- Understand the physiological basis of normal liver function, including absorption and secretion
- Know the genetic and environmental factors in the aetiology of liver disease
- Understand the pathophysiology of infective agents in the liver
- Understand the pharmacological basis of therapy in liver disorders
- Know the possible impact on the hepatobiliary system of other system disorders and vice versa

The aetiology of liver disease varies according to age. In neonates, infective, genetic and metabolic causes are the most common. As the child gets older, autoimmune/infective causes predominate.

Embryology of the hepatobiliary system

The liver is the largest intra-abdominal organ, with synthetic, metabolic, exocrine and endocrine functions. Liver development occurs through a progressive series of reciprocal tissue interactions between the embryonic endoderm and mesoderm. Application of this knowledge has allowed production of 'hepatic-like' tissue from embryonic stem cells, which may ultimately lead to their use in transplantation.

Overview of liver development

During gastrulation, a process which takes place in all animals, where the single layered blastula becomes a tri-layered gastrula comprising endoderm, ectoderm and mesoderm, the *endoderm* layer forms and leads to a primitive gut tubular structure comprising foregut, midgut and hindgut regions (Fig. 21.1).

The liver originates from the ventral foregut. The first sign is formation of the hepatic diverticulum adjacent to the developing heart (Fig. 21.2). Anteriorly it becomes the liver and intrahepatic biliary tree. Posteriorly it forms the gall bladder and extrahepatic bile ducts. Hepatoblasts invade the septum transversum, forming the liver bud. This undergoes accelerated growth as it is vascularized and colonized by haematopoietic cells, becoming the major fetal haematopoietic organ. Hepatoblasts are bi-potential, becoming either the lumen of the intrahepatic bile ducts or differentiating into hepatocytes. Between antenatal day 17 and into the perinatal period, focal dilations appear forming intrahepatic bile ducts, while the remainder regress.

Defects in early liver bud growth can be lethal. The molecular genetics of Alagille syndrome exemplify the
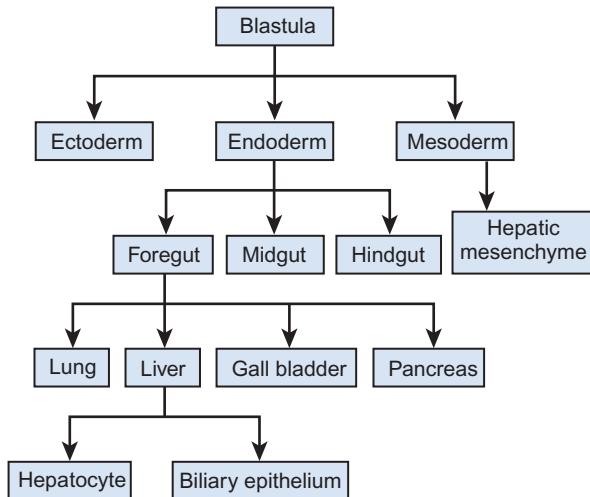
Fig. 21.1 Schematic depiction of embryological hepatic development.

Question 21.1

Bile and the biliary tract

Concerning bile and the biliary tract, which of the following statements are true (T) and which are false (F)?

A. Bile is essential for the effective absorption of dietary fat

B. Bile is normally secreted into the jejunum and absorbed in the caecum

C. Bile is rich in copper

D. The absence of bile leads to dark, tarry stools

E. The gall bladder is easier to visualize on ultrasound scan in a starved patient

Answer 21.1

A. True; B. False; C. True; D. False; E. True. See below for discussion.

interaction between endoderm and mesenchyme (see also Table 21.2). Mutations in the Notch ligand gene Jagged-1 leads to a paucity of intrahepatic bile ducts. Jagged-1 expressed in the portal mesenchyme activates NOTCH-2 in adjacent hepatoblast, required to maintain bile duct morphogenesis.

Anatomy of the liver and biliary tree

The falciform ligament divides the liver anteriorly; the round ligament and umbilical fissure inferiorly. The right lobe is further divided by the gall bladder fossa into the right hemiliver and quadrate lobe. The fourth lobe (caudate) is posterior and surrounds the inferior vena cava. The biliary tree connects the liver and duodenum, the primary purpose being bile transport and storage, under neuronal and hormonal regulation. Bile is formed in hepatocytes, and is transported into the extrahepatic ducts via the cannaliculi. Bile flows into the small intestine or into the cystic duct and then into the gall bladder, regulated by the sphincter of Oddi (Fig. 21.3).

Blood supply and venous drainage

The arterial supply to the liver *in utero* is the left hepatic artery derived from the left gastric artery; the middle hepatic artery (common hepatic artery) derived from the coeliac trunk; and the right hepatic artery derived from the superior mesenteric artery. The blood supply assumes the adult pattern during early infancy, with atrophy of right and left hepatic arteries.

Physiology of the biliary tract

Gut bile allows absorption of fat and excretion of cholesterol, bilirubin, iron and copper. Bile is secreted by the hepatocytes into the canalicular space by active and passive processes. It is the active process which generates bile flow. The products of active secretion comprise conjugated bile acids, conjugated bilirubin, glutathione, conjugates of steroid hormones and leukotrienes. Filterable solutes (plasma, glucose, electrolytes, low-molecular-weight organic acids and calcium) are generated by passive secretion induced by osmotic pressure and are called secondary solutes.

Between meals, the gall bladder relaxes and the sphincter of Oddi contracts, leading to the diversion of hepatic bile into the gall bladder for storage until the next meal (this observation becomes important when assessing a child with conjugated jaundice in whom you suspect biliary atresia, as a fasted ultrasound scan will fail to demonstrate a gall bladder). During a meal, the gall bladder contracts, the sphincter of Oddi relaxes and bile enters the duodenum. Bile acids are absorbed from the terminal ileum and return to the liver via the portal system. This is a process of both passive and active reabsorption. The most important mechanism is a sodium-coupled transporter present in the apical membrane of the enterocytes; the ileal bile acid transporter. In the distal ileum and large intestine, intestinal bacteria deconjugate bile acids, which are absorbed passively. A small amount of the bile acid is lost in the faeces.
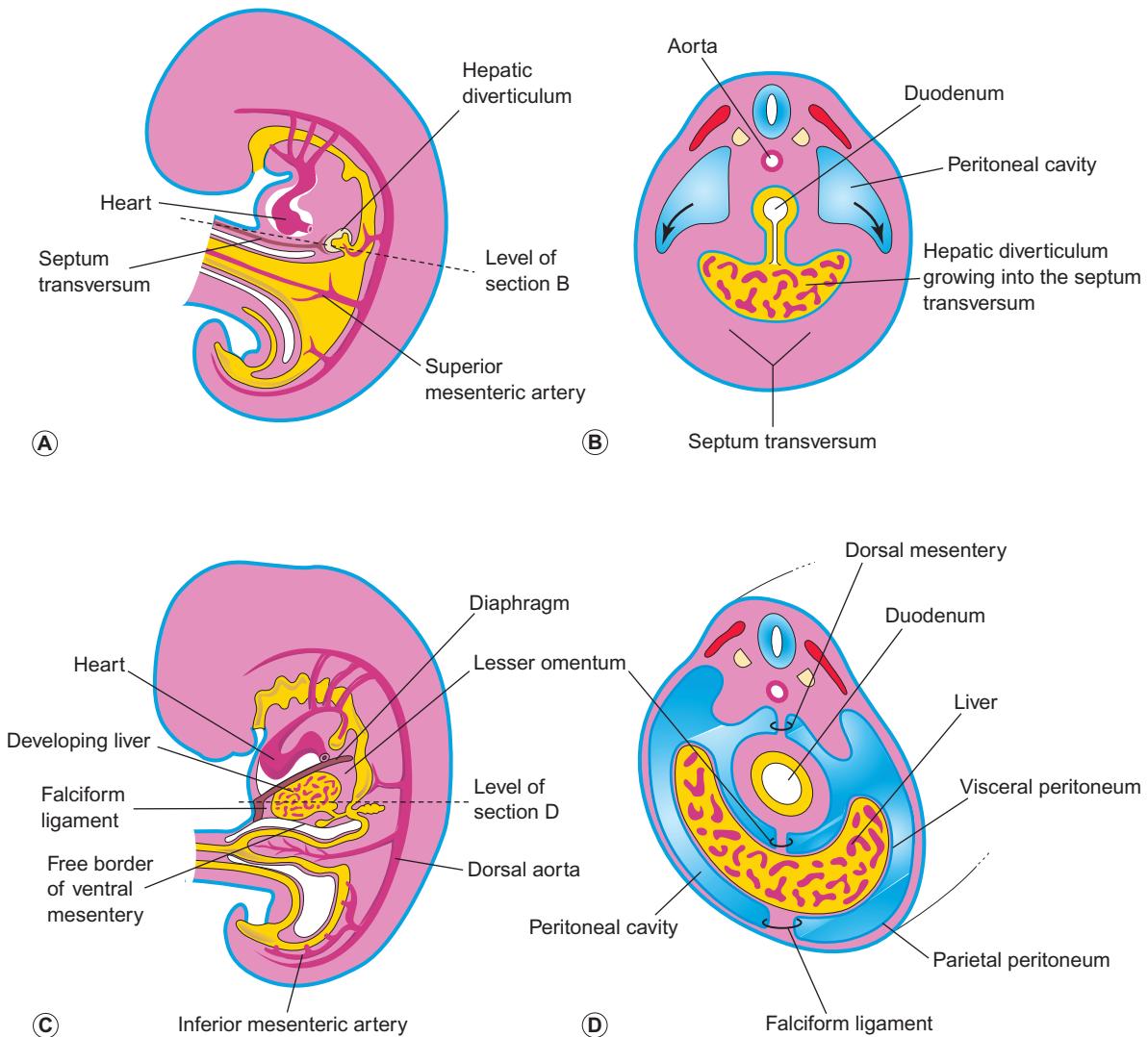
Fig. 21.2 Early development of the liver. A. Median section of a 4-week embryo. B. Transverse section of the embryo, showing expansion of the peritoneal cavity (arrows). C. Sagittal section of a 5-week embryo. D. Transverse section of the embryo after formation of the dorsal and ventral mesenteries. *(From Moore KL, Persaud TVN, Torchia MG. Before we are born, 8th edition, Saunders 2013, with permission.)*
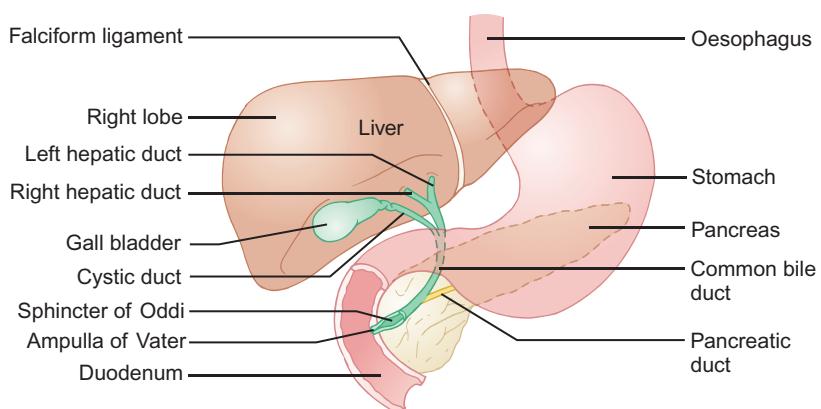
Fig. 21.3 Anatomy of the liver and biliary tree.

Function of the liver and its impact on homeostasis

In order to understand liver disease, it is necessary to understand how the liver regulates a number of important processes (Table 21.1).

Question 21.2

Interpretation of investigations

A 4-week-old baby girl is referred to the paediatric department for review of prolonged jaundice. The blood test results are as follows: Hb 142 g/L, WCC 9.8×10^9/L, Plt 521×10^9/L, total serum bilirubin 109 mmol/L, conjugated bilirubin 9 mmol/L, AST 42 μmol/L, ALT 19 μmol/L, GGT 32 μmol/L, alkaline phosphatase 1345 μmol/L. What do these results suggest? Select ONE answer only.

A. Biliary stasis

B. Mild hepatic necrosis

C. Possible biliary atresia and should be admitted for further imaging

D. Rapid bone growth of infancy

E. Vitamin D deficiency – this baby should be screened for possible rickets

Answer 21.2

D. Rapid bone growth of infancy.

This question demonstrates that, although commonly considered a 'liver enzyme', alkaline phosphatase is also produced during rapid bone growth – and can often be raised during so-called growth spurts.

Biochemical tests

Bilirubin, in particular conjugated (direct) bilirubin, is almost always raised in liver disease irrespective of its cause. It is produced from the breakdown of red blood cells, making unconjugated (indirect) bilirubin, which circulates bound to albumin although some is 'free' and hence able to enter the brain. Unconjugated bilirubin is metabolized in the liver to produce conjugated bilirubin which passes into the gut and is excreted in stool.

Transaminases are present in the liver, heart and skeletal muscle. They indicate the nature of liver dysfunction when taken in combination with a background history, e.g. raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

Table 21.1 The functions of the liver

Function	Effect of dysfunction	Assessment
Metabolism/storage		
Carbohydrate/ glycogen	Loss of glucose homeostasis	Hypoglycaemia on fasting
Lipid	Lipid accumulation Reduced oxidation of fatty acids	Dyslipidemia Raised lactate Increased ratio free fatty acid : beta-hydroxybutyrate Increased acyl carnitine Organic aciduria
Protein	Increased catabolism	Low branch chain amino acids, urea Hyperammonaemia Raised tyrosine, phenylalanine, methionine
Synthesis		
Albumin Factors II, VII, IX, X	Loss of muscle mass Coagulopathy	Low albumin; protein energy malnutrition Prolonged PT/PTT
Degradation		
Drugs	Prolonged drug effect, e.g. sedation	Clinical
Oestrogens	Telangiectasia; gynaecomastia.	Clinical
Toxic products	Encephalopathy	Abnormal EEG
Bile synthesis and excretion	Cholestasis	Conjugated hyperbilirubinaemia, raised LFTs
	Fat malabsorption Fat-soluble vitamin deficiency Pruritus	Hypercholesterolaemia
	Malnutrition	Anthropometry

EEG, electroencephalography; LFTs, liver function tests; PT, prothrombin time; PTT, partial thromboplastin time.

indicate hepatic necrosis and are indicators of hepatic damage. Alkaline phosphatase, although raised in liver disease, particularly biliary disease, can also be raised in rapid bone growth or secondary to vitamin D deficiency. Gamma-glutamyl transferase (GGT) is particularly associated with biliary obstruction and inflammation.

Assessment of liver synthetic function is useful when assessing liver disease. Albumin and coagulation are sensitive markers of liver dysfunction. Hypoglycaemia is a common finding in liver dysfunction.

Radiology

Radiological investigations such as an ultrasound scan can give valuable information about the liver's

architecture, such as the shrunken cirrhotic liver with heterogeneous appearance often seen in chronic liver disease, or the enlarged liver seen in some metabolic diseases such as glycogen storage disease type I. Developmental defects can be seen on fasting ultrasound scan, such as extrahepatic biliary atresia, where a gall bladder is not demonstrable after a fast (this is abnormal and must always be discussed with a tertiary centre). The other developmental defect commonly seen on ultrasound scan is a choledochal cyst (an outpouching of the bile ducts). Surgical correction is necessary as these can result in malignancy. Gallstones can be easily demonstrated on ultrasound scan as well as any ductal dilatation. It is also possible to assess the liver's blood supply, valuable in children who have liver disease or who have had a liver transplant, as vessel thrombosis or reversed vessel flow requires immediate assessment and management and is a poor prognostic sign. Other abdominal structures can be assessed, e.g. splenic enlargement associated with portal hypertension – a sequelae of chronic liver disease. The spleen is enlarged due to increased blood flow as a result of a stiffened cirrhotic liver (which is resistant to flow and therefore the blood takes the path of least resistance – see discussion below).

Neonatal liver disease

Jaundice in the neonatal period is common. About two-thirds of term babies have transient jaundice 3–5 days after birth. Most *do not* have liver disease. Unconjugated jaundice is often due to immaturity of the hepatic enzyme glucuronosyltransferase, responsible for glucuronidation of bilirubin. Unconjugated jaundice in the neonatal period may be due to 'breastmilk jaundice'. Other causes include haemolysis, sepsis and hypothyroidism. This is considered in detail in Chapter 11, Neonatal medicine. In contrast to this, *conjugated hyperbilirubinaemia* is often a reflection of hepatic dysfunction due to a number of potential causes, including biliary atresia or neonatal hepatitis syndrome.

Babies with significant liver problems usually have significant jaundice. Under these circumstances, the bilirubin level should be measured together with the fractional breakdown of the conjugated and unconjugated components. This will help to guide further investigation and management.

Disorders of bilirubin metabolism

Crigler–Najjar syndrome types I and II are rare autosomal recessive disorders which cause intense unconjugated hyperbilirubinaemia in the first days of life, which persists thereafter. In type I, there is no UDP-glucuronosyltransferase. Hyperbilirubinaemia is very severe despite phototherapy and may result in

Question 21.3

Bilrubin metabolism

A six-week-old male baby is referred to the general paediatric clinic as a 'hungry baby who cries all the time'. Upon review, the baby is alarmingly malnourished and jaundiced. The stool is white (Fig. 21.4) and urine dark orange. Which of the following is most likely to BEST describe the physiology underpinning the pale stool? Select ONE answer only. The stool is pale because it is lacking in:

A. Caesin

B. Hemosiderin

C. Ligandin

D. Lipase

E. Stercobilin
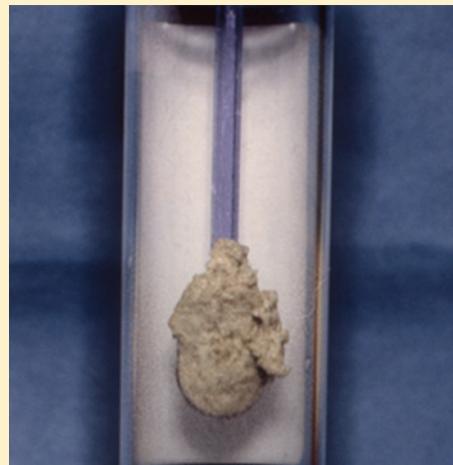
Fig. 21.4 Typical appearance of the acholic stool.

Answer 21.3

E. Stercobilin.

In order for bile to enter the stool it has to be conjugated, making bilirubin water soluble and easier to excrete. Once in the gut, conjugated bilirubin is either hydrolyzed and reduced by bacteria to form urobilinogen (which is colourless) or reabsorbed via the enterohepatic circulation. Most urobilinogen is eventually oxidized by intestinal bacteria to stercobilin in stool, which gives its brown colour. If conjugated bilirubin fails to be excreted into the gut, the stools will be pale.

In biliary obstruction, the amount of urobilinogen in the gut is reduced, so the urobilin in the urine is low. However, there is increased soluble conjugated bilirubin in the circulation which is excreted via the kidneys and results in the urine's dark colour.

kernicterus. Diagnosis is made by DNA analysis. In type I, there is no response to treatment with pheno-barbital, which causes cytochrome P450 enzyme induction. Acute treatment is with exchange transfusion and liver transplantation is a long-term option. In type II, some UDP-glucuronosyltransferase is present, so hyperbilirubinaemia is less severe. Phenobarbital therapy is effective, generally with a marked decrease in serum bilirubin. Therapies based on gene and cell transfer techniques are likely to be helpful in the future.

Conjugated neonatal jaundice

In normal circumstances, only a small fraction of bilirubin is conjugated. In neonates, conjugated hyperbilirubinaemia is defined as a serum conjugated bilirubin of greater than 25% of the total (current BSPGHAN guideline) or >25 µmol/L (NICE guidelines). This most commonly occurs when there is cholestasis. With neonatal cholestasis, there is impairment of bile excretion caused by defects in intrahepatic production or transmembrane transport of bile, or mechanical obstruction to bile flow. The biochemical features of cholestasis reflect the retention of components of bile in the serum (bilirubin, bile acids, and/or cholesterol). The pattern and severity of each of these abnormalities varies with the underlying disorder.

Classically, patients present with jaundice, pale (acholic) stool and dark urine. Pale stools occur as no bilirubin reaches the gastrointestinal tract and dark urine results from excretion of water-soluble conjugated bilirubin in the urine. Both of these features suggest cholestasis.

Biliary atresia

Biliary atresia is the commonest cause of neonatal liver disease and indication for liver transplantation in children. It occurs in 1:17,000 live births. It presents with conjugated jaundice, acholic stools and hepatomegaly. There is failure of passage of bile from the liver into the gall bladder and onto the small intestine. Bile is essential for carrying waste from the liver and promoting absorption of fats and fat-soluble vitamins. Biliary atresia results in chronic liver failure if surgical correction is not performed. The Kasai portoenterostomy attempts to allow diversion of bile from the residual small bile ducts. The surgery involves attaching the porta hepatis to a loop of small intestine. Up to 60% will achieve biliary drainage (bilirubin <20 µmol/L) within 6 months. Most of these children will reach adolescence with a good quality of life (but with cirrhosis/evidence of portal hypertension) without undergoing liver transplantation.

Questions 21.4 and 21.5

Jaundice in a 4-week-old infant

Olivia is a 4-week-old infant referred to a tertiary centre due to prolonged jaundice. She is thriving, but noticed to have very pale chalky white stools. Her urine is dark in colour. Baseline blood investigations revealed mildly raised transaminases. Her total bilirubin concentration was 220 µmol/L, with a conjugated fraction of 185 µmol/L. A fasting ultrasound scan was organized which demonstrated a completely contracted gall bladder despite adequate 4-hour fast. TIBIDA scan was also performed which showed no excretion of technetium even after a prolonged exposure (>24 hours). Olivia underwent Kasai procedure at 5 weeks of age and by 3 months of age her bilirubin had reduced to normal range (bilirubin concentration <20 µmol/L). She will be followed up long term for any signs of chronic liver disease, including portal hypertension.

Question 21.4
Where is the initial underlying defect MOST likely to occur? Select ONE answer only.

A. Extrahepatic biliary tree

B. Exocrine pancreas

C. Gall bladder

D. Intrahepatic biliary tree

E. Jejunum

Question 21.5
If her Kasai operation 'failed', she would develop rising bilirubin, abdominal distension due to ascites and faltering growth from chronic liver disease. Why would she develop faltering growth? From the following list, which of the statements are true (T) and which are false (F)?

A. She has a chronic health problem and is likely to suffer from neglect from carers

B. Her metabolic rate is markedly increased

C. Lack of gut bile decreases the absorption of fat and fat-soluble vitamins

D. The growth failure is secondary to adrenal suppression

E. The main cause is likely to be corticosteroid therapy

Congenital infection

Congenital infections are described in detail in Chapter 10, Perinatal medicine. The clinical features of congenital CMV, toxoplasmosis, rubella and syphilis include conjugated jaundice and hepatomegaly. However, any infection acquired around the time of birth, e.g. herpes simplex, varicella zoster virus or any bacterial infection, can cause cholestasis as hepatic bile flow is very sensitive to circulating endotoxins.

Genetically inherited cholestatic liver disease

The liver plays a number of important roles in amino acid metabolism, protein synthesis, carbohydrate metabolism and lipid metabolism. It is also the site of manufacture of a number of blood coagulation proteins. It is therefore key to much of the metabolic activity in the body and over 100 heritable forms of liver disease have been described. The clinical features and genetics of some of the genetically inherited diseases affecting the liver are summarized in Table 21.2.

Endocrine causes of neonatal hepatitis

There are two main endocrine causes of jaundice in a neonate presenting with conjugated hyperbilirubinaemia, hypothyroidism and hypopituitarism. The mechanisms of the development of jaundice in pituitary hormone insufficiency are not fully established; however, it is known that thyroid hormone and cortisol affect the bile acid-independent bile flow. Cortisol can influence bile formation and reduce bile flow. The measurement of serum cortisol forms part of the assessment of hypopituitarism – a low level raises suspicions, and is an indication for performing a short synacthen test. Growth hormone has also been shown to modulate bile acid synthesis and it is thought to be important for bile acid formation. All three hormones are important independently in bile acid formation and excretion. Clinical presentation of hypopituitarism depends on the patient's age, and the specific hormone deficiencies, which may be isolated or multiple. Presenting features may include hypoglycaemia, hyponatraemia and prolonged jaundice, and in males small genitalia and undescended testes. The possibility of septo-optic dysplasia should be considered whenever congenital hypopituitarism is diagnosed. In addition to the neuroendocrine deficiency, these patients variably have optic nerve hypoplasia and midline brain defects including agenesis of the septum pellucidum. Jaundice usually improves as the underlying endocrine disorder is treated.

Recent scientific advances which have improved clinical practice – GeneChip Project

In infancy, many genetic causes of cholestasis present in a similar way, making the diagnosis challenging. Current diagnostic techniques are expensive and time-consuming, but newer genetic technologies (microarray and DNA sequencing) have been developed which can screen for many genes in multiple patients simultaneously, reducing cost and time to diagnosis. This will ultimately allow a diagnosis to be made in more genetic causes of cholestasis.

Acute liver failure in infancy

In infancy, acute liver failure may present with subtle signs such as irritability, sleepiness or hypoglycaemia. Bruising, petechiae or, more commonly, bleeding or oozing from previous venepuncture sites/umbilical stump should lead one to suspect an underlying coagulopathy. Jaundice will inevitably be present.

Question 21.6

Jaundice and bleeding at 2 days of age

Jaiden is two days old. He was born at term by normal delivery. He received vitamin K orally. He is brought to the emergency department by ambulance with widespread bruising and oozing from his umbilical cord. He is deeply jaundiced. His parents report that he has been a quiet baby until today, when they just cannot get him to stop crying. On examination, he is very unsettled, and

Table 21.2 Some of the commoner genetic diseases affecting the liver presenting with conjugated hyperbilirubinaemia

Name	Frequency	Genetics	Associated features	Treatment
Alpha-1-antitrypsin deficiency	1:1600	AR (*SERPINA1* gene) 3 alleles: M, S and Z. Most common deficiency is Z-amino acid substitution.	Presentation in neonatal period is with conjugated jaundice, acholic stools and intrauterine growth restriction. Variable hepatomegaly. Hepatitis, cirrhosis and liver failure.	Cirrhosis and risk of malignant transformation. Family screening. Alcohol and smoking advice. Liver transplantation for chronic liver disease.
Alagille syndrome	1:100,000	AD with incomplete penetrance, due to defects in the *JAG1* gene on chromosome 20 coding for the ligand Notch1.	The expression of Notch1 found in many of the organs, e.g. liver, kidney and heart. Cardiac, renal and dysmorphic features common, i.e. characteristic facies (broad forehead, hypertelorism, deep set eyes, and small pointed chin). Butterfly vertebrae due to fusion of anterior arch of vertebral body are commonly found in the thoracic spine.	Supportive with vitamins. Medication to control intense pruritus. May need transplantation for chronic liver disease.
Tyrosinaemia type 1	1:100,000	AR	Defect of fumaryl acetoacetase, the terminal enzyme in tyrosine degradation, leading to accumulation of toxic metabolites. Patients present with acute liver failure. Hepatocyte dysplasia is a key feature. These patients are at risk of HCC.	Dietary restriction, nitisone (NTBC). Liver transplantation prevents the development of HCC.
Niemann–Pick disease	1:120,000	AR *NPC1* or *NPC2* genes encode intracellular lipid trafficking proteins leading to accumulation of intracellular unesterified cholesterol in many tissues, e.g. the brain.	Hepatosplenomegaly. Hydrops fetalis and ascites. Ascites is also a feature of NPA and NPB. Neurological impairment develops, becoming more obvious with age. Most children develop loss of upward gaze due to vertical supranuclear ophthalmoplegia (pathognomonic). Other neurological features include ataxia, seizures, severe developmental delay and dementia.	Liver and bone marrow transplantation. The first approved specific therapy for NPC disease is miglustat; capable of inhibiting the first step in glycosphingolipid synthesis. Clinical trials and observational studies suggest that it delays the progression of neurological symptoms.
Progressive familial intrahepatic cholestasis	Exact frequency unknown	AR PFIC-1 and PFIC-2	Jaundice, hepatomegaly, pancreatitis, pruritus, steatorrhoea, growth faltering and early progression to cirrhosis. Characteristic is a low/normal serum GGT discordant with the degree of cholestasis. Low/normal serum cholesterol is also a feature.	Treatment is supportive. Biliary diversion is considered to aid excretion of bile salts. Progressive liver cirrhosis will eventually lead to the need for liver transplantation.

AR, autosomal recessive; AD, autosomal dominant; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; NPC, Niemann–Pick disease type C; NPA, Niemann–Pick disease type A; NPB, Niemann–Pick disease type B; NTBC, 2-(2-nitro-trifluoromethylbenzoyl)-1,3-cyclohexenedione; PFIC, progressive familial intrahepatic cholestasis.

jittery. His temperature is 40°C. Capillary refill time is 5 seconds centrally. He is not dysmorphic. Urgent blood investigations are performed and the results are:

Hb 122 g/L, WCC 18.4 × 10⁹/L, Platelets 62 × 10⁹/L, PT 46 seconds

ALT 2654 µmol/L, AST 1129 µmol/L, GGT 3458 µmol/L, alkaline phosphatase 762 µmol/L, blood glucose 1.9 mmol/L

What is the most likely reason for this child's coagulopathy? Select ONE answer only.

A. Disseminated intravascular coagulopathy (DIC)

B. Haemophilia A

C. Idiopathic thrombocytopenic purpura (ITP)

D. Infantile acute lymphoblastic leukemia (ALL)

E. Vitamin K deficiency

Answer 21.6

A Disseminated intravascular coagulopathy (DIC).

Jaiden most likely has a metabolic or septic cause for his presentation. He has acute liver failure. As in all children presenting *in extremis*, an ABCDE approach is key to assessing and managing this situation. His pyrexia suggests an infective cause. His bruising and oozing from umbilical stump are due to coagulopathy. There is no need to have a definitive diagnosis before starting treatment. He was found to have disseminated herpes simplex infection.

Liver histology will demonstrate necrosis with inclusion bodies within intact hepatocytes. Infants with herpes simplex infection typically present in early infancy with irritability, fever, unstable blood glucose, possible oozing from the umbilical cord stump or venepuncture sites. The condition is rapidly progressive without treatment. Even with adequate management, the outlook is bleak, with liver transplantation still a possibility after the acute infective phase has resolved due to progressive, often irreversible, liver damage. In addition to herpes simplex infection, there are a number of other causes of acute liver failure (see Table 21.3), including tyrosinaemia, galactosaemia (see Case history, Galactosaemia) and neonatal haemochromatosis (see below).

Neonatal haemochromatosis

Neonatal haemochromatosis is an iron storage disorder. Iron is a vital substrate for many physiological processes. Iron exists as transferrin (bound to apotransferrin). Most of the iron used for red blood cell haemoglobin production is obtained from haemoglobin breakdown of senescent red blood cells. These red blood cells are phagocytosed by macrophages (in the spleen, liver, bone marrow). Proteolytic enzymes in the macrophages degrade these ingested cells and release haem and globin molecules as separate entities. The globins are broken down to amino acids, used for protein production. Iron is released from haem, leaving a porphyrin ring, which is converted to bilirubin. Failure of these processes or excessive iron absorption leads to accumulation in the liver (as well as other tissues). This results in damage and the clinical features of elevation in transaminases and jaundice (conjugated), together with hypoalbuminaemia and severe coagulopathy.

Neonatal haemochromatosis is considered an alloimmune disorder (where mothers develop an abnormal immune response to fetal liver protein which results in liver damage and a direct or indirect effect on fetal iron storage). It is rare in the first pregnancy; however, risk in subsequent pregnancies is as high as 70%. In addition to the features already described, high serum iron level with hypersaturation of iron-binding capacity and elevated ferritin levels are seen. The clinical course is progressive with death from liver failure without liver transplantation. The diagnosis is based on demonstrating iron storage outside the liver, e.g. in salivary glands, pancreas or brain on magnetic resonance imaging.

Case history

Galactosaemia

A term infant is discharged home orally fed. She becomes mottled and unresponsive on day 3 of life and is rushed to hospital by ambulance, with high pyrexia. Blood glucose on admission is 1.6 mmol/L. She is mottled and capillary refill time is 4 seconds. Following fluid bolus, she is noted to be deeply jaundiced (total bilirubin 192 µmol/L, conjugated 167 µmol/L).

Her parents report that she has had vomiting and diarrhoea. She has lost 12% of her birth weight. Bruising is present and initial blood investigations reveal a coagulopathy and renal impairment. She is commenced on intravenous antibiotics for presumed sepsis. She was kept nil by mouth and started on intravenous fluids. A blood and urine culture demonstrated a pure growth of *Escherichia coli*.

She was investigated for neonatal cholestasis (including Gal-1-PUT, urine and plasma amino acids, bloods as per BSPGHAN guideline and a fasting ultrasound scan).

Galactosaemia was diagnosed. The combination of Gram-negative sepsis with hypoglycaemia, conjugated jaundice and coagulopathy are typical of this disease. It is autosomal recessive, caused by

deficiency of galactose-1-phosphate uridyltransferase and has an incidence of 1 : 45,000. Typically, infants present in the early neonatal period with sepsis and liver failure. Characteristic 'oil drop' cataracts are found on ophthalmoscopy. Classically, diagnosis is suggested by detection of urinary reducing substances without glycosuria. Diagnosis is confirmed by demonstrating reduced enzyme activity in blood (Gal-1-PUT). Misleading results can be obtained in the presence of recent blood transfusion.

Mitochondria and liver disease

Mitochondria are present in every cell. Tissues that need large amounts of energy, e.g. brain, heart, liver, renal tubules, etc., are affected, at least in part, because they run out of fuel. Neonates may present with acute liver failure, together with seizures, cardiomyopathy and renal failure. In the older child, it may present as hepatic steatohepatitis, cholestasis, or cirrhosis with chronic liver disease, with typically subtle ill-defined onset. Lactic acidaemia is a key feature. The liver disease is usually progressive and fatal. Prognosis is poor. Liver transplantation is contraindicated in children with multi-organ involvement, but may be possible in those with disease confined to the liver. Several specific molecular defects (mutations in nuclear genes such as *SCO1*, *BCS1L*, *POLG*, *DGUOK*, and *MPV17* and deletion or rearrangement of mitochondrial DNA) have been identified in recent years. Prospective, longitudinal multicentre studies will be needed to address the gaps in our knowledge in these rare liver diseases.

Acute liver failure in the older child

Acute liver failure (ALF) is the development of hepatic necrosis in the absence of pre-existing liver disease. The aetiology is varied, with acute hepatitis A and B being the commonest cause in developing countries, while seronegative hepatitis is the main cause in children worldwide. The clinical presentation is with jaundice, encephalopathy and coagulopathy. In the older child, it may represent the first presentation of a previously unrecognized autoimmune or metabolic liver disease (Table 21.3).

Complications and pathophysiology of acute liver failure

Cerebral oedema leads to hepatic encephalopathy, coma, brain herniation and eventually death. Detec-

Table 21.3 Causes of acute liver failure

Neonate/infant up to 6 months	
Infection	Septicaemia Hepatitis B Adenovirus Echovirus Coxsackie B Herpes simplex
Metabolic	Neonatal haemochromatosis Tyrosinaemia type 1 Mitochondrial disease Fatty acid oxidation defects
Poisoning	Paracetamol
Children >6 months	
Infection	Hepatitis A/B/E Epstein–Barr virus Parvovirus B19
Autoimmune	Autoimmune type 1 or II
Drug	Paracetamol overdose Anti-epileptics: sodium valproate, carbamazepine Isoniazid Halothane
Metabolic	Wilson's disease Alpers' disease

tion of encephalopathy is a clinical feature of ALF. It may vary from subtle deficit in higher brain function (e.g. mood, concentration in grade I encephalopathy) to deep coma (grade IV encephalopathy). Patients presenting with acute and hyperacute liver failure are at greatest risk of developing cerebral oedema and grade IV encephalopathy. The pathogenesis remains unclear but is likely to be a consequence of several phenomena:

- Accumulation of toxins, e.g. ammonia. This affects neurotransmitter level and neuroreceptor activation.
- Autoregulation of cerebral blood flow is impaired resulting in anaerobic glycolysis and oxidative stress. Neuronal cells are particularly sensitive to this and expand, causing a rise in intracranial pressure.
- Inflammatory mediators.

Coagulopathy is due to the liver's role of production of coagulation factors. This results in prolongation in prothrombin time, which is used to monitor severity of hepatic injury. There is also platelet dysfunction. Progressive thrombocytopenia with loss of larger and more active platelet is almost universal.

Systemic inflammatory response syndrome (SIRS) is seen in up to 60% of all patients, regardless of whether infection has been identified, resulting in multi-organ failure. The mechanism behind this is thought to be

due to impaired immune function, which increases the risk of sepsis. Routinely, patients are treated with antibiotics and antifungals.

Hyponatraemia is an almost universal finding which results from water retention in response to *hypoalbuminaemia*, as well as a shift in intracellular sodium transport from inhibition of Na/K-ATPase. Hypokalaemia, hypophosphataemia and metabolic alkalosis are often also present.

Hypotension results from peripheral vascular dilatation and reduced systemic vascular resistance. Cardiac output increases as a compensatory mechanism. There is tissue hypoxia and lactic acidosis. Acute respiratory distress syndrome (ARDS) can cause respiratory compromise.

Indications for transplant in acute liver failure

These are:

- Worsening coagulopathy, which is unsupported by blood products and not responsive to administration of vitamin K. Vitamin K provides co-factor for prothrombin time (PT) but rarely corrects it.
- Worsening encephalopathy

Contraindications for transplant in acute liver failure

Contraindications are:

- Multisystem disease
- Irreversible brain damage
- Pre-existing life-limiting disorders

Presentations of liver disease in the older child

Chronic liver disease is defined as liver disease persisting for longer than 6 months. Chronic hepatitis covers a wide range of diseases that lead to progressive inflammatory damage/fibrosis. The most common is autoimmune disease. In addition, hepatitis due to viral infection may also evolve from an acute inflammatory process to chronicity.

The main aetiologies of liver disease in the older child include:

- Autoimmune liver disease
- Chronic hepatitis infection
- Drug-induced liver disease
- Multi-system disease affecting the liver (e.g. cystic fibrosis)
- Genetic: Wilson's disease, alpha-1-antitrypsin deficiency

Clinical manifestations and complications of chronic liver disease

In chronic liver disease, the liver often becomes stiffened as cirrhosis develops, making blood flow more difficult, resulting in portal hypertension. Portal hypertension is an increase in portal venous pressure leading to the formation of portosystemic collaterals at various sites, resulting in varices at the distal oesophagus, anal canal, falciform ligament (umbilical varices) and abdominal wall. *Caput medusae* are distended and engorged paraumbilical veins, which are seen radiating from the umbilicus across the abdomen to join systemic veins. *In utero*, the umbilical vein normally closes within the first few weeks of life. However, in portal hypertension, the umbilical vein is re-canalized.

Children with portal hypertension may develop splenomegaly, which causes secondary thrombocytopenia (due to platelet consumption) as blood is diverting into the systemic circulation, bypassing the liver. Splanchnic vasodilation contributes to this process and several endogenous vasodilators have been implicated, e.g. glucagon, prostacyclin, endotoxins, and nitric oxide. This vasodilation is associated with reduced arterial pressure and peripheral resistance and increased cardiac output. The plasma volume increases as a result of renal sodium retention, which often precedes the increase in cardiac output and ascites and can be prevented or reversed by sodium restriction and spironolactone. The expanded blood volume represents another mechanism that contributes to further increases in portal pressure.

Hepatorenal syndrome occurs in fulminant and chronic liver disease. Portal hypertension leads to inappropriate activation of the renin–angiotensin–aldosterone system, the sympathetic nervous system and arginine vasopressin – all of which result in sodium and water retention and the development of ascites. In severe cases renal failure can occur. Management is with careful fluid balance, colloid fluid expansion, dialysis or hemofiltration. Transjugular intrahepatic portosystemic shunt or transjugular intrahepatic portosystemic stent shunting (often abbreviated as TIPS or TIPSS) can effectively reduce portal hypertension and may lead to recovery from hepatorenal syndrome.

Individuals with significant hepatic disease cannot metabolize circulating oestrogens, specifically androstenedione, resulting in increased levels of oestradiol in the circulation. Gynaecomastia and spider naevi may develop. *Spider naevi* are typically found on the trunk and consists of a central arteriole with numerous small vessels radiating out.

Ascites accumulates because of increased pressure in the portal venous system carrying blood from the

gut and spleen to the liver (portal hypertension) and a low level of the protein albumin in the blood (hypoalbuminaemia). Albumin is reduced in cirrhosis due to the liver being unable to produce it. Ascites may become infected and this diagnosis should be considered in children with liver disease and pyrexia. Albumin infusions and therapeutic paracentesis can help acutely, but reaccumulation generally occurs.

Autoimmune liver disease

Although this is an uncommon problem in childhood (incidence 1 : 10,000 in the UK), during life autoimmune liver disease affects approximately 6% of the world's population, nearly three quarters of whom are female. Females respond in a different way to males in response to infection, vaccination, and trauma, exhibiting increased antibody production and a more T-helper (Th)2-predominant immune response, whereas a Th1 response and inflammation are usually seen in males. In the female-predominant autoimmune diseases that manifest during the acute phase, there appears to be an antibody-mediated pathology.

Although the exact mechanism for autoimmune hepatitis (AIH) remains elusive, a genetic predisposition has been found and there is an association with HLA B8/DR3. Following activation of inflammatory response in autoimmune hepatitis, cytokine release leads to macrophage activation and hepatocellular lysis. The genes a person inherits affect the number of cells in the adaptive immune system (i.e. producing, storing, and transporting immune cells and cytokines). Whilst this response is helpful in mounting a response to certain cancers and infections, in some individuals this response is exaggerated and this leads to the body's host immune system attacking its own tissues, resulting in autoimmune disorders.

It is helpful to determine whether the target of the autoimmune response is the parenchyma (autoimmune hepatitis), biliary tree (sclerosing cholangitis) or both (overlap syndrome). Some 20% of children with autoimmune liver disease also have another autoimmune disorder (at the time of presentation, especially type 1 diabetes mellitus and Crohn's disease), or will have a family history of a first-degree relative with an autoimmune disorder. In addition, children may present with coagulopathy or hypoalbuminaemia. Ascites may be a presenting feature associated with the low serum albumin. These features are associated with chronic liver disease, which has usually already developed by the time the child presents clinically.

Treatment modalities for autoimmune hepatitis

Corticosteroids should be commenced at presentation. The dose can be tapered once transaminases normalize.

The addition of disease-modifying antirheumatic drugs (DMARDs), e.g. azathioprine, can be helpful, but maintenance of remission is generally achieved with low-dose prednisolone. Ciclosporin-A and tacrolimus have both also been used to treat steroid-resistant AIH. Both are relatively well tolerated. They do have significant side effects and therefore are not used routinely as a first-line therapy.

How do steroids dampen the immune response?

There are a number of proposed mechanisms by which steroids have the ability to reduce the host's immune response, including:

- *Suppression of T cells* – steroids are able to reduce the production of cytokines, thereby inhibiting the proliferation and interaction of T cells.
- *Suppression of B cells* – steroids prevent binding of interleukins to B cells, thereby preventing proliferation and antibody production.
- *Suppression of neutrophils* – steroids have the ability to prevent all the processes that neutrophils use to attack potential targets, including: adhesion, chemotaxis, phagocytosis, and the release of toxic substances.
- *Suppression of macrophages* – steroids down-regulate the expression of Fc receptors on macrophages, thereby preventing phagocytosis.
- *Diminished production of prostaglandins and leukotrienes*.

Children with established cirrhosis at presentation are unlikely to respond to medical therapy and require transplant. Recurrence after transplant occurs in 25% of patients with AIH. Other indications are fulminant liver failure and cirrhotic complications.

Question 21.7

Viral hepatitis

You are called to see a newborn infant on the postnatal ward. She is 3 hours old, and the midwife looking after the child hands you details of the mother's HBV status

Maternal status: HBsAg +, HBeAg –, Anti HBe +

What treatment would you instigate in this case? Select ONE answer only.

A. Hepatitis B immunoglobulin only

B. Hepatitis B vaccine only

C. Hepatitis B vaccine and immunoglobulin

D. Neither – treatment is not necessary

E. Wait for the baby's blood serology to come back before deciding on management

Table 21.4 Immunization schedule in the UK (2015)

Maternal status				
HBsAg	HBeAg	Anti-HBe	HBIG	HBV vaccine
+	+	–	Yes	Yes
+	–	–	Yes	Yes
+	Not determined		Yes	Yes
+	–	+	No	Yes
Acute HBV infection in pregnancy			Yes	Yes

Anti-HBe, antibody to e antigen; HBeAg, hepatitis B non-structural e antigen; HBsAg, hepatitis B surface antigen; HBIG, hepatitis B immunoglobulin; HBV, hepatitis B virus.

Viral hepatitis A, B, C and E

Viral hepatitis has a worldwide distribution. Hepatitis A and E are acute illnesses, while hepatitis B and C, which are perinatally transmitted, may become chronic with a lifetime risk of significant liver disease and liver cancer (Table 21.5).

Children of HBsAg mothers should be immunized at birth (Table 21.4). Vaccination is not available for HCV, but current therapy with pegylated interferon and ribavirin will clear infection in 70–90% of children. Management includes monitoring for the development of complications, consideration of antiviral therapy and psychological support for the child and family.

Recent scientific advances which have improved clinical practice – advances in therapy for HCV

Hepatitis C remains a leading cause of mortality worldwide and often the need for liver transplantation. Pegylated interferon has revolutionized its management. Pegylation refers to the cross-linking of polyethylene glycol (PEG) molecules to the interferon molecule, which delays renal clearance permitting less frequent dosing. In 2011, the standard of care for many patients with HCV genotype 1 infection became a combination of an oral protease inhibitor (PI), boceprevir (BOC) or telaprevir (TVR), along with pegylated IFN and ribavirin. BOC and TVR directly inhibit viral replication.

The introduction of sofosbuvir into clinical practice in 2013 was an important advance, as it provides a higher cure rate, fewer side effects, and/or a dramatically shorter course of therapy compared to prior treatment regimens. It allows many patients to be treated successfully without the use of pegylated interferon. Sofosbuvir inhibits the RNA polymerase that the hepatitis C virus uses to replicate its RNA.

Drug-induced liver disease

Many drugs can prove toxic to the liver. The key to diagnosis is an accurate history, of drugs taken in the last 3 months (including over-the-counter/herbal) and recent dose changes. Specific treatment is only needed in paracetamol and sodium valproate toxicity, where *N*-acetylcysteine and carnitine, respectively, may be beneficial. Other drugs linked to liver dysfunction include indomethacin, ibuprofen, antibiotics and anti-epileptics. Paracetamol overdose should be considered in a child who presents with sudden hepatic failure and a paracetamol level should be obtained even without supportive history. Transaminases may be normal at presentation, but rise due to hepatic necrosis, peaking at 3–5 days. Paracetamol is primarily metabolized in the liver into toxic and non-toxic products (see Figure 7.4).

Three metabolic pathways are responsible:

1. Glucuronidation – accounts for up to two thirds of paracetamol metabolism.
2. Sulfate conjugation may account for a further 20–30% of metabolism.
3. The hepatic cytochrome P450 enzyme system metabolizes paracetamol, forming NAPQI (*N*-acetyl-*p*-benzo-quinone imine). It is then irreversibly conjugated with the sulph-hydryl groups of glutathione.

All three pathways produce products that are inactive, non-toxic, and eventually excreted by the kidneys. In the third pathway, however, the intermediate NAPQI is toxic. Production of NAPQI is due to two isoenzymes of cytochrome P450: CYP2E1 and CYP1A2. At usual doses in a child without underlying liver disease, NAPQI is quickly detoxified by conjugation with glutathione. Following overdose, this pathway is saturated, leading to NAPQI accumulation with renal and hepatic side effects. *N*-acetylcysteine reduces paracetamol toxicity by replenishing body stores of the antioxidant glutathione. Glutathione reacts with the toxic NAPQI metabolite so that it does not damage cells and can be safely excreted.

Table 21.5 Different viral forms of hepatitis infection

Virus	Type	Incubation period	Transmission route	Clinical presentation	Diagnostic tests	Treatment
A	RNA	30 days	Faecal–oral	Acute with nausea, abdominal pain, jaundice, hepatomegaly Rare cause of acute liver failure	Serum: anti-hepatitis A virus (HAV) IgM antibodies and the determination of total anti-HAV by enzyme immunoassay.	Supportive Illness self-limiting
B	DNA	30–180 days	Bodily fluids Vertical	May be asymptomatic Fulminant hepatic failure in 1–2% 30–50% have chronic carriage 10% develop cirrhosis Late risk of hepatocellular carcinoma	HBsAg, HBeAg, anti-HBe, anti-HBs, anti-HB core. Quantitative hepatitis B virus DNA. HBV genotype (for those considered for interferon).	Interferon and lamivudine Prevention: antenatal screening
C	RNA	40–80 days	Bodily fluids Vertical	Rarely acute infection 50% develop chronic liver disease, despite often having normal LFTs, and progress to cirrhosis with risk of hepatocellular carcinoma in later life	HCV antibody In chronic infection, consider alpha-fetoprotein estimation and USS	Pegylated interferon and ribavirin in combination
E	RNA	21–60 days	Faecal–oral Animal reservoir	After a short prodromal phase, clinical features last from days to weeks, including: jaundice, fatigue and nausea. Fatal in 2% due to fulminant liver failure.	HEV antibody detection Elevated transaminases	Supportive Illness self-limiting

HAV, hepatitis A virus; HBV, hepatitis B virus; HBeAg, hepatitis B non-structural e antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HEV, hepatitis E virus; LFTs, liver function tests.

Case history

Paracetamol and liver disease

A child has liver disease. Is it safe to prescribe paracetamol?

This is frequently a cause of debate. Due to the above pathways being impaired, toxic levels of paracetamol can soon accumulate. Likewise, other medications that are metabolized by the cytochrome P450 pathway will also accumulate in children with liver disease. However, paracetamol has been used safely in children of all ages, including those with chronic liver disease. Its use is often avoided in patients with liver disease due to the perceived notion that paracetamol is known to cause liver failure (in overdose) and therefore often is mistakenly thought to worsen underlying liver disease. There is no evidence of increased risk of hepatotoxicity at currently recommended doses (generally two thirds of the normal dose). Paracetamol can therefore be used with caution in liver patients, and is in fact preferred to other forms of analgesia/anti-pyretic, e.g. ibuprofen, as the NSAIDs have antiplatelet properties, which should be avoided in children with liver disease.

Question 21.8

Jaundice in an older child

Adam is 15 years old. He is referred to the paediatric department with a history of jaundice following recent gastroenteritis. His mother tells you that he may have had previous episodes of yellow discoloration of his eyes. On assessment, he is not malnourished. He has mild jaundice. Abdominal examination is unremarkable. He has no stigmata of chronic liver disease. What do you want to do next? Select ONE answer only.

A. Admit for urinary copper collection

B. Admit him for intravenous acyclovir

C. Check FBC and split bilirubin

D. Check FBC, full LFTs, arrange an abdominal ultrasound examination, perform serological tests for hepatitis

E. Nothing – he is a teenager and he is probably just trying to avoid school

Wilson's disease

Wilson's disease is an autosomal recessive disorder of copper metabolism characterized by excessive deposition of copper in the liver, brain, and other tissues. The gene *ATP7B* has been mapped to chromosome 13 (13q14.3) and is expressed primarily in the liver, kidney, and placenta, coding for a P-type (cation transport enzyme) ATPase that transports copper into bile and incorporates it into ceruloplasmin. Mutations can be detected in 90%. Most are homozygous for *ATP7B* mutations. A normal variation in the *PRNP* gene can modify the course of the disease by delaying the age of onset and affecting the type of symptoms that develop. This gene produces prion protein, which is active in the brain and other tissues and is also involved in copper transport. Wilson's disease is best appreciated with an understanding of copper metabolism. The body's daily copper requirement is met by dietary intake. Copper is absorbed by the intestine in a non-toxic form. Copper is released into the circulation by a copper transporter protein, copper-transporting ATPase 1 (ATP7A), located on the membrane of enterocytes. It is albumin-bound, and transported to the liver. In the hepatocytes, the ATOX1 chaperone protein delivers the copper to its binding targets. Some is bound to metallothionein for storage, with the remainder being excreted into ATP7B-regulated biliary canaliculi. It is the ATP7B which mediates transfer of copper to apoceruloplasmin which forms ceruloplasmin. Ceruloplasmin is subsequently released into the blood and acts as a source of copper for peripheral organs, e.g. the brain and kidney.

Mutations in *ATP7B* lead to reduction in conversion of apoceruloplasmin into ceruloplasmin, and therefore low levels of serum ceruloplasmin. Failure of excretion of copper leads to hepatotoxicity. Excess copper causes mitochondrial damage, resulting in oxidative damage to cells, allowing copper to spill over into the blood, and deposition in other organs such as the renal and neural tissue, leading to toxic damage. Typical presentation is in an older child who is noted to have behavioural issues in class, or whose school performance has suddenly deteriorated or develops dysarthria. Other presentations include acute liver failure, insidious symptoms of chronic liver disease or in combination with autoimmune liver disease. Diagnostic work-up includes urinary copper excretion following penicillamine challenge, liver copper deposition detected on liver biopsy, serum copper and ceruloplasmin. Treatment is life-long with oral penicillamine or zinc acetate – a copper chelator. Failure of medical management leads to the need for liver transplantation.

Cystic fibrosis-associated liver disease

Cystic fibrosis is an autosomal recessive multi-system disorder in which respiratory features and pancreatic insufficiency dominate the clinical features. It is discussed in detail in Chapter 17, Respiratory medicine. During adolescence, a significant proportion of children develop liver disease. Cystic fibrosis-associated liver disease (CFALD) results from bile salt malabsorption, with approximately one quarter of young people presenting with features of biliary cirrhosis. Transaminases and alkaline phosphatase are typically raised. Bilirubin is usually normal. Blood tests and even imaging may underestimate the degree of liver dysfunction, and histology may demonstrate steatosis, chemical cholangitis and portal fibrosis. The major complication is portal hypertension with variceal haemorrhage, but indications for liver transplant are based on the balance between lung function, early hepatic dysfunction and quality of life. Post-transplant, lung function appears to stabilize and liver function returns to normal.

Alpha-1-antitrypsin deficiency

Although previously mentioned as a cause of neonatal cholestasis, alpha-1-antitrypsin deficiency may also

present in adolescence, without previous symptoms. It may present with hepatitis/cirrhosis. There is no specific predictor of disease progression. The diagnosis is made when a reduced level of alpha-1-antitrypsin is detected in the plasma.

Fatty liver disease (non-alcoholic fatty liver disease)

Steatosis is accumulation of fat in hepatocytes. In children, steatosis can be induced by drugs (methotrexate), inherited as a metabolic disease or secondary to obesity. Non-alcoholic fatty liver disease (NAFLD) is a heterogeneous disorder, associated with hyperinsulinaemia and insulin resistance. Poor diet (high in saturated fats) and inadequate physical exercise leads to hyperinsulinaemia and consequently hepatic steatosis. There are several mechanisms by which excess triglycerides are acquired and accumulate in hepatocytes. Formation of steatotic droplets is abnormal in NAFLD. Visceral adipose tissue dysfunction in obesity and insulin resistance results in aberrant cytokine expression; many cytokines have a role in liver injury in NAFLD. Clinical features include hepatomegaly with or without mildly deranged transaminases.

The metabolic syndromes associated with NAFLD include: Bardet–Biedl, polycystic ovary, Alström and Turner's. Liver ultrasound scan may demonstrate fat around the liver and/or fatty infiltration, but there should be no obvious other pathology. Liver biopsy demonstrates hepatic steatosis and inflammation with deposits in the liver parenchyma. There is no proven therapy, but in adults, diet and exercise may reverse the progression of liver disease to cirrhosis and liver failure.

Liver tumours

Hepatoblastoma

Liver tumours are rare in childhood. The most common, however, is hepatoblastoma, which presents at <4 years (most commonly seen at <18 months). Common presenting features are palpable abdominal mass with abdominal distension, anorexia, weight loss, vomiting and jaundice. Physical examination should always focus on associated syndromes, e.g. Beckwith–Wiedemann syndrome, familial adenomatous polyposis and glycogen storage disease type I. A detailed family history is also essential to identify possible risk factors, e.g. bowel cancer in first- or second-degree relatives, often at a young age (more common in familial adenomatous polyposis). Typically, α-fetoprotein (AFP) is raised, which can also be used to monitor response to treatment. AFP is a plasma protein which represents the fetal form of albumin. At birth, it falls to undetectable levels in the first 8 months of life. A positive level (often in the 1000s) is suggestive of pathology and most likely a tumour (yolk sac or hepatic). AFP is produced by the yolk sac and liver, and, subsequently, after the yolk sac has involuted, by the liver alone. Treatment is chemotherapy (cisplatin) followed by resection or transplantation dependent on the extent of disease and residual metastases following treatment.

Hepatocellular carcinoma

Hepatocellular carcinoma can occur either in isolation, due to underlying progressive chronic liver disease and cirrhosis, as a result of metabolic disease (ornithine transcarbamylase (OTC) deficiency, tyrosinaemia and progressive familial intrahepatic cholestasis (PFIC)) or secondary to infective causes (chronic hepatitis B and C). Management is resection, often in combination with adjuvant chemotherapy or liver transplantation in the absence of distant metastases. Any chronic liver disease and cirrhosis has the potential for dysplastic change, and therefore all chronic liver disease should be monitored with regular ultrasound examinations of the liver and AFP.

Timing of transplant

As discussed above, some forms of liver disease are only amenable to treatment by liver transplantation. The exact indications for liver transplantation vary by condition and therefore it is impossible to summarize this in a single list. Many children with cirrhosis/portal hypertension have well compensated liver function and it may be difficult to decide when transplantation is necessary. Useful indicators include:

- Persistent rise in total bilirubin >150 mmol/L
- Prolongation of prothrombin ration (INR >1.4)
- Fall in serum albumin <35 g/L
- Reduction in psychosocial development
- Chronic hepatic encephalopathy
- Refractory ascites
- Recurrent variceal bleeding despite optimum management
- Intractable pruritus
- Severe metabolic bone disease
- Diminishing quality of life

Transplantation should be considered before there is an effect on quality of life. It should be considered early, as the assessment and identification of a suitable donor is time-consuming, and preparation is key with regards to immunizations prior to transplant, optimizing medical treatment of the complications of liver disease (e.g. nutritional support) as well as adequate

preparation of the child and their family. One-year patient survival is currently 92% following transplant. Most deaths occur within the first 3 months and are due to vascular or biliary complications.

In *inherited metabolic disease*, the indications for liver transplantation are variable depending on the underlying diagnosis. Although 50–70% of children with alpha-1-antitrypsin deficiency may develop cirrhosis, only 20–30% require transplantation in childhood. Glycogen storage disease type I is not usually an indication for liver transplantation unless the medical management is not tolerated, there is development of multiple hepatic adenomata or poor quality of life. Glycogen storage disease types III and IV may progress to cirrhosis, at which point liver transplantation is indicated due to hepatic dysfunction.

Indications for transplantation in acute liver failure have been described earlier in the chapter.

Liver disease as a part of multi-system disease

The liver plays a role in a number of extrahepatic illnesses.

Cardiac disease and the liver

The pathophysiology of hepatic dysfunction in cardiac disease relates to hypoxia, congestion and low cardiac output. Chronic low cardiac output (from any cause) results in reduced blood flow within the liver. Compensatory increased portal blood flow may occur. Jaundice and raised transaminases are usual. Chronic fluid retention leads to sodium retention and increased circulating blood volume. Initially, the renin–angiotensin–aldosterone system is suppressed, but as liver disease progresses this system becomes activated. *Hepatic congestion* results when there is an increase in right atrial or ventricular pressure, e.g. pulmonary atresia or tetralogy of Fallot. Sinusoidal engorgement causes derangement of transaminases in the face of a normal bilirubin level. Clinical features include hepatomegaly, hypoalbuminaemia, cirrhosis and portal hypertension.

Gastrointestinal disease and the liver

Liver disease may develop in children with intestinal failure. The causes include reduced stimulation to bile flow. As a result, biliary sludge/gall stones form. In addition, as the terminal ileum is responsible for reabsorption of bile salts, there is impaired processing which leads to a reduced bile acid pool, altering the composition of bile and leading it to be more lithogenic. Clinical features of terminal ileum disease

include steatorrhoea, abdominal pain, obstructive jaundice, fat-soluble vitamin deficiency and anaemia.

Inflammatory bowel disease may be associated with chronic hepatitis +/− autoimmune sclerosing cholangitis. The pathogenesis of this association relates to exposure of cytokines produced in the lamina propria of the intestine; production of autoantibodies; and reduction in suppressor T cells. Presentation is often with hepatomegaly with or without jaundice and the stigmata of chronic liver disease.

Intestinal failure-associated liver disease (IFALD) is due to increased risk of sepsis and lack of extrahepatic circulation, leading to portal and pericellular fibrosis. Children with IFALD invariably have hepatosplenomegaly at presentation. Liver enzymes are raised and a conjugated hyperbilirubinaemia predominates. Manipulation of the type of lipid in the parenteral nutrition, reintroducing enteral intake and reducing risk of sepsis have been shown to help. However, in some the only treatment is small bowel or multivisceral transplant.

Renal disease

Many syndromic conditions, e.g. Alagille syndrome are associated with renal as well as liver disease, such as renal tubular dysfunction and glomerular disease. In infantile polycystic disease (autosomal recessive), hepatic fibrosis as well as renal cysts may occur in combination.

The liver and haematological disease

In *sickle cell disease* sequestration can occur as a result of the HbS increasing blood viscosity. Hepatic sinusoids are a common site for sequestration and lead to capillary obstruction. Clinical features include haemolytic anaemia, unconjugated jaundice, splenomegaly (prior to autoinfarction), hepatomegaly, progressive liver disease due to necrosis and infarction, gallstones and viral hepatitis.

Veno-occlusive disease following liver transplantation

Veno-occlusive disease (VOD) is a serious complication of bone marrow transplant. It usually presents in the first month post-transplant. The features are similar to those seen in Budd–Chiari syndrome (a rare syndrome usually caused by hepatic vein thrombosis or obstruction). These include variable degrees of jaundice, hepatomegaly, elevated jugular venous pressure and ascites.

Diagnosis of VOD is made by abdominal ultrasound scan demonstrating retrograde flow within the

portal veins and/or increased hepatic resistance. Liver biopsy may also help, demonstrating occlusion of hepatic venules, necrotic hepatocytes, fibrosis and cirrhosis. Management is supportive. Defibrotide (a thrombolytic drug) can lead to complete resolution of symptoms. Liver transplant may be considered at a later stage for ongoing chronic liver disease.

Recent scientific advances – making liver from embryonic stem cells

Embryonic stem cells are capable of unlimited self-renewal and can differentiate into any cell type. Recent advances have allowed the generation of hepatocytes from embryonic stem cells. An understanding of the stage-specific genes expressed during normal liver development has allowed researchers to monitor the progress of hepatic differentiation *in vitro*.

Further reading

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Daniel Morgenstern, Rachel Dommett

Oncology

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Understand the development of cancer
- Know about genetic and environmental factors in the aetiology of malignancies
- Know about the pathophysiology of malignancy
- Understand the basis of the presentation of common malignancies of childhood including acute leukaemia, Wilms' tumour, lymphoma, neuroblastoma and brain tumours
- Know about the scientific basis of the investigations used in oncological conditions, such as radionucleotide (MIBG or technetium bone scan) and functional (FDG-PET) imaging.
- Know about specific syndromes associated with increased risk of malignancy, e.g. Beckwith–Wiedemann syndrome and Wilms' tumour
- Understand the basis of treatment for childhood cancer
- Understand the pharmacology of drugs used in the treatment of childhood malignancies, including monoclonal antibodies

What is cancer?

Most simply, cancer can be described as uncontrolled cellular proliferation. Most healthy cells have a limited potential for replication and their proliferation, differentiation and death is carefully controlled. During cancer development, cells undergo a multistep process in which they gradually acquire genetic mutations allowing them to escape these normal controls. Benign, or low-grade, tumours tend to grow locally and have not developed the potential to metastasize (spread to other tissues). By contrast, high-grade, or malignant, tumours are highly proliferative (have a high 'mitotic index' when examined under the microscope) and tend to metastasize. However, a benign tumour does not necessarily equate with a benign clinical course, particularly if the tumour is growing close to and impinging on a vital structure (such as a low-grade glioma growing within the optic pathway which, untreated, may lead to blindness).

The biology of cancer is complex. However, although the details vary between cancer types, the underlying principles are similar. Normal cells and tissues have mechanisms designed to prevent cancer development and a cell must overcome these in order to become malignant. The key features of cancer development are shown in Figure 22.1.

Question 22.1

The development of cancer

The following are features of cancer development:

A. Abnormal cellular metabolism
B. Evading apoptosis
C. Genetic instability
D. Immune escape
E. Inducing angiogenesis
F. Insensitivity to anti-growth signals
G. Limitless replicative potential
H. Self-sufficiency to growth signals
I. Tissue invasion and metastasis
J. Tumour-promoting inflammation

From the following list of tumour characteristics and therapeutic approaches, choose the *predominant* mechanism at work. Select ONE answer only for each question.

1. Down-regulation of cell surface major histocompatibility complex (MHC) by tumour cells.
2. Overexpression of telomerase by tumour cells.
3. Treatment with bevacizumab, a monoclonal antibody against vascular endothelial growth factor A (VEGF-A).
4. Treatment of Philadelphia chromosome positive leukaemia with imatinib, an inhibitor of BCR-ABL kinase.

Answer 22.1

1. D. Immune escape.
2. G. Limitless replicative potential
3. E. Inducing angiogenesis
4. H. Self-sufficiency to growth signals
   See below for discussion.

Fig. 22.1 Key features of cancer development. *(Adapted from Hanahan and Weinberg (2011), Cell 144:646–74.)*

contact with neighbouring cells) designed to maintain tissue stability and prevent overgrowth. Cancer cells acquire mutations such that they become insensitive to these signals.

- *Limitless replicative potential* – normal cells are able to divide only a limited number of times before they enter a state known as senescence. This is controlled by the successive shortening of telomeres, repetitive sequences of DNA base pairs that cap the end of chromosomes and which are lost following each replication. Cancer cells acquire the ability to overcome telomere shortening, either through re-expressing telomerase that allows them to rebuild lost telomeres, or through other mechanisms.
- *Evading apoptosis* – cells have many inbuilt mechanisms to trigger programmed cell death (apoptosis) in the event of significant DNA damage or other insult. In cancer cells, the balance between pro- and anti-apoptotic signals is altered, and these protective mechanisms are bypassed.
- *Tissue invasion and metastasis* – in order to metastasize to new sites, cancer cells need to acquire a number of capabilities, including the ability to invade into blood vessels or the lymphatic system, to survive as a detached single cell or clump of cells and to invade the target tissue and survive in this new environment.
- *Inducing angiogenesis* – as tumours grow, they need to ensure the development of new blood vessels to ensure adequate supply of oxygen and nutrients. Cancer cells produce various signals, such as vascular endothelial growth factor (VEGF), that stimulate the growth of new blood vessels.
- *Immune escape* – there is growing evidence for a role of the immune system in controlling cancer

Cancer occurs when normal protective mechanisms are lost. Cancer develops when cells develop one, or more, of the following:

- *Self-sufficiency in growth signals* – normal cells require external signals (growth factors) to trigger them to proliferate. Many cancer cells have mutations in cell surface receptors such that these receptors become constitutively active even in the absence of growth factors, or may express abnormally high levels of these receptors.
- *Insensitivity to anti-growth signals* – normal tissues have multiple anti-proliferative signals (such as

development and therefore a requirement for developing cancers to develop mechanisms by which they can evade detection and elimination by the immune system.

- *Tumour-promoting inflammation* – the importance of the tumour microenvironment is increasingly recognized. Non-cancer cells within a tumour may play a role in stimulating tumour growth, for example, through inflammatory cells enhancing angiogenesis.
- *Genetic instability* – cancer cells need to acquire multiple genetic mutations in order to achieve many of the characteristics outlined above. Increased genetic instability helps to enhance the acquisition of these mutations.
- *Abnormal cellular metabolism* – cancer cells must survive in relatively inhospitable tissue environments, such as the marked hypoxia in the centre of a large tumour. Many cancer cells alter their energy metabolism as an adaptation.

Oncogenes and tumour suppressor genes

Genetic abnormalities in cancers can be divided into those that result in over-activation of a particular gene or pathway and those that result in loss of function. Gain of function of (proto-) oncogenes, such as a growth factor receptor signalling pathway or transcription factor, enhances malignant progression (Fig. 22.2). Conversely, the loss of function of tumour suppressor genes, such as those that trigger apoptosis or block cell cycle progression in the presence of DNA damage, also drives cancer development.
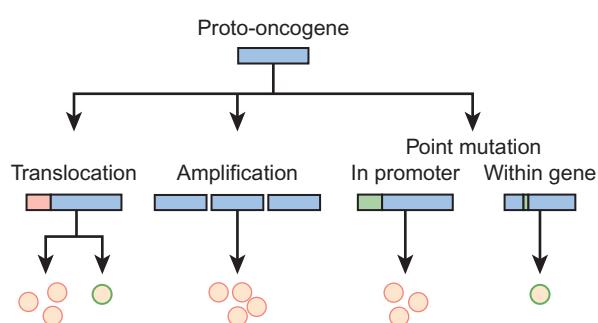
Fig. 22.2 **Illustration of potential mechanisms of proto-oncogene activation. Chromosomal translocation may lead to increased expression of the oncogene driven by the promoter region of another gene, or the formation of a novel fusion protein with abnormal activity. Gene amplification leads to increased oncogene expression, as may point mutation within the promoter region. Alternatively, point mutations within the coding region of the gene itself may lead to expression of a protein with abnormal activity, e.g. a constitutively active receptor.**

Epidemiology and aetiology – who gets cancer?

Incidence

Cancer is rare in childhood and accounts for less than 1% of all cancers. In the western world around 1 in 500 children will develop some form of cancer by 14 years of age. In the UK approximately 1600 children are diagnosed with cancer each year. The 12 major diagnostic groups (and most common tumour types in children) are: leukaemias; lymphomas; brain and spinal tumours; sympathetic nervous system tumours (neuroblastoma); kidney tumours (Wilms' tumour); soft tissue sarcomas (rhabdomyosarcoma); bone tumours (osteosarcoma, Ewing's sarcoma); liver tumours (hepatoblastoma); retinoblastoma; gonadal and germ cell tumours; epithelial tumours (carcinomas); and others. The incidence of different tumours varies dramatically with age (Fig. 22.3).

In infants, the most common solid malignancies are embryonal tumours such as neuroblastoma, retinoblastoma and hepatoblastoma. The incidence of acute lymphoblastic leukaemia (ALL), the most common type of leukaemia seen in childhood (and the most common childhood malignancy overall), is highest among children aged 2–3 years. Brain and spinal tumours are, as a group, the most common solid tumours seen in children. By contrast, lymphoma, particularly Hodgkin's lymphoma, bone tumours and malignant melanoma are rare in early childhood, but show a marked increase in incidence in adolescence. Gonadal germ cell tumours display a bimodal distribution in boys with a peak in infancy and early childhood, and their incidence rises again in teenagers. Carcinomas are rare in children, but become progressively more common in adolescents and younger adults. Overall (for reasons not fully understood), childhood cancer is about one-fifth more common among boys than girls. Outcomes have improved dramatically over the last 40 years due to the introduction of chemotherapy and other treatment modalities, and collaborative national and international clinical trials (Fig. 22.4).

Why have survival rates for childhood cancer improved over the last 40 years?

Paediatric oncology has led the way in treating patients in clinical trials; this has allowed new treatment approaches to be developed and tested. Children are managed according to well-defined treatment protocols that have undergone frequent revision as more has been learnt about the best way to treat particular cancer types. Overall, childhood cancers are rare and

Infants   **Children**   **Adolescents and young adults**
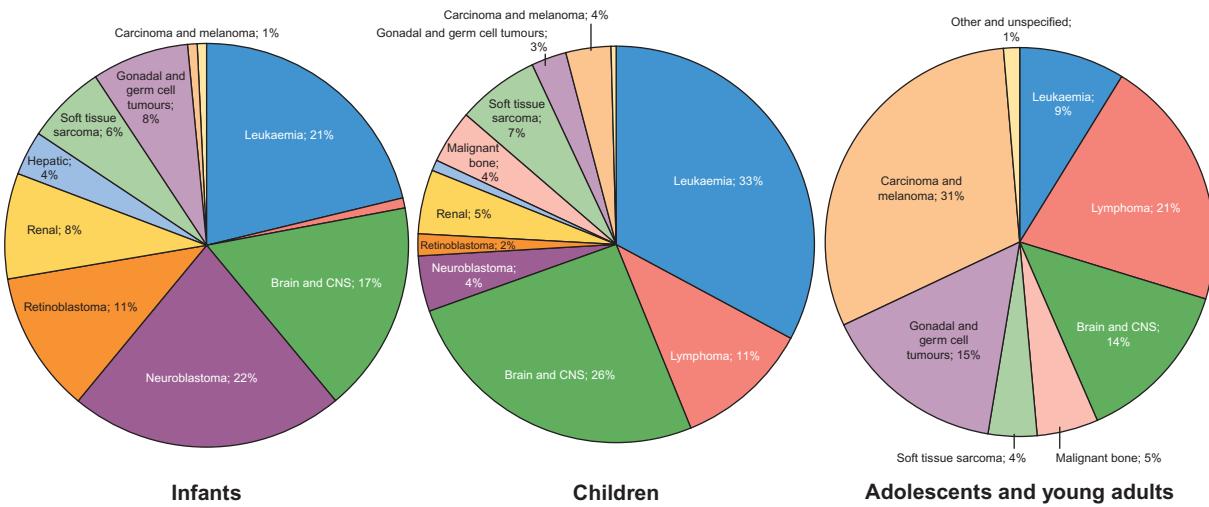
Fig. 22.3 Variation in the incidence of different tumours by age. *(Based on data from the National Registry of Childhood Tumours Progress Report 2012.)*
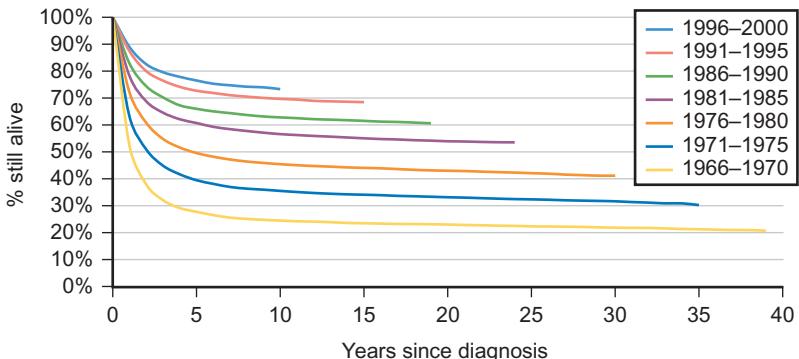
Fig. 22.4 Improvements in overall survival rates for all childhood cancers over successive time periods from 1966–2000. *(From National Cancer Intelligence Network (NCIN).)*

clinical trials typically require national and/or international collaboration in order to recruit sufficient numbers of patients. Clinical trials for childhood ALL have typically been UK-based, whilst those for rarer solid tumours (such as neuroblastoma, rhabdomyosarcoma or hepatoblastoma) have only succeeded because of international collaboration.

Most of the historical improvement in outcomes has come about from the development of standardized protocols using a combination of cytotoxic chemotherapy agents plus (where appropriate) surgery and/or radiotherapy. As our understanding of the molecular basis of childhood cancer has improved, this has led to better risk stratification and adapted therapy. The hope for the future is that it will also be possible to target these molecular abnormalities to provide specific targeted therapies.

What is the role of clinical trials in paediatric oncology?

Significant improvements have been made in the outcomes for childhood cancer patients over the last 30–40 years (see Recent advances in science that have changed clinical practice), largely as a result of collaborative clinical trials. Newly diagnosed patients will be treated as part of a Phase III clinical trial or according to an established treatment protocol where no trial is currently open. These trials will typically seek to compare two established treatment regimens in a randomized study.

By contrast, new drugs (such as new molecularly-targeted agents) are generally explored at a limited number of centres and typically these studies recruit patients with relapsed or refractory disease for whom

there are no standard treatment options. Initial Phase I studies are designed to assess toxicity and gather information about drug metabolism (pharmacokinetics). They may also include pharmacodynamic analyses that are designed to demonstrate the effect of the drug on its target (e.g. inhibition of a particular enzyme). Subsequent Phase II studies then focus on obtaining evidence of efficacy against a particular disease or diseases. New drugs that are particularly promising may then be taken forward to Phase III studies and may ultimately become incorporated into standard upfront therapy. The ways in which clinical trials have helped improve outcomes of childhood cancer is considered further in Box 37.9.

Aetiology

Although there is much in common between adult and paediatric cancers, there are also fundamental differences in how they arise. The most common adult cancers (breast, colon, prostate and lung) are carcinomas, i.e. a cancer derived from epithelial cells, and typically result from acquired chronic cellular insults, for example from tobacco smoke. By contrast, the most common paediatric solid tumours (brain tumours, neuroblastoma, Wilms' tumour and rhabdomyosarcoma) typically arise in young children who have not had such exposures. Childhood cancers tend to derive from primitive, poorly differentiated cell types and likely represent an abnormality arising from fetal development. Indeed, there are striking parallels between cellular behaviour during fetal development and malignancy, such as proliferation, invasion and cellular migration to new tissues. In many cases, a greater understanding of the normal processes of embryological development has aided our understanding of how paediatric cancers arise.

The precise cause of most childhood cancers remains unclear but is likely to involve an interaction between environmental factors (e.g. viral infection) and host genetic susceptibility.

Potential environmental risk factors

Radiation

Published evidence confirms that there is a small increased risk of malignancy associated with radiation exposure from medical imaging such as CT scanning, although this is unlikely to be a significant contributory factor in most instances.

Infection

Worldwide, the most important examples of childhood cancers caused by infections are Burkitt's

lymphoma, Hodgkin's lymphoma and nasopharyngeal carcinoma (all associated with Epstein–Barr virus), hepatocellular carcinoma (hepatitis B) and Kaposi sarcoma (HHV8). However, overall these associations account for a very small proportion of childhood cancer in western countries. The early childhood peak of leukaemia incidence in affluent western populations and the persistently lower incidence in socio-economically disadvantaged groups and less developed countries has suggested that acute lymphatic leukaemia could be associated with an abnormal response to a common infectious agent.

Other environmental triggers

Parental smoking during pregnancy, or during the period prior to conception, has been implicated as a cause of hepatoblastoma and a meta-analysis has shown a 10% increase in risk of all cancers with maternal smoking during pregnancy. Overall, environmental risk factors have not been established for the vast majority of childhood cancers.

Known genetic risk factors

The risk of developing leukaemia in Down's syndrome is increased 30-fold compared with the general population. Cancer predisposition syndromes have provided vital clues to the underlying genetics of cancers, however they account for less than 5% of cases.

This is well illustrated in hereditary retinoblastoma, which provides a model for understanding the principles of inherited predisposition, as it is linked to a single gene. Familial retinoblastoma accounts for approximately 40% of cases. Presentation is usually early (first year of life) and bilateral. Sporadic cases present later, are unilateral and are not associated with a positive family history. Survivors of familial retinoblastoma have a very high risk of developing second primary tumours, of which osteosarcoma is the most common. These features of retinoblastoma were noted by Knudson and led him to propose the 'two-hit' mutational hypothesis. This states that two mutations are necessary in a cell for a tumour to develop. In hereditary cases, the first mutation is germline, while the second is somatic. In sporadic cases, two somatic mutations are required in the same cell for a tumour to develop. Knudson's hypothesis was confirmed in the 1980s with the identification of the retinoblastoma tumour suppressor gene (*RB1*). Retinoblastoma results as a consequence of two mutations in the *RB1* gene within the somatic cells of the retina.

In comparison to retinoblastoma, familial clusters of other embryonal tumours are rare. For example, in Wilms' tumour, inherited cases are thought to represent only 1% of all cases. Beckwith–Wiedemann is the most common syndrome associated with Wilms' tumour. Organomegaly, macroglossia, hemihypertrophy, neonatal hypoglycaemia and exomphalos are all features of this fetal overgrowth syndrome. Around 10% of cases develop tumours, of which Wilms' is the most common, and imprinting of genes on chromosome 11 has been implicated as a causative mechanism. Other syndromes associated with Wilms' tumour include Denys–Drash, WAGR (Wilms' tumour, aniridia, genitourinary tract abnormalities and mental retardation) and isolated hemihypertrophy.

Neurofibromatosis type 1 (NF1) is inherited as an autosomal dominant condition, although many cases are new mutations. NF1 is associated with an increased risk of brain and spinal cord tumours, particularly low-grade gliomas of the optic pathway.

Although familial causes for childhood cancer are infrequent, a thorough family history is very important when assessing any new case of childhood cancer and referral to a geneticist for further assessment may be appropriate. In patients with a strong family history (particularly of breast cancer, brain tumours or sarcoma), a diagnosis of Li–Fraumeni syndrome should be considered. This cancer predisposition syndrome results from mutation and loss of function of the p53 tumour suppressor gene and may be inherited, or occur *de novo* in a cancer patient. Knowledge of a cancer predisposition syndrome (e.g. NF1, familial retinoblastoma) is important when planning treatment, as it may be necessary to avoid certain treatment modalities (e.g. radiotherapy) to reduce the risk of secondary malignancies.

Cancer risk in survivors of childhood cancer

Survivors of childhood cancer have an increased risk of developing a subsequent malignancy. This may reflect a genetic predisposition but may also be due to the treatment they received for their first cancer. Radiotherapy is associated with second malignancies that may arise many years later, particularly in parts of the radiation field that received lower doses of radiation that damage but do not kill cells. Breast cancer in patients who received thoracic radiotherapy for Hodgkin's lymphoma is a particular risk. Chemotherapy drugs (such as cyclophosphamide and etoposide) are associated with a small increased risk of secondary leukaemia.

Patterns of presentation

Early symptoms of cancer in children are often non-specific and easily explained by more common illnesses, which can lead to delays in diagnosis.

Repeat attendance without a unified diagnosis warrants further investigation or referral. The history should include a developmental review, as loss of previously attained developmental milestones in a young child and changes in school performance in an older child may be the only indicators of spinal cord compression or an underlying brain tumour. Common patterns of presentation are shown in Table 22.1.

Paraneoplastic phenomena

Paraneoplastic phenomena are symptoms that are not directly attributable to the tumour but arise as part of the body's response to the disease. Such cases are rare in paediatric oncology, with most systemic symptoms (pain, lethargy, pallor) being directly related to tumour spread, such as bone marrow invasion. Perhaps the best example is opsoclonus-myoclonus-ataxia syndrome (also known as 'dancing eyes') associated with neuroblastoma.

Table 22.1 Common patterns of presentation in children with malignancy

Presenting complaint	Suspicious features
Pancytopenia	• Pallor/lethargy due to low haemoglobin • Recurrent fever/infection due to low white count • Bruising and/or petechiae due to low platelets Occurs due to displacement of marrow by leukaemia or disseminated malignancy.
Lymphadenopathy/ unexplained mass	• Lymph node with diameter greater than 2 cm • Non-tender, rubbery, hard or fixed in character • Supraclavicular or axillary location • Associated with other features, e.g. pallor or lethargy or hepatosplenomegaly • Systemic symptoms – fever, weight loss, night sweats ('B symptoms')
Respiratory symptoms	• Orthopnoea – suggestive of intrathoracic mass • Reduced air entry – consider a pleural effusion or tumour bulk
Bone and joint pain and swelling	• Persistent back pain – rarely innocent in children • Night pain • Reluctance to weight-bear or new limp These may reflect bone marrow infiltration with leukaemia, metastases, spinal tumour or impending/actual spinal cord compression
Abdominal mass	• Association with general malaise, e.g. neuroblastoma • Hypertension (secondary to compression of renal vasculature in Wilms' tumour or neuroblastoma) N.B. May be painless and isolated finding, e.g. Wilms' tumour
Raised intracranial pressure	• Headache (classically upon waking but timing can be non-specific), especially if associated with vomiting or ataxia • Papilloedema (a late sign of raised intracranial pressure) • III and VI cranial nerve palsies (false localizing signs)
Neurological signs	• Cranial nerve deficits or cerebellar signs, including head tilt • Visual disturbances or abnormal eye movements • Behaviour change, deteriorating school performance or developmental regression • Increasing head circumference in infants
Endocrine or systemic disturbances	• Diabetes insipidus • Growth hormone deficiency • Precocious puberty

Question 22.2

Opsoclonus-myoclonus-ataxia syndrome
A child presents with opsoclonus-myoclonus-ataxia syndrome ('dancing eyes'). Which class of agents is most likely to result in an immediate improvement of symptoms? Select ONE answer only.

A. Anticonvulsants
B. Antifungals
C. β-lactam antibiotics
D. Chelation agents
E. Immunosuppressants

Answer 22.2

E. Immunosuppressants.
Dancing eyes are likely to be a paraneoplastic phenomenon and this, in turn, is likely to be caused by a neuroblastoma. As the name suggests, patients present with abnormal eye movements and/or abnormal jerking muscle contractions. It is thought that these symptoms relate to the body's immune response to the presence of neuroblastoma, with the production of anti-tumour antibodies that cross-react with antigens on nerve fibres. Such patients require investigation and treatment for an underlying neuroblastoma, but often also require specific treatment with immunosuppression to bring their symptoms under control.

Principles of treatment

Investigations and diagnostic work-up

Basic blood tests may provide important information. An abnormal full blood count may suggest leukaemia if blast cells are seen, and in solid tumours (such as neuroblastoma) may reflect bone marrow infiltration. Thrombocytosis is common in hepatoblastoma. A coagulation profile is important for the surgeon undertaking a biopsy and in some forms of leukaemia. Wilms' tumour is associated with an acquired form of von Willebrand's disease. An assessment of renal function may reveal early signs of tumour lysis syndrome that is important for immediate management. Haematuria is a recognized feature of Wilms' tumour at presentation and urinalysis should be performed in all children with an abdominal mass.

Tumour markers

The role of serum tumour markers is relatively limited in children. However, tumour markers can be useful at diagnosis, during treatment and for disease surveillance during follow-up for some tumour types. The initial diagnostic evaluation of any child in whom a malignant germ cell tumour or liver tumour is suspected should include measurement of serum alpha-fetoprotein (AFP) and β-human chorionic gonadotrophin (β-HCG). AFP is associated with epithelial liver tumours, e.g. hepatoblastoma and hepatocellular carcinoma, yolk sac tumours and embryonal carcinomas. AFP levels must be interpreted with caution in infants (when normal ranges are very different than in older children). β-HCG is associated with certain malignant germ cell tumours. Some germ cell tumours may be treated without tissue diagnosis on the basis of radiological findings and raised tumour markers.

Urine catecholamine metabolites (homovanillic acid (HVA) and vanillylmandelic acid (VMA)) are elevated in >80% of cases of neuroblastoma and should be measured in any child with an abdominal mass or suspicion of a sympathetic nervous system tumour. A single spot sample is sufficient, as levels are expressed as ratios with creatinine.

Radiology

A full radiological evaluation of all sites of disease is mandatory. Specific staging investigations will be dictated by pathology but initial investigations are generally required prior to biopsy (Table 22.2).

Table 22.2 Initial radiological investigations for suspected cancer

Investigation	Indication/information available
Chest X-ray	Exclude a mediastinal mass in suspected leukaemia (T cell) or lymphoma Detection of pulmonary metastases, e.g. in Wilms' tumour
Bone X-ray	Evaluation of a suspected bone tumour (cortical destruction, cortical elevation, new bone formation, soft tissue swelling)
Ultrasound	Assessment of any abdominal mass Has the advantage of being readily available and does not require sedation or general anaesthetic, unlike MRI/CT
MRI/CT	3D assessment of tumour position and size, evidence of lymphatic spread, relationships to surrounding structures

Pathology

In most cases, the diagnosis will be confirmed by histological examination. Leukaemia is confirmed by bone marrow aspiration but a definitive tissue biopsy is usually required for solid tumours. There are exceptions, as some diagnoses can be made using tumour markers and radiology alone (e.g. certain germ cell tumours) and rarely tumour location makes biopsy impossible (e.g. brainstem tumours).

Staging

Staging schemes differ between tumour types, but typically localized tumours are described as low-stage (stage 1 or 2), whilst those that have metastasized are stage 4. In general, paediatric tumours are not staged according to the TNM (tumour, node, metastasis) system frequently used for adult carcinomas. In most cases, the tumour stage will be one of a number of factors in determining exactly how the patient is treated. The staging investigations will vary depending on the diagnosis and an understanding of the likely pattern of metastatic spread. Examples are listed in Table 22.3.

Questions 22.3 and 22.4

An unwell 3-year-old boy

A 3-year-old boy is referred to paediatric outpatients by his GP. He has presented three times over the last month with symptoms of an upper respiratory tract infection. He has had two courses of antibiotics for presumed tonsillitis and today has developed a non-blanching erythematous rash. He is pale, lethargic and febrile. On examination, he has modest

generalized lymphadenopathy, his abdomen is soft but his spleen is palpable 3 cm, testicular size is normal for age.

Investigations:

Haemoglobin: 6.3 g/L

White cell count: 53×10^9/L

Platelets: 22×10^9/L

Peripheral blood film: no blast cells seen

Urea and electrolytes: normal

Chest X-ray: normal

Question 22.3

Which TWO of the following are the most important procedures to establish the diagnosis and plan treatment?

A. Blood culture

B. Bone marrow examination

C. Epstein–Barr viral antibodies

D. Lumbar puncture

E. Lymph node biopsy

F. Erythrocyte sedimentation rate

G. Chest CT

Question 22.4

What is the most likely diagnosis? Select ONE answer only.

A. Acute lymphoblastic leukaemia

B. Acute myeloblastic leukaemia

C. Epstein–Barr virus infection

D. Hodgkin's disease

E. Meningococcal septicaemia

Answers 22.3 and 22.4

Question 22.3: Which of the following are the most important procedures to establish the diagnosis and plan treatment?

B. Bone marrow examination; D. Lumbar puncture.

Bone marrow examination will confirm the diagnosis of his pancytopenia. Given the likely diagnosis of leukaemia, a lumbar puncture must be performed to exclude CNS disease. Samples should be sent for cytogenetics and MRD (minimal residual disease) assessment which will influence risk stratification. Lymph node biopsy is not indicated as Hodgkin's lymphoma is unlikely. Blood culture will not reveal the underlying diagnosis. A coagulation screen is unlikely to identify the cause of his pancytopenia. Erythrocyte sedimentation rate (ESR) may be elevated but this does not help to confirm the diagnosis. In the context of a normal chest X-ray (CXR), a chest CT is not necessary and will not aid the diagnosis.

Question 22.4: What is the most likely diagnosis?

A. Acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia is the most common type of leukaemia in childhood. The differential diagnosis includes acute myeloid leukaemia; immunophenotyping will distinguish between them. Epstein–Barr virus infection is possible but unlikely with these blood test results. Hodgkin's disease is unlikely as there is no mediastinal enlargement. Meningococcal septicaemia is unlikely as presentation is over several weeks.

Table 22.3 Common staging investigations

Investigation	Role	Disease example
Lumbar puncture	Detection of disease in CSF	Leukaemia, parameningeal rhabdomyosarcoma, non-Hodgkin's lymphoma, brain tumours, e.g. medulloblastoma
Bone marrow aspirate and/or trephine	Detection of disease in bone marrow	Leukaemia, lymphoma, neuroblastoma, Ewing's sarcoma, rhabdomyosarcoma
Lymph node biopsy	Assessment of loco-regional spread of disease	Rhabdomyosarcoma
CT chest	Detection of pulmonary metastases	Wilms' tumour, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma
Bone scintigraphy using Technetium-99m	Detection of bone remodelling (growth or repair)	Osteosarcoma, Ewing's sarcoma
PET (positron emission tomography) CT with fluorodeoxyglucose	Assessment of sites of metabolic activity	Hodgkin's lymphoma – used to assess extent of disease and response to treatment
MIBG (iodine 131-metaiodobenzylguanidine) scan	Assessment of MIBG avid sites	Neuroblastoma – 90–95% of tumours are MIBG avid. Iodine 131-MIBG is taken up by sympathetic neurons, and is a functioning analogue of norepinephrine

Cancer genetics

Cancer genetics can be used for risk stratification or, less commonly, to direct a specific treatment. Perhaps the best example of the use of cancer genetics for risk stratification relates to amplification of the *MYCN* oncogene in neuroblastoma. MYCN is a transcription factor responsible for driving the expression of many downstream target genes.

Approximately one third of neuroblastoma tumours have amplification (multiple copies) of the region of chromosome 2p that contains the *MYCN* gene. Analyses have demonstrated that these tumours behave much more aggressively than those without *MYCN* amplification. This is particularly true for infants with metastatic disease; their survival is approximately 90% if *MYCN* amplification is absent, but historically less than 20% for those with amplification. Consequently, determination of *MYCN* status is now a routine part of the work-up in neuroblastoma.

In addition to amplification, many tumours show characteristic loss or gain of individual parts of one or more chromosomes. For example, neuroblastoma tumours often show loss of 1p or 11q, or gain of 17q, while in Wilms' tumour loss of 1p and 16q are seen. Another abnormality is translocation, whereby a piece from one chromosome becomes fused with another from a different chromosome. Such translocations may bring together two different genes and lead to the production of a fusion protein or overproduction of a protein product. The best-characterized example is the Philadelphia chromosome seen in chronic myeloid leukaemia (CML; a rare diagnosis in paediatrics) and in a subset of patients with ALL. The Philadelphia chromosome comprises a translocation involving chromosomes 9 and 22 and brings together the Bcr transcription factor with the Abl kinase. This results in over-activity of the Abl downstream pathway and malignant transformation. Particularly exciting is the development of a drug (imatinib) specifically designed to target this abnormal fusion protein, the use of which has revolutionized the treatment for patients with these conditions.

A number of paediatric solid tumour types also frequently have chromosomal translocations and, in many cases, the presence of these abnormalities is crucial in confirming the precise diagnosis. Ewing's sarcoma is characterized by the presence of a range of different chromosomal translocations, all of which involve the *EWS* gene on chromosome 22. A subset of rhabdomyosarcoma tumours also has characteristic translocations involving fusions between *FOXO1* and *PAX3* or *PAX7* genes.

Risk stratification

Prognostic factors vary between tumour types but may include patient age, primary tumour site, size and location, presence of metastases, histological subtype and the presence of specific genetic markers, such as amplification of the *MYCN* oncogene in neuroblastoma or the presence of fusion genes in rhabdomyosarcoma. Risk stratification means that patients with the same overall diagnosis may be treated in very different ways. For example, localized neuroblastoma in an infant may be managed with observation only, whilst metastatic neuroblastoma in an older child will require intensive multi-modal therapy.

As more is learnt about the underlying biology of paediatric cancers, the systems for risk-stratifying patients are becoming increasingly complex. In some diseases, the risk stratification process is dictated by treatment response. In ALL, disease assessment now includes measurement of minimal residual disease (MRD) that uses a PCR technique to detect the presence of very low numbers of abnormal leukaemic blasts in a bone marrow sample after initial treatment. Such techniques allow the detection of disease below the level at which it may be apparent under the microscope and make it possible to predict which patients are at a higher risk of disease relapse and would therefore benefit from treatment intensification. In bone tumours, completeness of surgery and the degree of tumour necrosis (which reflects chemosensitivity) are important prognostic factors and can further influence postoperative management and risk stratification.

Management of childhood cancer

The management of childhood cancer is complex. The main treatment modalities include chemotherapy, radiotherapy, surgery and biological approaches such as molecularly targeted agents and immunotherapy.

Chemotherapy

Chemotherapy may be used as: primary curative treatment, e.g. in acute lymphoblastic leukaemia; to control primary or metastatic disease before definitive local treatment with surgery and/or radiotherapy (neo-adjuvant), e.g. in sarcoma or neuroblastoma; or as adjuvant treatment to deal with residual disease and to eliminate presumed micro-metastases. For many tumour types, chemotherapy is used both before and after surgery. Some protocols, for example those for acute lymphoblastic leukaemia (ALL), make use of prolonged courses of oral chemotherapy known as

'maintenance' to prevent relapse. In order to act as an effective chemotherapeutic agent, drugs must either block cell replication or induce cellular death (apoptosis). Cell replication requires the complete function of the cell cycle (Fig. 22.5). The cell cycle itself is divided into four active phases – G_1, S, G_2 and M – and a resting phase G_0. G_1 is the 'gap phase' during which there is synthesis of the components required for DNA synthesis. It is followed by the DNA synthesis (S) phase before a second gap phase (G_2). Here the cell prepares for mitosis. The final phase of the cell cycle for actively replicating cells is the mitotic phase (M).

Different classes of chemotherapy agent work in different ways and at different parts of the cell cycle, but essentially all trigger the death of rapidly proliferating cells. Some drugs (e.g. vinca alkaloids like vincristine) block the function of the spindle apparatus required for mitosis, whilst others (e.g. etoposide) cause DNA strand breaks or directly damage DNA by forming crosslinks (e.g. cyclophosphamide). Antimetabolites (e.g. methotrexate) interfere with the synthesis of DNA. Further details are listed in Table 22.4.

Most chemotherapy is administered intravenously and paediatric cancer patients will generally require a central venous line to allow administration of chemotherapy and regular blood sampling. However, particularly for patients with leukaemia, intrathecal (i.e. direct injection into the spinal fluid) chemotherapy is also important to treat or prevent CNS disease, since most systemically administered chemotherapy does not adequately cross the blood–brain barrier. Most chemotherapy drugs are not specifically targeted to cancer cells and consequently also affect other rapidly proliferating normal cells in the body (Table 22.5). Some chemotherapy agents have specific side effects (Table 22.6). Typically, chemotherapy is given in a number of repeated cycles to allow recovery of normal tissues (particularly the bone marrow) between cycles.

Question 22.5

Chemotherapy

Following is a list of mechanisms of action:

A. Direct DNA damage

B. Increase in apoptosis

C. Inhibition of DNA repair

D. Inhibition of DNA synthesis

E. Reduction in mitosis by impairment of spindle apparatus

Which mechanism from the list provided BEST explains the mechanism of action of the following chemotherapy agents? Select ONE answer only for each question. Note: each answer may be used once, more than once or not at all.

1. Methotrexate

2. Vincristine

3. Etoposide

Answer 22.5

1. D. Inhibition of DNA synthesis. Methotrexate is an antifolate agent that reduces synthesis of DNA.

2. E. Reduction in mitosis by impairment of spindle apparatus. Vincristine inhibits the spindle apparatus involved in mitotic cell division.

3. A. Direct DNA damage. Etoposide is an inhibitor of the topoisomerase enzyme that helps with DNA unwinding during replication. Inhibition of this enzyme leads to DNA strand breaks.

Table 22.4 Phase specificity and mechanisms of action of chemotherapy drugs

Phase of cell cycle	Category of agent	Example	Mechanism of action
G_1	Enzyme	Asparaginase	Degrades essential amino acid L-asparagine. Tumour cells deficient in L-asparagine synthetase are unable to produce more of this amino acid
S	Antimetabolites	Methotrexate Cytarabine Mercaptopurine	Block synthesis of normal nucleic acids required for DNA synthesis
G_2	Epipodophyllotoxins	Etoposide	Inhibits topoisomerase type II preventing DNA repair and entry into mitosis
Mitosis	Vinca alkaloids	Vincristine	Block microtubule assembly preventing formation of mitotic spindle required for chromosome division
Not phase specific	Alkylating agents	Cyclophosphamide Ifosfamide	Cross-link DNA strands preventing DNA replication
	Antibiotics	Doxorubicin Actinomycin	Bind to DNA between base pairs preventing DNA transcription Free-radical production leading to apoptosis
	Platinums	Cisplatin Carboplatin	Bind to DNA preventing replication and transcription triggering apoptosis
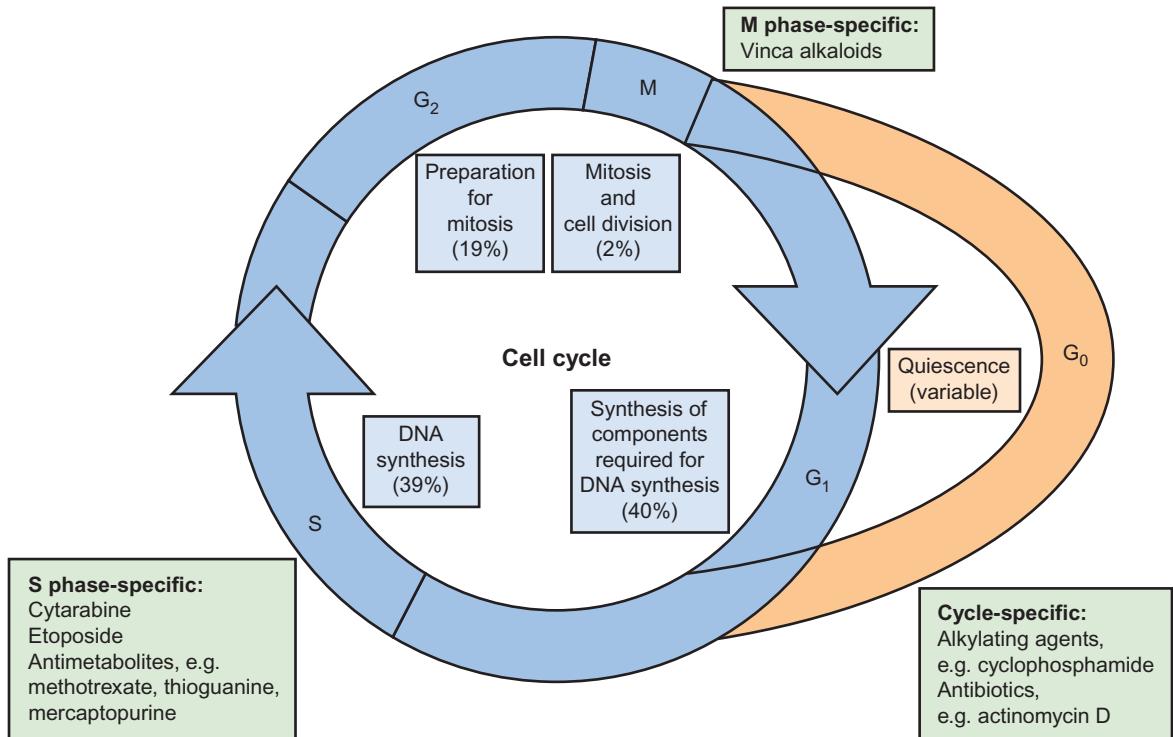
Fig. 22.5 Schematic representation of the normal cell cycle and action of chemotherapeutic agents.

Table 22.5 General side effects of chemotherapy

Target	Side effects
Bone marrow	Anaemia, thrombocytopenia, neutropenia and increased risk of infection
Hair follicles	Alopecia
Intestinal mucosa	Mucositis, diarrhoea
Chemoreceptive trigger zone (CTZ) in brain	Nausea and vomiting
Gonads	Increased risk of infertility

Myeloablative chemotherapy and stem cell transplant

In addition to standard dose chemotherapy, treatment of some cancers involves the use of myeloablative chemotherapy that completely destroys the patient's bone marrow such that it is unable to recover spontaneously. In the setting of relapsed leukaemia, such chemotherapy may be used as part of a conditioning regimen for an allogeneic bone marrow transplant (BMT) in which the bone marrow is reconstituted using stem cells from a donor (e.g. a sibling or matched unrelated donor). These patients are then at risk of graft-versus-host disease (GvHD) in which the newly reconstituted donor-derived immune system (particularly T lymphocytes) attacks host tissues, such

as the skin or gut. Allogeneic BMT procedures are not typically used for solid tumours. However, for some diseases (e.g. neuroblastoma and some brain tumours), myeloablative chemotherapy does have proven anti-tumour effects. In these cases, the patient's bone marrow is 'rescued' using infusion of the patient's own blood stem cells which have previously been harvested and stored – a process known as autologous stem cell rescue. These procedures carry significant risks of toxicity, particularly infection.

Radiotherapy

External beam radiotherapy involves the use of targeted X-rays to kill tumour cells through the induction of free radicals and DNA damage, leading to apoptosis. Radiotherapy remains a key component of the treatment of many extra-cranial solid tumours and most brain tumours. Concerns about the side effects of radiotherapy, specifically damage to growth and function of normal tissues, are greater in children than adults. The developing brain is particularly susceptible, which limits the use of radiotherapy in infants and typically infant brain tumour protocols rely on chemotherapy to avoid or delay the use of radiotherapy. Targeted radiotherapy techniques such as proton beam therapy and brachytherapy that focus the radiation field and reduce exposure to normal tissue are increasingly being used in children with the aim of

Table 22.6 Specific side effects of some chemotherapy agents

Class of chemotherapy	Example	Toxicity	Toxicity monitoring
Anthracyclines	Doxorubicin	Cardiac toxicity	Echocardiogram
Alkylating agents	Cyclosphosphamide	Haemorrhagic cystitis	Urinalysis
Vinca alkaloids	Vincristine	Neurotoxicity, constipation, jaw pain, foot drop	Clinical assessment
Platinums	Carboplatin, cisplatin	Ototoxicity Nephrotoxicity	Audiology Renal function
Antibiotics	Bleomycin	Lung toxicity	Lung function
Steroids	Dexamethasone	Immunosuppression, hyperglycaemia, mood disturbance, avascular necrosis, hypertension	

reducing long-term side effects. For some tumours (such as neuroblastoma), targeted molecular radiotherapy may be used, using a radiolabelled small molecule (e.g. MIBG) that is taken up by tumour cells.

Surgery

Surgery has an important role to play in both the diagnosis and the management of most solid tumours and in many cases complete excision of the tumour is an important determinant of overall outcome.

Oncological emergencies

Table 22.7 provides a summary of commonly encountered oncological emergencies.

Supportive care

Given the significant side effects of treatment, great care must be taken in managing toxicities, and 'supportive care' for these patients is therefore critical. In addition to bacterial infection, patients with prolonged immunosuppression are at risk of viral and fungal infections that require specific management and are associated with high mortality. Prophylaxis against fungal infections and *Pneumocystis jirovecii* (*carinii*) pneumonia (PCP) is used in certain treatment regimens. Other supportive care measures include blood product replacement, management of nausea and vomiting and nutritional support.

Questions 22.6 and 22.7

A 9-year-old girl with lethargy and petechiae

A 9-year-old girl is seen in the emergency department. She is afebrile but pale, lethargic and poorly responsive to questions. She has petechiae over her arms and legs.

Investigations:

Haemoglobin:	42 g/L
White cell count:	142×10^9/L
Neutrophils:	13×10^9/L
Lymphocytes:	80×10^9/L
Platelets:	5×10^9/L
Film:	multiple blast cells
Sodium:	138 mmol/L
Potassium:	7.8 mmol/L
Urea:	7.9 mmol/L
Creatinine:	60 µmol/L
Calcium:	2.01 mmol/L (2.20–2.50)
Magnesium:	0.65 mmol/L (0.66–1.00)
Phosphate:	1.73 mmol/L (1.2–1.8)
Albumin:	36 g/L
Urate:	600 µmol/L (130–280)

Question 22.6
What is the most likely cause for her reduced level of consciousness? Select ONE answer only.

A. Anaemia-related hypoxaemia

B. Brainstem compression

C. Hyperviscosity syndrome

D. Increased intracranial pressure

E. Meningococcal meningitis

Question 22.7
What is the explanation for the biochemistry results? Select ONE answer only.

A. Acute kidney injury (acute renal failure)

B. Pseudoaldosteronism

C. Renal tubular acidosis

D. Syndrome of inappropriate anti-diuretic hormone secretion (SIADH)

E. Tumour lysis syndrome

Table 22.7 Summary of commonly encountered oncological emergencies

Emergency	At risk	Cause	Features	Management
Tumour lysis syndrome	High-count ALL and NHL (especially B cell)	Rapid lysis of malignant cells on initiating chemotherapy, risk of acute renal failure	Hyperkalaemia, hyperuricaemia, hyperphosphataemia, Hypocalcaemia, metabolic acidosis (if severe)	Hyperhydration before and during initiation of therapy Urate precipitation: reduced with allopurinol, or urate oxidase in high-risk cases Treat hyperkalaemia Haemofiltration, if severe
Hyperviscosity syndrome	High-count leukaemia	Sludging of venous blood in small vessels	Can affect eyes, lungs, brain, digits, kidneys, penis	Hydration, urate oxidase, prompt chemotherapy; avoid transfusion unless essential Leucopheresis, if severe
Superior vena cava (SVC) obstruction	Mediastinal mass, e.g. Hodgkin's lymphoma, T-cell leukaemia	Compression of vasculature and/or airway	Dyspnoea, chest discomfort, hoarseness or cough, plethora, facial swelling, engorgement of veins of the chest wall	Empirical treatment may be required based on imaging alone as sedation or anaesthesia for diagnostic purposes is hazardous
Raised intracranial pressure	Brain tumours	Mass effect	Headache, vomiting, ataxia, papilloedema, III and VI cranial nerve palsies (false localizing signs)	Steroids Mannitol Surgical decompression
Spinal cord compression	Brain/spinal tumours, neuroblastoma, sarcoma, lymphoma	Mass effect	Back pain, loss of developmental milestones, abnormal gait, sensory loss, and bladder and bowel disturbance	Urgent MRI imaging Surgical decompression or urgent chemotherapy
Acute abdomen Neutropenic enterocolitis/ typhilitis	Neutropenic patients	Bacterial invasion of bowel wall leads to inflammation, full-thickness infarction, perforation, sepsis and coagulopathy	Right lower quadrant abdominal pain, fever, watery or bloody diarrhoea, nausea, vomiting, abdominal distension	Antibiotics, bowel rest, surgical review Most cases resolve with conservative management
Febrile neutropenia	All patients	Bacteria (skin or gut flora, Gram-negative organisms, including *Pseudomonas*, Gram-positive organisms)	Fever >38°C and a neutrophil count $<1.0 \times 10^9$/L	Broad spectrum antibiotics

ALL, acute lymphoblastic leukaemia; NHL, non-Hodgkin's lymphoma.

Question 22.6: What is the most likely cause for her reduced level of consciousness?

C. Hyperviscosity syndrome.

Her full blood count shows that she is profoundly anaemic (Hb 42 g/L), which may be a contributing factor. More worryingly, however, is the very high white blood cell count reflecting the presentation of acute leukaemia. An important consideration is that of hyperviscosity syndrome due to the large number of circulating blast cells. This can lead to poor perfusion, particularly of the brain, and in severe cases to stroke and death. Blood transfusion in this situation is dangerous since it may exacerbate hyperviscosity and urgent expert advice must be sought. She does not show clinical signs of acute brainstem compression or increased intracranial pressure. Meningococcal meningitis is unlikely as she is afebrile and not clinically septicaemic.

Question 22.7: What is the explanation for the biochemistry results?

E. Tumour lysis syndrome.

These results (hyperkalaemia, hypocalcaemia and hyperuricaemia) are indicative of tumour lysis syndrome. Pretreatment, spontaneous tumour lysis syndrome can occur and differs from the post-chemotherapy syndrome in that there is less risk of hyperphosphataemia. As leukaemic blasts die (either spontaneously or following the start of chemotherapy), their cellular contents are released into the circulation. Cellular nucleic acids are metabolized by enzymes including xanthine oxidase to produce uric acid that is excreted in the urine and stool. At high concentrations, uric acid may precipitate to produce urate crystals that damage the renal tubules and impair renal function. This may be further exacerbated by hyperphosphataemia. Allopurinol can help to prevent tumour lysis syndrome by inhibiting xanthine oxidase and thereby limiting the production of uric acid. However, in cases such as this with established tumour lysis (or individuals at high risk), rasburicase is preferred. This is a recombinant enzyme (urate oxidase) that directly metabolizes uric acid to the more soluble allantoin, which is then excreted. However, rasburicase can cause severe haemolysis in patients with G6PD-deficiency, and G6PD status should be confirmed first in at-risk patient populations.

In this child, acute kidney injury is not supported by these results; pseudoaldosteronism would also not explain all the biochemical abnormalities. SIADH would result in hyponatraemia. Renal tubular acidosis would cause hypokalaemia.

She should ideally be transferred to a paediatric oncology centre and may need intensive care. She should initially be managed with hyperhydration (ensuring a good urine output) and rasburicase. ECG monitoring is indicated because of her hyperkalaemia. This should be urgently checked since potassium is often falsely elevated in patients with high-count leukaemia due to spontaneous lysis of blasts in the blood sample before it reaches the laboratory. If confirmed, or in the presence of suggestive ECG changes (peaked T waves), urgent management with calcium gluconate, salbutamol and/or insulin/dextrose should be initiated. In the setting of tumour lysis and established renal impairment, haemodialysis may be required. Blood transfusion should be avoided unless there are specific indications and must be undertaken with caution.

Long-term follow-up

Monitoring of specific organ toxicities (e.g. cardiac, renal, hearing) occurs before, during and after treatment. There is increasing recognition of the need for long-term follow-up for patients treated for childhood cancer in order to address the late toxicities of chemotherapy and other treatment modalities. Examples of late effects are outlined in Table 22.8.
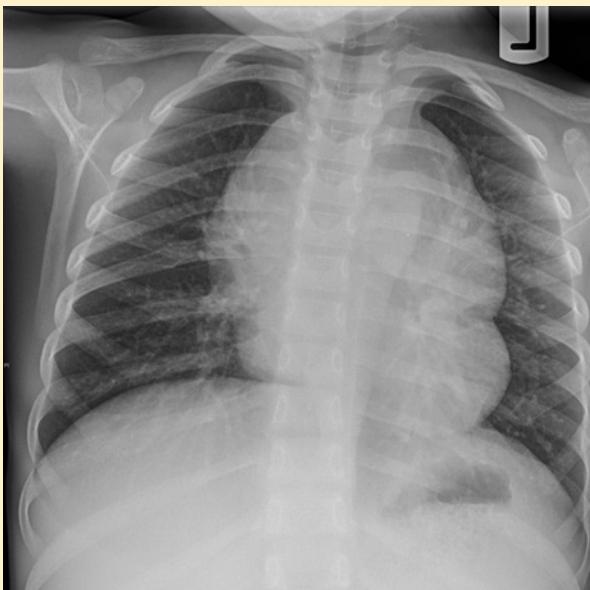
Table 22.8 Examples of late effects of treatment

Endocrine	Growth hormone deficiency Hypothyroidism Delayed puberty
Cardiac	Impaired systolic function
Renal	Chronic renal impairment and tubular leak
Fertility	Impaired gonadal function and reduced fertility
Psycho-social	Increased risk of education, employment and personal relationship difficulties
Intellectual/school	Increased risk of neurocognitive problems, particularly following cranial radiotherapy at a young age
Cancer	Increased risk of second malignancies

Questions 22.8 and 22.9

A breathless child

A 3-year-old boy presents to A&E with a 4-day history of shortness of breath that has significantly worsened over the last 24 hours. On examination, he is plethoric in the face and there are distended veins apparent in the neck. He is tachypnoeic and shows signs of increased work of breathing; air entry is poor. Chest X-ray is shown below:

Question 22.8

From the following list (A–J) select the TWO most likely diagnoses?

A. Acute lymphoblastic leukaemia

B. Congenital malformation

C. Germ cell tumour

D. Medulloblastoma

E. Neuroblastoma

F. Non-Hodgkin's lymphoma

G. Osteosarcoma

H. Pneumonia

I. Thymoma

J. Tuberculosis

Question 22.9

Which of the following is/are appropriate immediate management steps? Answer with true (T) or false (F).

A. Administer high-dose steroids

B. Check plasma urate concentration

C. Emergency referral to a paediatric oncology centre

D. Insertion of a cannula in the right arm and administration of 3 L/m^2/day intravenous fluids

E. Urgent bone marrow aspirate performed under general anaesthetic

F. Urgent full blood count and clotting profile

Answers 22.8 and 22.9

Question 22.8: Which two of the following are likely diagnoses?

A and F. Acute lymphoblastic leukaemia (ALL) and Non-Hodgkin's lymphoma.

This child has obstruction of the superior vena cava (SVC). The chest X-ray shows a large mediastinal mass and the most likely cause is T-cell lymphoma or T-ALL. Neuroblastoma and germ cell tumours can also present with mediastinal masses, although would be less likely to result in SVC obstruction. Osteosarcoma would not present with a large soft tissue mass like this and the appearances are not suggestive of a pneumonia. Medulloblastoma is a form of brain tumour, whilst congenital malformation would be very unlikely to present acutely at his age.

Question 22.9: Which of the following is/are appropriate immediate management steps?

A. False; B. True; C. True; D. False; E. False; F. True.

This patient most likely has acute leukaemia or lymphoma and urgent blood tests, including for signs of tumour lysis syndrome, are vital. In view of the mediastinal mass, the patient must be referred urgently to a paediatric oncology centre for further management. In view of the signs of superior vena cava obstruction, the patient should not be hydrated via the upper limbs, but should initially have a cannula sited in the lower limbs for hydration. General anaesthetic is contraindicated in patients with large mediastinal masses since this may precipitate complete airway obstruction. Although steroids are likely to form part of the treatment schedule, these should only be instituted at the paediatric oncology centre and will require careful monitoring in view of the risk of tumour lysis syndrome.

Symptom control and palliative care

Despite improvements in survival rates, a significant number of children will still die from their cancer. Indeed, childhood cancer is the leading cause of disease-related death in children in the UK and overall the second most common cause of death in childhood beyond infancy after trauma/injuries. Consequently, it is vital that the medical, emotional and psychological needs of patients (and their families) for whom there is no further curative treatment available are addressed. To this end, such patients will often be cared for by a dedicated symptom management or palliative care team, who will focus on addressing symptoms (such as pain, constipation, breathlessness or seizures).

Specific malignancies

Questions 22.10 and 22.11

A fall during physical education lesson at school

A 7-year-old boy attends the emergency department following a fall at school, when he tripped over and hurt the side of his head. His teacher reports that he has been increasingly unsteady on his feet during P.E. lessons over the last few weeks. His school was concerned that he had lost interest in lessons and his writing had deteriorated. His mother reports that he had vomited and complained of headache several times. On examination, his blood pressure is 98/50 mmHg, he has truncal ataxia and past-pointing. There is no evidence of papilloedema on fundoscopy.

Question 22.10

What is the most likely cause for his ataxia? Select ONE answer only.

A. Ataxia-telangiectasia

B. Basilar migraine

C. Cerebral abscess

D. Idiopathic intracranial hypertension

E. Long QT syndrome

F. Opsoclonus-myoclonus-ataxia syndrome

G. Post-varicella infection

H. Posterior fossa tumour

I. Subdural haematoma from head trauma

Question 22.11

Which of the following investigations is the most useful at this stage? Select ONE answer only.

A. 24-hour blood pressure profile

B. ECG

C. EEG

D. Lumbar puncture

E. MRI scan of head and spine

Answers 22.10 and 22.11

Question. 22.10: What is the most likely cause for his ataxia?

H. Posterior fossa tumour.

The most likely cause is a posterior fossa tumour. Opsoclonus-myoclonus-ataxia syndrome is a paraneoplastic feature of neuroblastoma, but causes dancing eyes and myoclonus, and neuroblastoma is rare at this age. Subdural haematoma from head trauma can cause ataxia, but the history preceded his fall. Basilar migraine would not cause such a prolonged history of ataxia. In ataxia-telangiectasia, the ataxia would be gradual and progressive. Idiopathic intracranial hypertension presents with headache and vomiting but would not cause ataxia. Long QT syndrome could cause falls at school but not vomiting and ataxia. Post-varicella infection can cause ataxia but not the other clinical features. A cerebral abscess is possible but unlikely in a previously well child.

Headaches and vomiting are the classical symptoms of raised intracranial pressure (ICP). Beyond infancy, the skull can be considered a closed, inelastic structure. Consequently, an increase in the volume of any of the intracranial contents (brain tissue, CSF, blood, tumour) will ultimately lead to a rise ICP. Initial changes may be compensated by reductions in CSF and blood volumes, but once these mechanisms are exhausted, further increases in volume will lead to dramatically increased ICP. Typically, headaches associated with raised ICP are worst in the morning due to combination of raised ICP secondary to lying flat overnight, which may be accompanied by reduced overnight CSF reabsorption as well as raised PCO_2 due to hypoventilation. Whilst papilloedema is a useful sign of raised ICP, its absence does not exclude it.

He has cerebellar symptoms; the most common tumours at this site are medulloblastoma or low-grade astrocytoma, but ependymoma is also seen. Medulloblastomas are primitive neuroectodermal tumours (PNETs), the most common group of malignant brain tumours of childhood. Although the majority occur in the cerebellum (where they are called medulloblastoma), they may be supratentorial. Recent molecular analysis of these tumours demonstrates that there are at least four subtypes with different molecular drivers, clinical features and outcomes. Two of the subgroups show activation of specific cell signalling pathways (WNT/beta-catenin and SHH, sonic hedgehog); these pathways play a role in neurodevelopment and their involvement in tumour formation likely reflects the developmental nature of PNETs.

Question 22.11: Which of the following investigations is the most useful at this stage?

E. MRI scan of head and spine.

An MRI scan of the head and spine will be very helpful here (Fig. 22.6). This will identify the tumour and detect the presence of hydrocephalus. It delineates the lesion more clearly than a CT head scan and also allows for planning of surgery. As a medulloblastoma is the most likely diagnosis, given the history, imaging of the spine is also important to look for evidence of spinal metastases. An ECG will

only rule out prolonged QT syndrome. An EEG will exclude an underlying seizure disorder but not delineate the site of the tumour. Lumbar puncture is contraindicated because of the features of ICP.
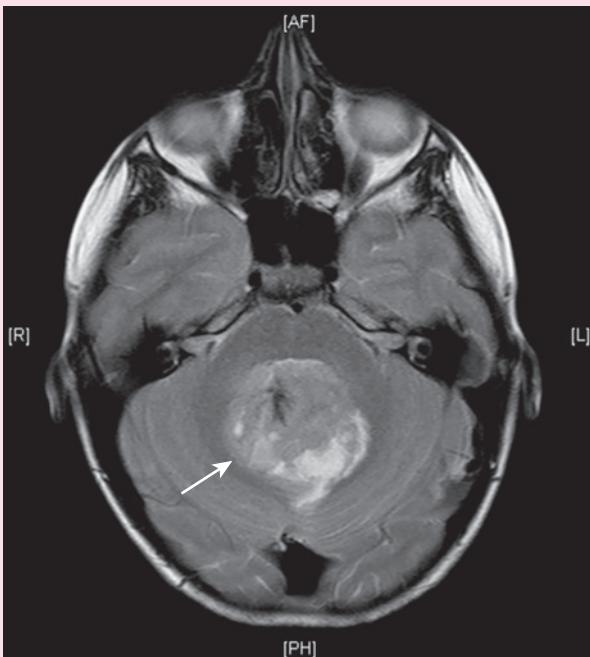
Fig. 22.6 MRI scan showing midline mass in the posterior fossa (cerebellum) typical of a medulloblastoma.

Question 22.12

Haematuria and an abdominal mass

A 2-year-old girl, Ellie, attends her GP's surgery with her mother. She has had one episode of haematuria but is otherwise well. There is no other history of note. Examination reveals a firm mass in the right side of the abdomen. Her blood pressure is 145/85 mmHg. Urinalysis reveals 3+ blood.

What is the most likely diagnosis? Select ONE answer only.

A. B-cell lymphoma
B. Hepatoblastoma
C. Nephroblastoma (Wilms' tumour)
D. Neuroblastoma
E. Multicystic dysplastic kidney disease (MCDK)
F. Rhabdomyosarcoma

Answer 22.12

C. Nephroblastoma (Wilms' tumour)

In view of the haematuria the most likely diagnosis is a right-sided Wilms' tumour (nephroblastoma). However, the differential diagnosis of an abdominal mass in a child of this age should include a neuroblastoma. Hypertension can occur in both Wilms' tumour and neuroblastoma but is rare with other abdominal tumours. B-cell lymphoma is less likely as she has no lymphadenopathy. Hepatoblastoma is less common than Wilms' tumour

at this age. It may be difficult to differentiate Wilms' tumour from hepatomegaly or a liver mass such as hepatoblastoma, although it should be possible on examination to palpate above a Wilms' tumour or neuroblastoma. Multicystic dysplastic kidney disease (MCDK) is usually detected on prenatal ultrasound, usually involutes but may cause hypertension and proteinuria. Rhabdomyosarcoma is rare in this age group and more commonly arises in the pelvis.

What else should you look for in your clinical evaluation?

Wilms' tumour is associated with a number of syndromes. The presence or absence of clinical signs of these syndromes should be documented; for example, hemihypertrophy, Beckwith–Wiedemann (macroglossia, umbilical defects, horizontal earlobe crease), WAGR (aniridia, Wilms' tumour, microcephaly, cryptorchidism).

In addition, evidence of metastatic disease should be sought. Most Wilms' tumours present as localized disease. The most common site for metastases in Wilms' tumour is the lungs but this is usually asymptomatic. However, around half of children with neuroblastoma present with advanced disease, and symptoms and signs often come from sites of metastasis, e.g. 'panda' eyes due to periorbital infiltration, or from constitutional symptoms associated with advanced disease such as cachexia and generalized wasting, or pallor, pyrexia or bruising associated with bone marrow infiltration.

What further investigations are warranted and why?

It is necessary to do the following:

- Repeat urinalysis to assess haematuria and exclude a UTI.
- Urine catecholamine metabolites (homovanillic acid (HVA) and vanillylmandelic acid (VMA)):

elevated in neuroblastoma. A single spot sample is sufficient.
- Ultrasound of the abdomen: to confirm renal or adrenal mass. Calcification is strongly suggestive of neuroblastoma.
- CXR and CT chest: staging for Wilms' tumour.
- MRI abdomen: further staging may demonstrate intra-abdominal lymphadenopathy more clearly than ultrasound.
- ECG/echocardiogram: patient is hypertensive and therefore evidence of heart strain should be sought. It is important to perform baseline investigations, as chemotherapy may include cardiotoxic agents.
- Blood tests, including full blood count, clotting, urea and electrolytes, liver function tests, ferritin, lactate dehydrogenase (LDH).
- Biopsy to establish definitive diagnosis: ultrasound/CT-guided needle biopsy or open procedure.
- Further staging: may be required, depending on the results of other investigations, e.g. bone scan or MIBG scan and bone marrow aspirates/trephines in neuroblastoma. Since Wilms' tumour very rarely metastasizes other than to the lungs, these investigations would not be required if a diagnosis of Wilms' tumour is confirmed.

Question 22.13

A painful, swollen knee

A 14-year-old girl is referred to paediatric outpatients with an 8-week history of pain and swelling in her left knee. She blames it on a minor sports injury, and has stopped playing sport. It initially settled down but then a month later it became swollen once again. She has seen her GP three times within the preceding 4 weeks with increasing rest pain, pain at night and increasing joint swelling. On examination, she appears well. There is an obvious swelling of the distal femur above the knee joint, which is slightly tender. Clinical examination was otherwise normal. An X-ray of the left knee is shown in Fig. 22.7.

What is the most likely diagnosis? Select ONE answer only.

A. Ewing's sarcoma

B. Osteosarcoma

C. Septic arthritis

D. Sports-related effusion of the knee joint

E. Tearing of the anterior cruciate ligament

Fig. 22.7 X-ray of left knee.

Answer 22.13

B. Osteosarcoma.

Osteosarcoma is most likely. Bone tumours account for 4% of all paediatric malignancies, of which osteosarcoma and Ewing's sarcoma account for more than 90%. Both have a peak incidence at 12–14 years of age, classically presenting with pain and subsequent swelling over the affected area. Over 90% of osteosarcomas are located in the metaphysis (growth plate) of bone. Around 80% occur in the bones around the knee (i.e. distal femur, proximal tibia or fibula). In contrast, most Ewing's sarcomas occur in the diaphysis (mid-shaft) of the bone and only about one third occur in the femur, tibia and fibula, collectively. Ewing's is more often associated with fever, soft tissue masses and nerve root pain. It may be difficult to distinguish Ewing's from chronic osteomyelitis on the basis of history, clinical examination and radiological findings. Septic arthritis is unlikely in the absence of fever. A sports-related effusion is less likely as she has not been undertaking vigorous sports for at least 4 weeks. Tearing of the ligament would produce pain but not swelling of the joint. The nature of the pain, causing waking at night, and the progressive swelling is not consistent with this.

The X-ray of the knee in Fig. 22.7 is consistent with the diagnosis of osteosarcoma, showing typical features of new bone formation, destruction of cortex and cortical elevation. This is known as 'Codman's triangle'. In Ewing's sarcoma, bone destruction gives rise to a 'moth-eaten' appearance. Cortical thickening also usually occurs. However, new bone formation is rare, unlike in osteosarcoma, and in addition, the soft tissue component of Ewing's may be visualized on plain X-ray.

Other investigations would include:

- MRI of the primary lesion: to allow accurate planning for biopsy as well as a baseline to assess response to chemotherapy prior to definitive surgery
- CXR and CT chest: to look for evidence of pulmonary metastases (10% in osteosarcoma, 25% in Ewing's at diagnosis)
- Technetium-labelled bone scan: if suggestive of metastatic lesions, these should be confirmed with MRI
- Bone marrow aspirates and trephines: in Ewing's up to 10% of patients have bone marrow involvement at diagnosis.

The molecular abnormalities driving osteosarcoma are not well understood. Ewing's sarcoma, however, typically shows a translocation involving the *EWSR-1* gene on chromosome 22. The most common translocation is t(11;22), bringing together *EWSR-1* with the transcription factor FLI1, although many other translocations have also been demonstrated.

Further reading

Children's Cancer and Leukaemia Group (CCLG), <http://www.cclg.org.uk>; [accessed 24.08.15]. Further information about the most common diagnoses.

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Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144(5):646–74.

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Irene A G Roberts, David O'Connor

Haematology

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Understand haematopoiesis in children
- Recognize the genetic and environmental factors involved in haematological disorders
- Understand the investigation and management of disorders of haematopoiesis
- Understand the normal coagulation pathway and its investigations
- Understand the pathophysiology, investigation and management of disorders of haemostasis/thrombosis
- Understand the role of major and minor blood group antigens and be aware of the potential complications of blood transfusions

Physiology of haematopoiesis

Haematopoiesis is the process through which all types of mature blood cell are produced. Haematopoietic stem cells (HSCs) are rare, multipotent cells characterized by their ability to both 'self renew' (proliferate) and to mature into fully differentiated cells of any of the haematopoietic lineages (Fig. 23.1). HSCs sustain blood cell production throughout life. The principal haematopoietic lineages are: the erythroid/megakaryocytic lineage, which gives rise to red cells and platelets; the granulocyte/macrophage lineage, which gives rise to granulocytes and monocytes; and the lymphoid lineage, which gives rise to B cells, T cells and NK cells. Amplification in cell numbers occurs as HSCs differentiate and it is estimated that each HSC can produce ~10^6 cells after undergoing up to 20 cell divisions. Disruption of stem cell function can result in a variety of blood disorders, including leukaemia (see Chapter 22, Oncology) and aplastic anaemia.

HSCs can be characterized on proteins expressed on the cell membrane, such as CD34. These cell markers can also be used to purify HSC for clinical applications, including haematopoietic stem cell transplantation (HSCT).

The regulation of haematopoiesis is complex. HSCs and their progeny are controlled by a network of interactions with haematopoietic growth factors and cellular components of the haematopoietic microenvironment (e.g. stromal cells) that maintain balanced blood cell production. Similar regulatory mechanisms respond to increased demand for specific blood cell types, such as increased red cell production in anaemia or increased granulocyte production in infection.

Development of haematopoiesis

Primitive haematopoiesis begins in the yolk sac during the first few weeks of embryonic life and gives rise mainly to red blood cells. Primitive haematopoiesis is transient and is replaced at 5–6 weeks' gestation by *definitive* haematopoiesis, which has the capacity to produce all blood cell types. Definitive HSCs develop in the aorta-gonad-mesonephros (AGM) region of the dorsal aorta.

HSCs migrate from the AGM to the fetal liver and spleen from 6–7 weeks' gestation. The liver then forms the primary site of haematopoiesis throughout fetal development. During the third trimester, haematopoiesis progressively increases in the bone marrow so that this becomes the main site of haematopoiesis shortly before birth. Initially, haematopoiesis occurs in all areas of bone marrow, becoming restricted to the axial skeleton and the proximal ends of the long bones later in childhood.
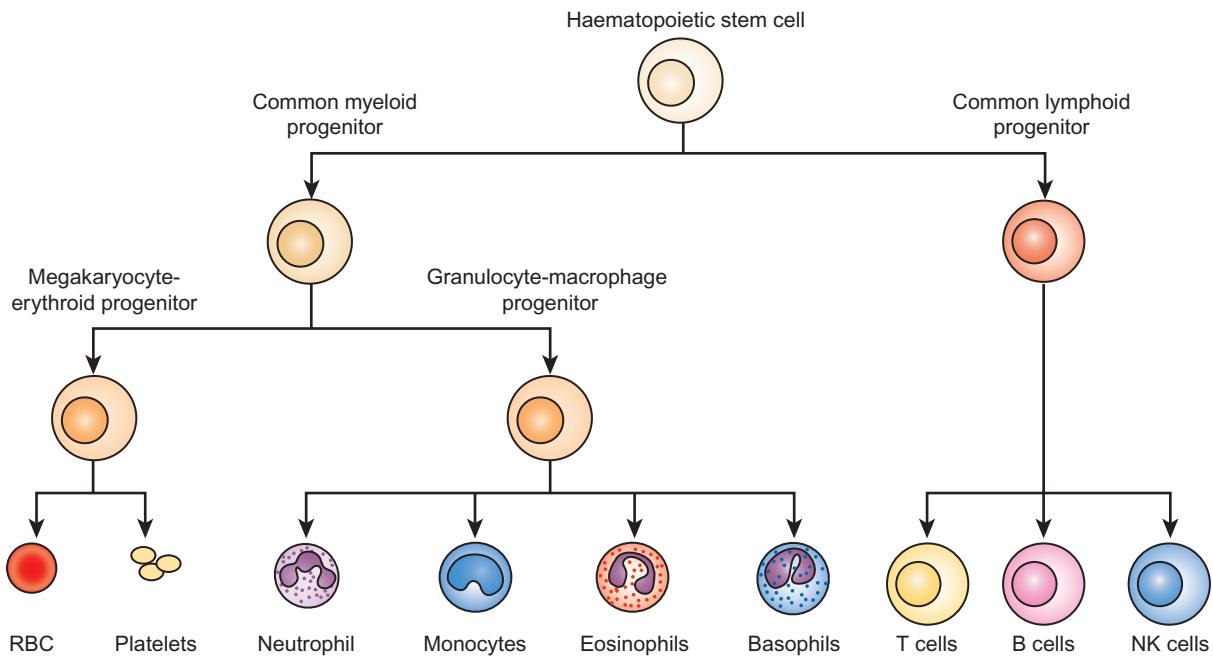
Fig. 23.1 Normal haematopoiesis: a hierarchy of haematopoietic stem cells, progenitor cells and mature blood cells of all lineages.

Table 23.1 Developmental changes in haemoglobin

Stage	Haemoglobin type	Globin composition
Embryonic	Hb Gower	$\zeta_2\varepsilon_2$
	Hb Portland	$\zeta_2\gamma_2$
Fetal	HbF	$\alpha_2\gamma_2$
Post-natal	HbA	$\alpha_2\beta_2$
	HbA$_2$	$\alpha_2\delta_2$
	HbF	$\alpha_2\gamma_2$

Physiology of red blood cells

Haemoglobin

Red cells are specialized cells that mainly function to deliver oxygen to the tissues and to remove carbon dioxide. They are biconcave (disc-shaped), lack a nucleus and contain large amounts of the oxygen-carrying protein haemoglobin (Hb). Each molecule of Hb consists of four globin chains and a central iron-containing haem group.

The composition of Hb changes in an ordered sequence during fetal development (Table 23.1). The first globin chains produced are epsilon (ε)- and zeta (ζ)-globin, followed almost immediately by gamma (γ)-globin chains, which together give rise to two types of embryonic Hb. Alpha globin synthesis begins shortly after this so that HbF ($\alpha_2\gamma_2$) is produced from 3–4 weeks of fetal life and is the predominant Hb until after birth. Adult Hb (HbA: $\alpha_2\beta_2$) remains at low levels (10–15%) until 30–32 weeks' gestation. After

this, the rate of HbA production increases at the same time as HbF production falls. As a result, the average HbF level at birth in term babies is 70–80%, with a HbA of 25–30%, small amounts of HbA$_2$ and sometimes a trace of Hb Barts (γ_4).

After birth, HbF falls rapidly (to ~2% at age 12 months) with a corresponding increase in HbA. In term babies there is little change in HbF in the first 15 days after birth. In preterm babies who are not transfused, HbF may remain at the same level for the first 6 weeks of life before HbA production starts to increase. This delay in HbA production (i.e. the switch from the γ-globin of HbF to the β-globin of HbA) makes the diagnosis of some haemoglobinopathies (see below) difficult in neonates.

The major function of Hb is to deliver oxygen to tissues. The binding and release of oxygen causes small changes to the configuration of globin chains in the Hb molecule, which in turn alters the affinity of Hb for oxygen. As oxygen is unloaded, the Hb molecule opens up allowing 2,3-diphosphoglycerate (2,3-DPG) to enter, reducing oxygen affinity and ensuring that the Hb molecule does not take up oxygen from the tissues. These changes in affinity result in the typical sigmoid shape of the oxygen dissociation curve, which is discussed in more detail in Chapter 17, Respiratory medicine.

Red cell metabolism

To function effectively, red cells must be able to generate energy (in the form of ATP) and reduce molecules
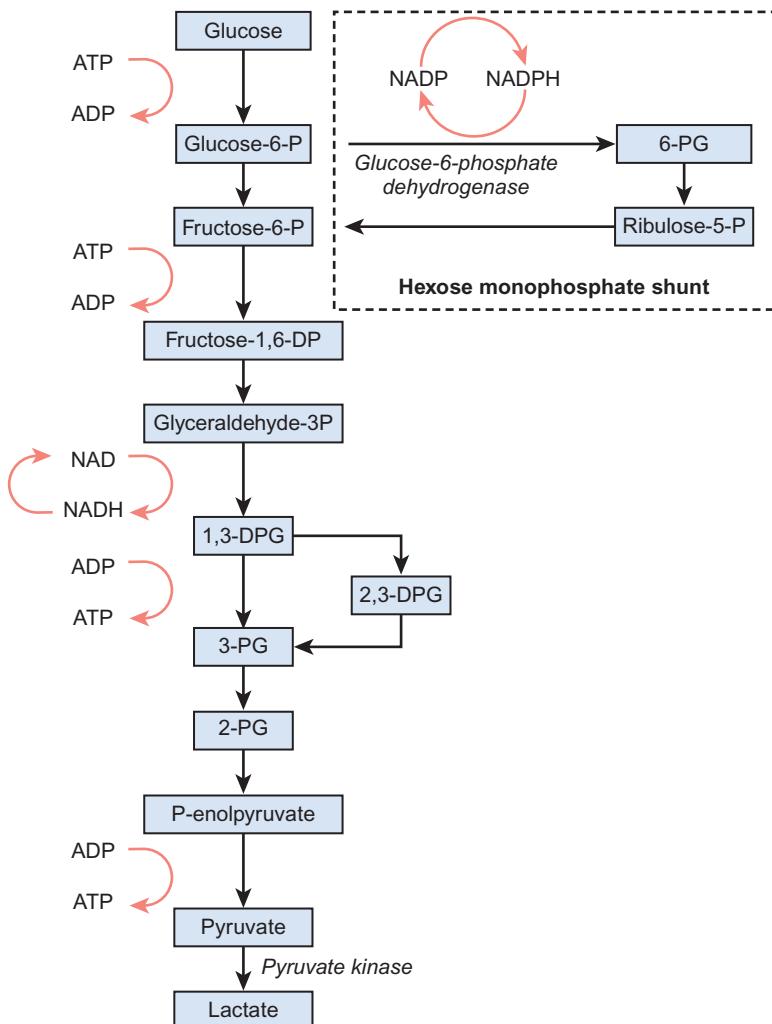
Fig. 23.2 Red cell metabolism: the Embden–Meyerhof pathway and pentose phosphate pathway.

to prevent oxidative damage. The Embden–Meyerhof pathway metabolizes glucose to lactate, producing two molecules of ATP, which are used to maintain red cell shape and osmotic gradient (Fig. 23.2). In addition, this pathway generates NADH (which is used to reduce iron to the active ferrous [Fe^{2+}] form) as well as 2,3-DPG. The pentose phosphate pathway is an alternative, essential glycolytic pathway, which generates NADPH, another important source of reducing power that maintains iron in the active form. Deficiency of glucose-6-phosphate dehydrogenase (G6PD), a key enzyme in the pathway, results in marked susceptibility to oxidative stress.

The red cell membrane

The average red cell lifespan is 120 days in older children but ~90 days in neonates, during which time each red cell is estimated to travel 300 miles through the circulation. To prevent damage to red cells and maximize their flexibility, the specialized red cell membrane consists of a complex lipid bilayer containing a number of key scaffolding proteins. The most abundant protein is spectrin, which forms tetramers and attaches to the membrane via the ankyrin protein. Abnormalities in these proteins cause membrane disorders such as hereditary spherocytosis and hereditary elliptocytosis.

Iron metabolism

Dietary iron is vital for erythropoiesis. Iron deficiency due to inadequate intake or chronic blood loss is the most common cause of anaemia worldwide. Foods rich in iron include meat (especially liver), nuts and pulses. Several of the genes which encode iron regulatory proteins have been identified. This has led to better understanding of iron metabolism in humans and to the identification of the genetic basis of several inherited iron overload and iron deficiency disorders.
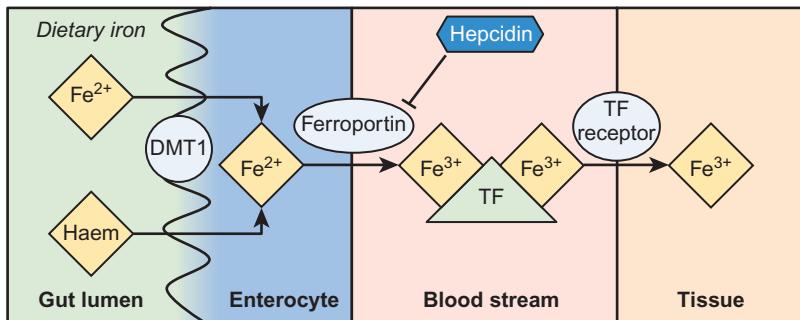
Fig. 23.3 Absorption of iron and distribution to tissues.

Iron absorption occurs in the duodenum:

- Iron in the diet is absorbed by enterocytes either in the Fe^{2+} form, via the divalent metal transporter (DMT)1 receptor (Fig. 23.3), or as haem.
- The iron transporter protein ferroportin then transports iron across the basolateral membrane of the enterocyte into the bloodstream.
- Iron is then bound to transferrin and transported to the tissues. Each molecule of transferrin can bind two molecules of iron and deliver this to cells that express transferrin receptors, including developing red cells.

The DMT1 receptor and the transferrin receptor 1 (TfR1) are both important regulators of body iron. The synthesis of these proteins is controlled by iron regulatory proteins (IRPs) that can bind to iron response elements (IREs) on genes. When iron levels are adequate, IRPs do not bind, which allows production of ferritin and therefore storage of iron. When iron deficiency occurs, IRPs bind to the IREs, blocking production of ferritin and enhancing synthesis of DMT1 and TfR1, which encourages increased iron absorption in the gut and uptake by the tissues. Mutations in DMT1 cause congenital anaemia. Mutations in the ferroportin gene are associated with congenital hyperferritinaemia and iron overload.

Iron is present in the body in several forms. The greatest amount of iron is in haemoglobin, which can be recycled once red cells reach the end of their life. The other main form of iron storage is ferritin, a water-soluble molecule found in many tissues. The serum ferritin concentration provides a fairly accurate estimation of total body iron levels (in the absence of inflammation) and is a useful investigation when iron deficiency is suspected. Iron is also present in an insoluble form called haemosiderin, in myoglobin in the muscles and in many important enzymes. In general, the amount of iron in the diet is excess to requirements and so typically only 5–10% of dietary iron is absorbed. However, during periods of increased need, such as iron deficiency, iron absorption can be increased to up to 30%.

Iron availability is very tightly regulated at both the cellular and systemic levels in order to avoid iron deficiency or iron overload. Key to this is *hepcidin*, a recently discovered small peptide hormone produced by the liver, which plays a major role in controlling iron flux to plasma from enterocytes and macrophages through degradation of the cellular iron exporter ferroportin (see Fig. 23.3). Under steady state conditions, normal hepcidin levels prevent excess iron absorption and iron overload. Similarly, in iron deficiency, hepcidin levels fall. Thus, the hepcidin–ferroportin axis is essential for the maintenance of iron homeostasis and mutations in the genes which encode proteins of the hepcidin-activating pathway are a major cause of iron overload. Hepcidin insufficiency and increased iron absorption are also characteristic of anaemia due to ineffective erythropoiesis. In this situation, hepcidin is suppressed by the high erythropoietic activity, despite high total body iron, thereby worsening both the iron overload and the anaemia. Similarly, hepcidin excess due to mutations in the hepcidin inhibitor, transmembrane protease serine 6 (TMPRSS6) leads to iron refractory iron deficiency.

There is no mechanism for regulating iron excretion if iron levels are too high. Therefore, patients receiving regular blood transfusions, and some patients with severe haemolytic anaemia, can become iron overloaded. Excess iron is then deposited in various organs, including the liver and heart, which can result in serious damage and organ failure (see later in chapter).

Disorders of haematopoiesis

Anaemia

Anaemia is defined as a haemoglobin level below the normal range. The normal range varies with age. Hb values are higher *in utero* due mainly to the higher oxygen affinity of HbF and fall during the first few months of life due to reduced red cell production. Thereafter, Hb values stabilize until puberty when

growth leads to an increased demand for iron and iron deficiency may develop, particularly in girls. A practical age-based definition of anaemia which takes these physiological factors into account is:

- Neonate: <130 g/L (at birth)
- 1–12 months: <100 g/L
- 1–12 years <110 g/L

Anaemia occurs through three main mechanisms:

- Insufficient red cell production
- Excessive red cell destruction (haemolysis)
- Increased red cell loss (bleeding)

Investigation of anaemia

The investigation of anaemia should begin with a full blood count and a blood film. If anaemia is associated with abnormalities in the white cell and platelet counts, a bone marrow disorder, such as leukaemia, should be suspected. However, where the white cell and platelet counts are normal, the mean cell volume (MCV) and mean cell haemoglobin (MCH) provide the most useful information about the likely aetiology (Table 23.2).

Iron deficiency results in a microcytic hypochromic anaemia (low MCV, low MCH). β-Thalassaemia is an important differential diagnosis, particularly in children from the Indian subcontinent. In β-thalassaemia carriers (β-thalassaemia trait), the MCH and MCV

are also low but the Hb is only slightly reduced (80–100 g/L). Further tests should be performed to confirm iron deficiency and rule out less common causes, such as thalassaemias and anaemia of chronic disease (Table 23.3).

Red cell aplasia

Red cell aplasia causes anaemia due to reduced or absent red cell precursors in the bone marrow. There are three main causes in childhood:

- Diamond–Blackfan anaemia
- Transient erythroblastopenia of childhood
- Parvovirus-induced aplastic crisis

Diamond–Blackfan anaemia

Diamond–Blackfan anaemia (DBA) is a rare (4–7 cases/million live births) genetic disorder that usually presents with anaemia at birth or during infancy. It may present in fetal life and occasionally in older children. DBA is associated with physical abnormalities in 50% of cases, including:

- Craniofacial abnormalities (cleft palate, typical facies)
- Thumb abnormalities (hypoplastic, triphalangeal)
- Growth restriction

In most cases, inheritance is autosomal dominant and a family history is present in 10–20% cases. Genetic studies have identified mutations in various ribosomal protein genes (the most common mutation being in *RPS19* which occurs in ~25% of cases). These studies indicate that defective ribosomal biosynthesis is the primary cause of DBA resulting in apoptosis and dysfunction in other key pathways. Ribosomes are vital for protein synthesis but their exact role in DBA is yet to be fully elucidated.

Laboratory tests in DBA will show:

- Macrocytic anaemia
- Low reticulocyte count (usually $<30 \times 10^9$/L)
- Normal white cell count

Table 23.2 Causes of microcytosis and macrocytosis with or without anaemia

Mean cell volume (MCV)	Causes
Reduced (microcytosis)	Iron deficiency Thalassaemia major or thalassaemia trait Anaemia of chronic disease
Increased (macrocytosis)	Folate deficiency Vitamin B_{12} deficiency Diamond–Blackfan anaemia Liver disease Hypothyroidism

Table 23.3 Differential diagnosis of microcytic anaemia

	Iron deficiency	Anaemia of chronic disease (g/dL)	β-thalassaemia major	β- or α-thalassaemia trait
Haemoglobin (g/L)	<100	~80–100	<60	~80–100
MCV/MCH	Reduced	Normal or slightly reduced	Very low for degree of anaemia	Reduced
Serum ferritin	Reduced	Normal or increased	Normal	Normal
TIBC	Increased	Normal	Normal	Normal
Serum transferrin receptor	Increased	Normal	Normal	Normal
Iron saturation	Reduced	Normal	Normal	Normal

MCH, mean cell haemoglobin; MCV, mean cell volume; TIBC, total iron-binding capacity.

- Normal or increased platelet count
- Increased HbF
- Increased levels of the red blood cell enzyme erythrocyte adenosine deaminase (eADA); measurement of eADA is a useful screening test for DBA since levels are elevated in most patients

When DBA is suspected, a bone marrow biopsy should be performed which will confirm the diagnosis by showing a reduction in erythroid precursors while other cell types are unaffected. Screening for ribosomal protein mutations is now available and can be useful to confirm the diagnosis.

After diagnosis, most patients are commenced on oral prednisolone, which induces a response in 70% of cases. It is usual to defer steroids until after initial MMR vaccination has been carried out. In children who are refractory to steroids, or where steroids cause unacceptable side effects, blood transfusions form the mainstay of treatment. Around half of all patients with DBA are maintained on regular transfusions, which leads to transfusional iron overload in the long term. Recently, HSCT has become a curative option for patients with DBA, usually using a healthy sibling donor.

Transient erythroblastopenia of childhood

The main differential diagnosis of DBA in neonates is parvovirus-induced red cell aplasia. The main differential diagnosis in infants and young children is transient erythroblastopenia of childhood (TEC). Although DBA usually presents in infancy and TEC has a median presentation of 2 years, overlap in age groups can occur. TEC is a rare (5 cases/million) transient red cell aplasia that is thought to be triggered by an unknown infective agent. It is important to differentiate TEC from DBA as recovery occurs spontaneously in TEC, usually within 4–8 weeks, and so usually no treatment is needed.

In the absence of a family history or physical abnormalities, laboratory tests can help to establish the diagnosis (Table 23.4). Anaemia in TEC is usually normocytic and is associated with neutropenia in some cases. HbF and eADA are normal.

Questions 23.1–23.3

A child with sudden onset of jaundice, fever and abdominal pain

A 4-year-old Lebanese boy presents to the emergency department with a short history of jaundice, fever, lethargy and mild abdominal pain. On examination, he looks extremely pale and his spleen tip is just palpable. His mother reports that he is normally an active boy and has had no previous hospital attendances. He eats well and had consumed a large dish of broad beans at a family celebration the day before.

Investigations:

Hb 38 g/L

WBC 5.3×10^9/L

Neutrophils 3.2×10^9/L

Platelets 220×10^9/L

MCV 82 fL

MCH 29 pg

Reticulocytes 11.2%

Unconjugated bilirubin 180 µmol/L

LDH 680 IU/L (NR 180–300 IU/L)

Haptoglobin: not detectable

Parvovirus antibody: IgG positive

Direct Coombs test: -ve

G6PD: 0.2 U/gHb (NR 3.1–11 IU/gHb)

Blood film: polychromasia, fragmented red blood cells, schistocytes

Question 23.1

Which of these features suggests that the haemolysis is intravascular rather than extravascular? Select ONE answer only.

A. Fragmented red cells

B. Hyperbilirubinaemia

C. Increased lactate dehydrogenase (LDH)

D. Spherocytes

E. Splenomegaly

Question 23.2

Which of these drugs must be avoided in children with this condition? Select ONE answer only.

A. Antihistamines

B. Co-trimoxazole

C. Cyclophosphamide

D. Dexamethasone

E. Hydroxycarbamide (hydroxyurea)

Question 23.3

What is the most appropriate next treatment step? Select ONE answer only.

A. Blood transfusion

B. Dexamethasone

C. Erythropoietin

D. Intravenous immunoglobulin

E. Splenectomy

Table 23.4 Differentiating Diamond–Blackfan anaemia (DBA) and transient erythroblastopenia of childhood (TEC)

	DBA	TEC
Physical abnormalities	50%	Absent
Family history	10–20%	Absent
MCV	High	Normal
Neutrophil count	Normal	Reduced in up to 50%
HbF	Increased	Normal
eADA	Increased	Normal
Mutations in ribosomal protein genes	Found in >50%	No
Spontaneous recovery	Occasional	Always

eADA, erythrocyte adenosine deaminase; MCV, mean cell volume.

Increased red cell destruction (haemolysis)

Causes and mechanisms of haemolytic anaemia

Haemolysis increases the breakdown of red blood cells. If the bone marrow is unable to compensate for the increased red cell turnover, anaemia develops. Haemolysis can be broadly grouped into inherited causes (usually due to intrinsic red blood cell abnormalities) and acquired causes (usually due to extrinsic abnormalities, such as antibody-mediated destruction in immune haemolytic anaemias; Table 23.5). In children, intrinsic red cell abnormalities account for the majority of cases.

Blood tests show a characteristic profile in haemolytic anaemia:

- Reduced Hb
- Raised reticulocytes (immature red blood cells)

Table 23.5 Causes of haemolytic anaemia

Inherited haemolytic disorders	
Red cell membrane defects	Hereditary spherocytosis Hereditary elliptocytosis
Red cell enzyme defects	G6PD deficiency Pyruvate kinase deficiency
Haemoglobinopathies	Sickle cell disorders, e.g. sickle cell anaemia Thalassaemias
Acquired haemolytic disorders	
Autoimmune	Idiopathic SLE, JIA Infection-associated, e.g. varicella zoster, EBV PNH Lymphoproliferative disease, e.g. Hodgkin's lymphoma
Microangiopathic	HUS Thrombotic thrombocytopenic purpura Haemangiomas (e.g. Kasabach–Merritt syndrome)
Infection	Malaria Septicaemia
Other	Hypersplenism Burns Poisoning (e.g. lead, arsenic, naphthalene)

EBV, Epstein–Barr virus, HUS, haemolytic-uraemic syndrome, JIA, juvenile idiopathic arthritis; PNH, paroxysmal nocturnal haemoglobinuria; SLE, systemic lupus erythematosus.

- Raised unconjugated bilirubin
- Raised lactate dehydrogenase (LDH) – the LDH enzyme is present at high levels in red blood cells and so during haemolysis, lysis of the red cells causes large amounts of LDH to be released into the circulation
- Low haptoglobin

Haemolysis may occur in the circulation (intravascular) or in various organs, such as the spleen (extravascular). Intravascular haemolysis leads to depletion of haptoglobin, increased LDH and large numbers of fragmented red blood cells, called schistocytes. Haptoglobin binds free haemoglobin in plasma to form a haptoglobin–haemoglobin complex, which is then removed from the circulation by the reticuloendothelial system (mostly the spleen). After haptoglobin is depleted, free haemoglobin is filtered by the kidney. This reabsorption is overwhelmed in severe cases of intravascular haemolysis. LDH is present in many tissues but has high concentrations within red blood cells.

Extravascular haemolysis usually takes place in the spleen or liver but can also occur in the lung. Haemolysis occurs when spleen and liver macrophage Fc receptors

bind immunoglobulin attached to red blood cells and then either ingest small portions of the cell membrane creating spherocytes or phagocytose the whole cells. Amino acids from the globin chains are recycled and the iron is removed from the haem and reused. The haem is degraded into unconjugated bilirubin.

In most cases the blood film provides useful clues to the diagnosis and aetiology, for example:

- Polychromasia – an increase in immature red blood cells (reticulocytes), which appear lilac-coloured on most blood film stains
- Sickle-shaped cells – diagnostic of sickle cell disorders
- Spherocytes – seen in hereditary spherocytosis but also in immune haemolytic anaemias
- Fragmented red cells, e.g. 'bite' cells – typical of oxidative haemolysis (e.g. G6PD deficiency), other red cell fragments or schistocytes in

intravascular haemolysis, e.g. in haemolytic-uraemic syndrome (HUS)

The direct antiglobulin test

The direct antiglobulin test (DAT), which detects the presence of antibodies coating red blood cells, is essential for the diagnosis, or exclusion, of immune-mediated haemolytic anaemia. To perform the test, red blood cells are incubated with anti-human globulin (AHG) and if antibody is present on the cells, the AHG will cause agglutination. This agglutination is recorded as a positive DAT. Examples of conditions in children in which the DAT is positive are:

- Haemolytic disease of the newborn (HDN)
- Autoimmune haemolytic anaemia
- Drug-induced haemolytic anaemia
- Haemolytic transfusion reactions

Case history

A 5-year-old girl with known hereditary spherocytosis (HS) presents with pallor and lethargy that has developed over the last 2 days. She is not jaundiced but she has a 5 cm palpable spleen and her Hb is 32 g/L. She had been very well until the previous week, when she developed signs of a mild coryzal illness, followed by increasing lassitude and anorexia.

What is the pathogenesis of HS and how is it inherited?

HS is the most common of a group of inherited disorders of the red cell membrane that also includes hereditary elliptocytosis. Most cases of HS are due to a mutation in the spectrin or ankyrin genes that encode for a key red cell membrane structural protein, which anchors the lipid membrane of the red cell to the protein skeleton. Loss of this anchoring effect allows small membrane fragments to be lost during red cell passage through the spleen. As membrane loss progresses, the red cells gradually become spherical. Eventually these spherocytic red cells are destroyed in the spleen resulting in haemolytic anaemia.

Inheritance of HS is usually autosomal dominant although up to 25% of cases are autosomal recessive or are the result of *de novo* mutations.

What are the usual clinical features and how would you confirm the diagnosis?

The clinical features of HS vary widely in severity from patient to patient. In most cases, HS causes only mild anaemia (Hb 80–100 g/L), variable

splenomegaly (typically 1–2 cm) and fluctuating jaundice (unconjugated hyperbilirubinaemia), particularly at times of infection. In more severe cases, haemolysis can lead to a more profound chronic haemolytic anaemia. HS usually presents in early childhood or in the neonatal period, when it typically causes early-onset jaundice with or without anaemia. Most neonates with HS will not require treatment apart from phototherapy for jaundice. Around 25% of affected neonates will require 1–3 transfusions due to moderately severe haemolytic anaemia during the first 1–2 months of life, but transfusion dependence after this time is extremely uncommon.

In the majority of cases, the diagnosis of HS can be made based on a positive family history and the presence of spherocytes on the blood film. Blood tests will usually show a mild anaemia and raised reticulocytes and bilirubin. In neonates, the most important differential diagnosis is haemolytic disease of the newborn due to ABO alloantibodies. In alloimmune haemolysis, the DAT is almost always positive in contrast to HS where the DAT is negative. In those without a family history, typical blood film findings and exclusion of other conditions is usually sufficient for diagnosis. The osmotic fragility test, which was commonly used for the diagnosis of HS, is now unavailable in most laboratories and rarely used.

Most patients do not require any treatment other than prophylactic oral folic acid to prevent megaloblastic anaemia. Splenectomy improves the anaemia in HS. However, the side effects of splenectomy (increased susceptibility to infection

and risk of thrombosis) mean that this approach is restricted to children who are failing to thrive or who develop transfusion dependence. Pigment gallstones due to chronic haemolysis are also common in older children and in adult life.

What is the likely cause of the deterioration in this case?

Pallor and lethargy suggest anaemia. The absence of jaundice indicates this is unlikely to be due to increased haemolysis. Therefore, the most likely

cause is a severe reduction in red cell production (red cell aplasia) due to infection with parvovirus B19. The patient's recent coryzal illness supports this diagnosis. Parvovirus B19 can precipitate an aplastic crisis in any chronic haemolytic disorder, including sickle cell anaemia.

Diagnosis can be confirmed by showing a low Hb (often 20–30 g/L) with markedly reduced reticulocytes and IgM antibodies against parvovirus B19. Treatment is supportive, with blood transfusion if clinically necessary.

Red cell enzyme defects

Glucose-6-phosphate dehydrogenase deficiency

The most common red cell enzyme deficiency which causes haemolytic anaemia is deficiency of glucose-6-phosphate dehydrogenase (G6PD), which protects the cell from oxidative damage. G6PD catalyses the first step of the pentose phosphate pathway, regulating the rate of the pathway. Since G6PD deficiency is an X-linked disorder, it predominantly affects boys, although female carriers may be mildly affected. G6PD deficiency is most prevalent in patients of African, Mediterranean or Asian origin. Worldwide, more than 400 million people are affected.

The majority of patients are asymptomatic most of the time, although some rare mutations in the G6PD gene cause chronic haemolytic anaemia. One of the commonest presentations of G6PD deficiency is neonatal jaundice. Jaundice may be severe enough to cause kernicterus. Globally, it is by far the most common cause of severe hyperbilirubinaemia. Despite marked hyperbilirubinaemia, the Hb is usually normal or very slightly reduced, as the jaundice is believed to be predominantly due to liver dysfunction rather than haemolysis.

After the neonatal period, G6PD deficiency usually presents as an acute haemolytic crisis that can be precipitated by an infection, certain drugs (Table 23.6) or by ingesting broad beans.

Blood tests during an acute haemolytic crisis due to G6PD deficiency will show:

- Reduced Hb
- Raised reticulocytes
- Hyperbilirubinaemia
- Increased LDH

Acute haemolysis in G6PD deficiency causes fragmented red cells, 'bite' cells and polychromasia. If special stains are used, red cell inclusions made up of denatured Hb, known as Heinz bodies, may be seen. However, between haemolytic crises, the blood film in

Table 23.6 Drugs that should be avoided in G6PD deficiency

Drug group*	Examples
Sulphonamide antibiotics	Co-trimoxazole Dapsone
Other antibiotics	Nitrofurantoin Chloramphenicol
Antimalarials	Primaquine Chloroquine
Analgesics	Aspirin

*In addition to these drugs, patients with G6PD deficiency should avoid exposure to naphthalene (mothballs) and ingestion of broad beans (other types of bean do not induce haemolysis in G6PD deficiency).

G6PD deficiency is completely normal and the reticulocyte count is not increased. Treatment of G6PD deficiency is unnecessary except during severe haemolytic episodes, when red cell transfusion may be required. Diagnosis is confirmed by measuring red cell G6PD levels although levels can be falsely elevated during an acute crisis. If there is any doubt about the diagnosis of G6PD deficiency, enzyme levels should be repeated when the patient has recovered. Parents and children should be advised about avoiding potential triggers and given a list of the most commonly used drugs which may precipitate acute haemolysis.

Pyruvate kinase deficiency

Pyruvate kinase deficiency is much less common than G6PD deficiency and should only be considered in the presence of a family history or after excluding G6PD deficiency. Deficiency of pyruvate kinase in red blood cells results in insufficient ATP production, leading to 'rigid' cells and subsequent haemolysis. Pyruvate kinase deficiency may present as hydrops fetalis, neonatal haemolytic anaemia or chronic haemolytic anaemia in early childhood. The level of anaemia is variable, but is surprisingly well tolerated because increased 2,3 DPG levels shift the O_2 dissociation curve to the right. Nevertheless, some patients are transfusion dependent. Pyruvate kinase

deficiency is inherited as an autosomal recessive disorder and produces typical 'prickle' red cells which can be recognized by examination of the blood film. Diagnosis can be made by measuring pyruvate kinase enzyme levels. It is usually necessary to test both the affected child and their parents to confirm the diagnosis.

Autoimmune haemolytic anaemia

Autoimmune haemolytic anaemia (AIHA) occurs when individuals produce an antibody against their own red cells. AIHA is divided into 'warm' and 'cold' types, depending on whether the antibody binds most strongly at 37°C (warm AIHA; usually IgG antibodies) or 4°C (cold AIHA; usually IgM antibodies). In children, AIHA most commonly presents during an intercurrent infection and usually resolves spontaneously. However, it may also occur in association with another immunological disorder such as systemic lupus erythematosus (SLE) or juvenile idiopathic arthritis (JIA), or a lymphoproliferative disorder such as Hodgkin's lymphoma.

Diagnosis of AIHA is confirmed by the characteristic blood film, haemolysis profile (unconjugated hyperbilirubinaemia, raised LDH, increased reticulocytes and reduced haptoglobin levels) and positive DAT. In cases that do not resolve spontaneously, immunosuppressive treatment may be required, such as steroids, azathioprine or ciclosporin.

Haemoglobinopathies

The haemoglobinopathies are a group of disorders that arise due to abnormal haemoglobin production. This can result from either:

- Inadequate globin chain production (α- and β-thalassaemia)
- Production of an abnormal globin chain (e.g. sickle cell anaemia)

Haemoglobinopathies are characterized by chronic haemolytic anaemia and are associated with a number of other important complications.

Questions 23.4 and 23.5

The child with lethargy and mild anaemia

A 14-year-old Indian girl presents to her family doctor with a history of tiredness and lethargy for several years. Her appetite is good and she eats well, although mainly vegetarian food. Her periods are regular and she denied menorrhagia. On examination she looked well, though slightly pale. She was not jaundiced and had no hepatosplenomegaly. Her mother reports that she is an active girl although she has recently been worried about her schoolwork. Her mother commented that she was found to be anaemic during her pregnancies and given iron tablets. Otherwise there is no relevant family history.

Initial blood results show:

Hb 108 g/L

WBC 5.3×10^9/L

Neutrophils 3.2×10^9/L

Platelets 240×10^9/L

MCV 62 fL

MCH 20.2 pg

Reticulocytes 1.2%

Serum iron 18 µg/L (NR 8–26)

Serum ferritin 28 µg/L (NR 6–40)

Iron-binding capacity 80 µg/L (NR 57–103)

Transferrin saturation 29% (NR 17–43)

Serum folate 12.2 nmol/L (NR 2.7–16.3)

HbF 2.1% (NR <1%)

HbA$_2$ 5.2% (NR 2–3.5%)

Question 23.4

Which is the most likely diagnosis? Select ONE answer only.

A. β-Thalassaemia trait

B. Folate deficiency

C. Glucose-6-phosphate dehydrogenase deficiency

D. Iron deficiency anaemia

E. Parvovirus infection

Question 23.5

What is the most appropriate next treatment step? Select ONE answer only.

A. Blood transfusion

B. Dietary advice

C. Oral iron

D. Oral iron and folic acid

E. Reassurance and explanation of the diagnosis

Answers 23.4 and 23.5

Question 23.4: Which is the most likely diagnosis?

A. β-Thalassaemia trait.

Question 23.5: What is the most appropriate next treatment step?

E. Reassurance and explanation of the diagnosis.
Of course, to know the treatment option, it is vital to get the correct diagnosis. Here, the rather low MCV in the presence of a normal ferritin and iron make β-thalassaemia trait easily the most likely option. In this instance, reassurance is all that is required.

Thalassaemias

The thalassaemias occur due to genetic defects that result in a reduced rate of synthesis of either α-globin or β-globin chains. α-Thalassaemia is usually due to α-globin gene *deletion*, whilst β-thalassaemia mainly occurs due to point *mutations* in the β-globin gene.

α-Thalassaemia

Each copy of chromosome 16 carries two copies of the α-globin gene and so normal individuals have four α-globin genes. Deletion of one or two copies of the α-globin gene results in α-thalassaemia trait, a condition that is generally asymptomatic. Loss of all four genes (α-thalassaemia major) leads to death *in utero* or during the first few hours of life with hydrops fetalis. Deletion of three genes results in HbH disease, which is characterized by microcytic hypochromic (low MCV, low MCH) anaemia and splenomegaly. In HbH disease, the excess of β-globin chains forms an abnormal haemoglobin called HbH, which consists only of β-globin chains, and can be detected using high-performance liquid chromatography (HPLC) or on the blood film using a brilliant cresyl blue stain. α-Thalassaemia trait does not show any abnormalities on HPLC and can only be confirmed using genetic tests to identify the α-globin gene deletions.

Case history

A 6-month-old boy of Pakistani origin presents with failure to thrive, pallor and hepatosplenomegaly. Feeding is very slow and he appears sleepy. There are no other symptoms of note and examination is otherwise unremarkable. The family moved to the UK six weeks earlier and have a healthy 2-year-old son. Parents are first cousins and know there is a family history of β-thalassaemia.

What is the likely diagnosis and how would you confirm this?

It is likely that this infant has β-thalassaemia major. This disease results from mutations in both copies of the β-globin gene on chromosome 11, resulting in the complete absence (or severe reduction) of β-globin production and an excess of α-globin chains. The free α-globin chains are highly unstable and precipitate in erythrocytes resulting in anaemia secondary to a combination of ineffective erythropoiesis and haemolysis. Anaemia triggers an increase in erythropoietin production, which drives extramedullary haematopoiesis.

Diagnosis is suggested by severe microcytic hypochromic anaemia and typical blood film changes including target cells, nucleated red blood cells and basophilic stippling. The diagnosis is confirmed by haemoglobin HPLC, which shows the absence of HbA. Genetic testing can identify mutations, which are classed as either β^0 or β^+, depending on whether they produce no β-globin (β^0) or reduced β-globin (β^+). Those with β^+ mutations may show a milder phenotype (β-thalassaemia intermedia).

High-performance liquid chromatography (HPLC): HPLC is a laboratory technique that can identify and measure the different types of Hb present in a blood sample. The pattern of Hb variants can be used for the diagnosis of most haemoglobinopathies, including β-thalassaemia and sickle cell disease, as well as uncommon haemoglobinopathies, such as HbC disease (Table 23.7).

Why does this condition typically present at this age?

Hb production gradually switches from HbF to HbA during the first 3–6 months of life. HbF is composed of α-globin and γ-globin chains ($\alpha_2\gamma_2$) and does not contain any β-globin. By contrast, HbA contains α-globin and β-globin ($\alpha_2\beta_2$). In a healthy 6-month-old infant ~95% of total Hb is HbA and less than 5% of total Hb is HbF. Thus, anaemia develops at the age of 3–6 months.

How would you treat this child and what complications must be prevented?

Children with β-thalassaemia major should be commenced on a regular (3–6-weekly) blood transfusion programme. This raises the Hb, and suppresses erythropoietin production facilitating normal growth and development.

The complications of regular lifelong transfusions for β-thalassaemia include progressive iron overload, transfusion-associated viral infection (e.g. hepatitis C) and the development of red cell alloantibodies (discussed later).

The extent of iron overload is assessed by monitoring serum ferritin levels. Iron chelation therapy is usually started once 10–15 red cell transfusions have been given and/or the serum ferritin increases above 1000 ng/mL. Traditionally, this has been in the form of subcutaneous infusions of desferrioxamine. However, effective oral preparations are now available.

Even in patients taking chelation, iron levels must be monitored using serum ferritin at 3-monthly intervals and assessment of potential sites of iron deposition, such as the heart and liver, at 1–2-year intervals using MRI scans, which can accurately

quantify iron deposition, avoiding the need for invasive biopsies.

Is it possible to cure this condition and can it be prevented in future pregnancies?

At present, the only cure for β-thalassaemia major is a haematopoietic stem cell transplant (HSCT), which carries significant risks.

Maternal screening for haemoglobinopathies with a full blood count (FBC) and HPLC is now part of routine antenatal testing in areas where there is a high prevalence of carriers. In areas of low prevalence, targeted screening of women from ethnic groups at highest risk (African, Caribbean, Indian subcontinent, Mediterranean) is performed. Newborn haemoglobinopathy screening is widely used in many countries, including the UK. Screening is aimed primarily at detecting cases of sickle cell disease, but will also identify most cases of β-thalassaemia major.

Recent development of pre-implantation genetic diagnosis (PGD) has allowed haemoglobinopathies to be prevented. This technique utilizes *in vitro* fertilization (IVF) in combination with molecular testing for globin mutations/deletions to allow unaffected embryos to be selected for embryo transfer. PGD remains a very specialized and expensive technique and is not yet widely available.

Table 23.7 Diagnosis of haemoglobinopathies by high-performance liquid chromatography (HPLC)

Disease	Hb variants
α-Thalassaemia trait	Normal
α-Thalassaemia major	Hb Barts (γ_4), HbH (β_4) and, in some cases, Hb Portland ($\zeta_2\gamma_2$)
β-Thalassaemia trait	$HbA_2 > 3.5\%$
β-Thalassaemia major	HbF 98%, HbA_2 2%, HbA 0%
β-Thalassaemia intermedia	HbF 70–80%, HbA 10–20%,
Sickle cell trait	HbS 40–50%, HbA 50–60%
Sickle cell disease	HbS 90–95%, HbF 5–10%
HbC disease	HbC 90–95%, HbF 5–10%
HbSC disease	HbS 40–50%, HbC 40–50%
HbS/β^0-thalassaemia HbS/β^+-thalassaemia	HbS > 50%, HbF 10–30%, HbA_2 > 3.5% HbS > 50%, HbA 10–15%, HbF 10–20%, HbA_2 > 3.5%

Sickle cell disease

Sickle cell disease (SCD) predominantly affects people of African, Caribbean, Middle Eastern or Indian descent. It occurs due to a point mutation in the β-globin gene (β^s-globin) that results in a single amino acid change (valine for glutamine) in the β-globin protein. The abnormal haemoglobin (HbS) is relatively insoluble and polymerizes when exposed to low oxygen tension. This results in the formation of characteristic sickle cells, which are dehydrated, rigid and less deformable than normal red cells and therefore can obstruct blood flow in the microcirculation. Any factor which increases the risk of polymerization will predispose to a sickle cell crisis; even small increases in the proportion of HbS will significantly increase this risk. Therefore, optimal hydration, oxygenation and increased quantities of HbF will be protective.

There are several forms of SCD, all of which have in common the presence of one or more copies of a β-globin gene mutation. The most common types of SCD are:

- Sickle cell anaemia – this occurs in people who are homozygous for the β-globin mutation (HbSS)
- HbSC disease – this occurs in people with a single β-globin mutation in combination with an HbC mutation (HbSC)
- S β-thalassaemia – this occurs in people with a β-thalassaemia mutation in combination with β^s-globin.

The clinical features of all types of SCD are similar, but they vary in severity both between patients and in different subtypes of the disease. In general, sickle cell anaemia has the worst clinical course, followed by S β-thalassaemia and then HbSC disease. All patients have chronic haemolytic anaemia. In addition, all patients are prone to recurrent, often unpredictable sickle cell crises, which may present as:

- Veno-occlusive (painful) crisis
- Sickle chest crisis
- Splenic/hepatic sequestration
- Aplastic crisis (secondary to parvovirus B19)
- Cerebral infarction (occurs in 11% of children unless they undergo regular screening which reduces this risk to <5%)

SCD is diagnosed using HPLC (see Table 23.7). Patients with sickle cell anaemia are unable to produce HbA and rely on HbS and small amounts of HbF.

Management of SCD is aimed at preventing complications and symptomatic treatment of painful sickle crises. The most important aspects of prevention of complications are:

- Avoidance of factors that may precipitate a crisis (e.g. cold, dehydration, over-strenuous exercise)

- Twice-daily penicillin prophylaxis and vaccination to prevent infection with encapsulated organisms (e.g. pneumococcus, meningococcus) – such infections are more common in sickle cell disease because most patients develop autoinfarction of the spleen before the age of 4 years
- Folic acid because of increased folate need due to chronic haemolysis.

Severity varies widely in SCD. A number of treatments now exist which are able to modify the severity and natural history of the disease:

- Hydroxycarbamide inhibits ribonucleotide reductase and is used to increase HbF, which reduces the occurrence of crises
- Regular (monthly) blood transfusions can prevent stroke in children with cerebrovascular disease and reduce sickle chest crises where hydroxycarbamide has not been effective. As with β-thalassaemia major, patients who have been transfused for more than a year will require iron chelation therapy.

HSCT is indicated for patients with CNS disease or with recurrent chest crises or painful crises despite hydroxycarbamide treatment.

Recent scientific advances which have improved clinical practice – prevention of stroke in sickle cell disease

Investigations into the pathogenesis of stroke in children with sickle cell disease clearly showed that these children had cerebral vasculopathy particularly affecting the middle cerebral artery (MCA). Transcranial Doppler scanning of these children showed that increased MCA blood flow correlated with the presence of vasculopathy and that children with the highest velocities on transcranial Doppler screening were at increased risk of developing a stroke within a few years. Since these findings appeared to be uniquely associated with sickle cell disease, the presumed mechanism of the vasculopathy was chronic intravascular haemolysis. The best known method of reducing intravascular haemolysis due to sickle cell disease is red cell transfusion. This led investigators to test whether regular red cell transfusion would be effective in arresting the progression of cerebral vasculopathy. The first randomized controlled trial of red cell transfusion for children with sickle cell disease and raised MCA transcranial Doppler velocity (STOP trial) showed that primary stroke could be prevented by administering regular transfusions to these children. This has now been incorporated into the routine surveillance of all children with sickle cell disease.

Bone marrow failure

Bone marrow failure is a rare condition that occurs when blood cell production is reduced due to defects in the number and function of bone marrow HSCs. Bone marrow failure usually affects all the main lineages (red cells, white cells and platelets), resulting in pancytopenia. Some rare disorders affect a single lineage (e.g. red cell aplasia, severe congenital neutropenia or amegakaryocytic thrombocytopenia).

Clinical symptoms of bone marrow failure are related to the reduction in mature blood cells of each lineage:

- Fatigue secondary to anaemia
- Increased infection secondary to neutropenia
- Bruising and/or bleeding secondary to thrombocytopenia

Case history

A 5-year-old boy has a 3-month history of increasing fatigue, pallor and bruising. His blood tests show marked pancytopenia. He is short for his age and has mild microcephaly but his developmental age is appropriate. Further examination reveals several café-au-lait patches and undescended testes.

What are the potential causes of pancytopenia and what is the most likely diagnosis in this case?

Pancytopenia is caused by the disruption of normal bone marrow function. It can be caused by:

- Bone marrow failure syndromes
- Acquired aplastic anaemia
- Acute leukaemia
- Bone marrow infiltration by lymphoma or solid tumours
- Gaucher's disease
- Osteopetrosis
- Infections such as HIV
- Drugs, including chemotherapy agents

In this case, the presence of congenital anomalies as well as blood count abnormalities (pancytopenia) suggests a genetic bone marrow failure syndrome (Table 23.8). This pattern of physical abnormalities suggests a diagnosis of Fanconi anaemia, which can also be associated with thumb and radial abnormalities, renal anomalies and a characteristic facies.

Initially, this patient should have a bone marrow examination to confirm a hypocellular bone marrow and rule out other conditions, including leukaemia.

What laboratory test can be used to confirm the diagnosis?

The 'gold standard' test for Fanconi anaemia is the chromosomal breakage test carried out in the presence of diepoxybutane (DEB). Lymphocytes are cultured to the metaphase stage of the cell cycle – in Fanconi anaemia, spontaneous chromosomal breakages or chromosomal breakages induced by DEB or mitomycin C confirm the diagnosis. It is advisable to test all siblings, as some patients with Fanconi anaemia have very few physical anomalies.

What is the pathophysiology of this disorder?

Fanconi anaemia is a disorder of a key DNA repair pathway, which is vital to maintain chromosomal integrity. To date, mutations have been identified in 16 different DNA repair genes. The proteins encoded by these 16 Fanconi anaemia (FANC) genes participate in a complicated network important in DNA repair that orchestrates incisions at sites of cross-linked DNA. This defect in DNA repair is believed to be responsible for the pleiotropic features of the Fanconi anaemia phenotype, which ranges from bone marrow failure to developmental defects and increased predisposition to leukaemia and other cancers.

What are the treatment options for bone marrow failure syndromes?

Children with inherited bone marrow failure syndromes should be managed by a specialist multidisciplinary team. If the patient is relatively well, it is reasonable to have a period of observation with transfusion if necessary. Androgens, such as oxymethalone result in a response in more than 50% of patients. However, they are associated with significant side effects, including hepatocellular carcinoma, and usually only provide transient benefit.

The only curative treatment for the haematological abnormalities in Fanconi anaemia is HSCT. However, this will not reduce the risk of solid tumour malignancies and children require lifelong monitoring.

Recent scientific advances which have improved clinical practice – gene therapy in Fanconi anaemia

In vitro experiments inserting functional genes into Fanconi anaemia cells have shown correction of haematological abnormalities and paved the way for early clinical trials. Although only showing limited efficacy, gene transfer promises to be a major advance in the treatment of many genetic diseases.

Table 23.8 Inherited bone marrow failure syndromes

Disease	Physical abnormalities	Affected gene(s)
Pancytopenia		
Fanconi's anaemia	Short stature, microcephaly, skin hyperpigmentation, upper limb abnormalities, renal anomalies, genital abnormalities	FANC genes *BRCA2*
Shwachman–Diamond syndrome	Pancreatic insufficiency, skeletal abnormalities, hepatomegaly	*SBDS*
Anaemia		
Diamond–Blackfan anaemia	Short stature, thumb abnormalities, craniofacial abnormalities	*RPS19* and other ribosomal genes
Thrombocytopenia		
Thrombocytopenia absent radii (TAR)	Absent radii, facial dysmorphism, lower limb anomalies, cows' milk intolerance	*RBM8A*

Other inherited bone marrow failure syndromes

Shwachman–Diamond syndrome

This is a multisystem disorder with a classical triad of bone marrow failure (particularly neutropenia), pancreatic insufficiency and skeletal abnormalities. It is caused by mutations in the *SBDS* gene, which is important for normal ribosome biogenesis.

Thrombocytopenia with absent radii (TAR) syndrome

This autosomal recessive disorder is characterized by the radial aplasia and absent or decreased megakaryocytes in the bone marrow. It typically presents with thrombocytopenia and can result in severe haemorrhagic complications in the neonatal period. The disease requires inheritance of a partial deletion of chromosome 1 in combination with an abnormal copy of the *RBM8A* gene.

Acquired aplastic anaemia

In most cases acquired aplastic anaemia is idiopathic although several specific causes have been identified including:

- Drugs (chloramphenicol, sulphonamides)
- Chemicals (benzene, pesticides)
- Ionizing radiation
- Viruses (Epstein–Barr virus, viral hepatitis)

Diagnosis of acquired aplastic anaemia requires a bone marrow biopsy to confirm marrow hypoplasia and to rule out other potential causes, particularly leukaemia. History and other investigations should focus on the exclusion of any of the inherited bone marrow failure disorders.

The mainstay of treatment of acquired aplastic anaemia in children is HSCT, which has an excellent outcome in this condition. Evidence suggests that aplasia occurs due to immune dysregulation and therefore patients without a suitable bone marrow donor are treated with immunosuppressive therapy, e.g. with anti-thymocyte globulin (ATG), an infusion containing antibodies targeted against human T lymphocytes. It has been shown to give good response rates in aplastic anaemia, particularly when combined with long-term ciclosporin.

Haemostasis

Normal haemostasis

Coagulation is essential for normal haemostasis and involves platelets, clotting factors and the vessel wall. The coagulation cascade describes the activation of clotting factors resulting in thrombin generation, which in turn converts fibrinogen to fibrin to produce a blood clot (Fig. 23.4). It is divided into the intrinsic and extrinsic pathways, which converge on the common pathway. Although this division is useful for the interpretation of laboratory tests (see below), in reality the two pathways operate in unison and a defect in either pathway can result in a bleeding disorder. The coagulation cascade is initiated by the exposure of tissue factor at the site of blood vessel damage, which then activates components of both the extrinsic and intrinsic pathways.

Investigation of bleeding disorders

Assessment of a child with a suspected bleeding disorder should always start with a clear history focusing on:

- Pattern of bleeding
- Bleeding challenges such as dental extraction or surgical procedures
- Family history

Question 23.6

A toddler with persistent bleeding from his mouth

An 18-month-old boy was taken by his mother to the family doctor because of persistent bleeding from a cut to the inside of his mouth and lip after a fall against furniture at home two weeks earlier. He was otherwise well and there was no family history of note. Full examination revealed a poorly healed cut on the inside of his bottom lip with recent oozing. He had no bruises or cuts elsewhere and no other abnormal findings.

Investigations:

Hb 101 g/L

WBC 6.4×10^9/L

Platelets 360×10^9/L

Prothrombin time 11.2 secs (NR 10.6–12.0)

Partial thromboplastin time 88 secs (NR 24–36)

Fibrinogen 3.0 g/L (NR 1.7–4.0)

Which of the following is the most likely diagnosis? Select ONE answer only.

A. Factor IX deficiency
B. Factor VII deficiency
C. Factor V deficiency
D. Von Willebrand disease
E. Vitamin K deficiency

Answer 23.6

A. Factor IX deficiency.

Table 23.10 is helpful in answering this question. There is a normal prothrombin time (suggesting normal levels of II, V, VII and X) but an elevated partial thromboplastin time (APTT). Therefore the problem is most likely to be a deficiency of factor VIII, IX, XI or XII. Vitamin K deficiency would cause elevation of PT and von Willebrand disease would typically present in adolescence and with a family history.

Fig. 23.4 Haemostasis: the 'coagulation cascade' of interacting coagulation factors.

Table 23.9 Tests included in the clotting screen

Test	Pathway measured	Clotting factors
PT	Extrinsic and common	II, V, VII, X
APTT	Intrinsic and common	II, V, VIII, IX, X, XI, XII
TT or fibrinogen	Fibrinogen only	Fibrinogen

APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time.

Table 23.10 Interpretation of the clotting screen

Result	Pathway(s) affected	Differential diagnosis
High PT, normal APTT	Extrinsic	Factor VII deficiency Warfarin treatment
High APTT, normal PT	Intrinsic	Haemophilia A/B Factor XI, XII deficiency Von Willebrand disease Lupus anticoagulant Heparin treatment
High PT, high APTT	Common pathway	Factor II, V or X deficiency Fibrinogen deficiency Vitamin K deficiency DIC

APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; PT, prothrombin time.

Initial investigations include a full blood count to identify thrombocytopenia and a clotting screen (Table 23.9), which should include:

- Prothrombin time (PT)
- Activated partial thromboplastin time (APTT)
- Fibrinogen level or thrombin time (TT)

Interpretation of these screening tests will provide a differential diagnosis and inform further testing (Table 23.10). Age-specific ranges must be used when interpreting clotting results.

Hereditary coagulation disorders

Inherited deficiency of any of the clotting factors can occur, but the most common deficiencies are:

- Haemophilia A (factor VIII deficiency; 1 in 5000 male births)
- Haemophilia B (factor IX deficiency; 1 in 25,000 male births)
- Von Willebrand disease (VWD)

Haemophilia A and B

Haemophilia A and B are X-linked disorders, although female carriers occasionally have mild symptoms. Male infants with a known or suspected family history of haemophilia should be screened at birth, but up to a third have no family history and are caused by new mutations.

Haemophilia usually presents with joint and soft tissue bleeds, typically when the infant begins to crawl or walk. However, neonates may present with intracranial haemorrhage and neonates with haemophilia should undergo cranial ultrasound. Increased bleeding is also seen with operative procedures, including circumcision or dental procedures. Circumcision in infancy may cause catastrophic bleeding and haemophilia is one of the commonest causes of circumcision-associated life-threatening haemorrhage.

The clotting screen in both haemophilia A and haemophilia B shows a markedly prolonged APTT with a normal PT. Diagnosis is confirmed by clotting factor assays showing a low factor VIII:C level in haemophilia A and a low factor IX:C level in haemophilia B. Diagnosis of mild haemophilia B may be difficult in the neonate due to physiologically low levels of factor IX (vitamin K dependent). If the diagnosis is in doubt, family studies should be performed and factor assays repeated at age 3–6 months.

Disease severity in haemophilia A and B is related to the plasma factor level:

- Severe: <1%
- Moderate: 1–5%
- Mild: >5%–40%

Historically, haemophilia was an extremely debilitating disease. Haemarthroses would lead to the development of arthritis, joint deformity and disability before adulthood. However, the development of factor concentrates from recombinant sources has revolutionized the clinical course. Bleeds should be treated with prompt administration of factor concentrate. The amount of factor given and the duration of treatment depends on the type of bleed. A single dose to increase factor levels >30% is usually sufficient for mild soft tissue bleeds, whilst regular doses over several days to maintain factor levels at 50–100% may be necessary in haemarthroses or other major bleeds, e.g. intracranial, gastrointestinal. Similarly, any operative procedures should be covered with appropriate factor treatment.

In severe haemophilia, prophylaxis with factor concentrate 2–3 times per week reduces spontaneous bleeding episodes and is now routinely started in children from around 2–3 years of age.

The main complication of factor treatment is the development of inhibitor antibodies that block efficacy of the factor. They are most commonly associated with factor VIII treatment and usually develop in children during the first 25 exposures. In patients who develop inhibitors, bleeds are usually treated with a factor VIII bypassing agent that can promote clot formation independently of the intrinsic pathway. Immune tolerance, involving the use of frequent high

doses of recombinant factor over several months, can be used to eliminate the inhibitor in the majority of cases.

Desmopressin (DDAVP) can be used as an alternative to factor concentrate in mild haemophilia A (not haemophilia B) to treat minor bleeds and as prophylaxis for minor procedures such as dental extraction. It functions by stimulating the release of factor VIII and von Willebrand factor and can be given intranasally or as an infusion.

Von Willebrand disease

Von Willebrand factor (VWF) is a large glycoprotein present in endothelial cells and platelets. It has two main functions:

- To promote platelet adhesion to damaged endothelium
- To bind and stabilize factor VIII, protecting it from proteolytic degradation.

Von Willebrand disease (VWD) occurs due to the reduced production of normal VWF or due to the production of an abnormal form of VWF. It is divided into three types:

- Type 1 – Partial deficiency, autosomal dominant, common, usually mild
- Type 2 – Production of functionally abnormal VWF, rare, variable severity
- Type 3 – Complete deficiency, autosomal recessive, very rare, severe

Presentation of VWD is usually with mucosal bleeding (particularly menorrhagia), easy bruising, or excessive bleeding following a surgical procedure. Type 1 VWD is often mild and may not present until adolescence or adulthood.

VWD can be confused with haemophilia A as the clotting screen will usually show a prolonged APTT and the factor VIII:C will be reduced due to the disruption of VWF binding. Diagnosis is therefore confirmed using the VWF ristocetin cofactor assay. In this test, the addition of ristocetin (an antibiotic) to the patient's plasma causes VWF to bind to platelets, resulting in agglutination. Agglutination is diminished or absent in VWD.

Bleeding in mild VWF can usually be treated with antifibrinolytic drugs such as tranexamic acid, which inhibits the conversion of plasminogen to plasmin, preventing the breakdown of fibrin clots. Tranexamic acid can also be used to prevent excessive bleeding during simple operative procedures, such as dental extraction. For more severe episodes of bleeding or prophylaxis in association with more extensive surgery, desmopressin may be used. VWF concentrate is reserved for major bleeding and for management of severe VWD.

Acquired coagulation disorders

Haemorrhagic disease of the newborn

The vitamin K dependent clotting factors (II, VII, IX, X) are low at birth and fall further in breastfed infants over the first few weeks of life. Vitamin K is therefore given to all infants on the first day of life to prevent bleeding. A single intramuscular dose of vitamin K is sufficient to prevent haemorrhagic disease of the newborn. Prior to the introduction of vitamin K prophylaxis, bleeding occurred in up to 1 in 100 births, with potentially life-threatening consequences, particularly intracranial or gastrointestinal bleeding. Although a single dose of oral vitamin K is usually effective, failure rates for single dose orally administered vitamin K in prevention of haemorrhagic disease of the newborn occur at rates of just over 1 per 100,000 live births. Therefore, if oral vitamin K is given, repeated doses should be administered on a weekly basis in breastfed babies as absorption is unreliable. Oral vitamin K is fat soluble and inadequately absorbed in children with malabsorptive states including cystic fibrosis or cholestatic jaundice.

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is a process in which excessive activation of the clotting system results in inappropriately increased fibrin deposition and consumption of clotting factors and platelets. It can be caused by a wide range of factors, including:

- Infection (Gram-negative, meningococcus)
- Malignancy
- Trauma or severe burns.

The clinical picture is usually dominated by excessive bleeding, although thrombotic complications can also occur. Investigations show prolonged PT and APTT, raised fibrinogen and low platelets. Treatment should focus on treating the cause. In severe cases, platelet transfusion and replacement of coagulation factors (e.g. by giving cryoprecipitate or fresh frozen plasma) may be required.

Lupus anticoagulant

The finding of an isolated prolonged APTT in an otherwise well child is a relatively common finding. Whilst this may indicate a clotting factor deficiency, the first step is to repeat the APTT with a 50:50 mixing step in which normal control plasma is mixed with the patient's plasma:

- If a clotting factor deficiency is present, the APTT will normalize
- If the APTT remains prolonged, this implies the presence of an inhibitor in the patient's plasma.

In children this is most commonly due to a lupus anticoagulant, an antibody that usually develops following viral infection (e.g. measles, adenovirus) or *Mycoplasma* infection. Importantly, the antibody mainly causes prolonged clotting in the laboratory test and usually has no clinical significance. In most cases it resolves within a few weeks. Children with persistence of lupus anticoagulant should be investigated for underlying autoimmune disease.

Thrombocytopenia in children

Case history

A 6-year-old girl presents with a 2-week history of easy bruising and gum bleeding when brushing her teeth. She has previously been well other than a mild coryzal illness two weeks ago. There is no family history of note. Her FBC shows a platelet count of 3×10^9/L but is otherwise entirely normal.

What is the differential diagnosis and which is the most likely diagnosis in this case?

There is a wide differential diagnosis for thrombocytopenia in children. If associated with other abnormalities in the FBC, acute leukaemia or bone marrow failure should be considered. However, in this case there is an isolated thrombocytopenia and possible causes are shown in Table 23.11.

As she is otherwise well and there is no previous history of any bleeding problems, the most likely diagnosis is immune thrombocytopenic purpura (ITP). This disorder occurs due to immune-mediated destruction of platelets leading to a low platelet count despite normal or increased marrow production. It is usually triggered by a viral infection, as suggested in this case by the recent coryzal illness.

What other investigations would you perform to confirm the diagnosis?

ITP is a diagnosis of exclusion and it is therefore imperative to rule out other potential causes based on findings in the history and examination. The blood film should always be examined but a bone marrow examination is not necessary unless other blood count abnormalities or clinical findings increase suspicion of leukaemia. The blood film is also important to assess for inherited platelet disorders or bone marrow failure.
Inherited platelet disorders:

- *Bernard–Soulier syndrome*: Deficiency of the platelet glycoprotein GPIb disrupts platelet–VWF binding resulting in a moderate bleeding tendency. Platelet count is mildly reduced and blood film examination shows characteristic giant platelets.

- *May–Hegglin anomaly*: An autosomal dominant disorder due to a mutation in the *MYH9* gene that codes for non-muscle myosin heavy chain IIa. Blood film shows large platelets and inclusions in the neutrophils. Patients are often asymptomatic or show only a mild bleeding tendency.

- *Glanzmann thrombasthenia*: This autosomal recessive disorder occurs due to deficiency of the platelet glycoprotein GPIIb leading to failure of platelet aggregation. This results in a severe bleeding tendency despite a normal platelet count.

Inherited platelet disorders are diagnosed using platelet function assays and family studies.

How would you treat her initially?

ITP in children is usually a self-limiting disease that will resolve spontaneously within a few weeks. In those with mild to moderate bleeding, it is usually possible to adopt a 'watch and wait' policy, as severe bleeding is rare even in children with a platelet count <10×10^9/L.

What other treatments are available if she fails to improve?

Treatment may be necessary in those with severe bleeding or when ITP fails to resolve within 6 months (chronic ITP) and bleeding problems are interfering with daily life. First choice treatment is usually a short course of oral steroids (prednisolone). Many haematologists recommend a bone marrow examination before starting treatment with steroids in case this treatment masks leukaemia which may also transiently respond to steroid treatment. Intravenous immunoglobulin may also be useful for management of acute bleeding episodes of moderate severity or to raise the platelet count preoperatively. Platelet transfusion is reserved for severe bleeding, such as a gastrointestinal or intracranial haemorrhage, although these complications are very uncommon in childhood ITP.

Table 23.11 Causes of thrombocytopenia in children

Inherited	• Bernard–Soulier syndrome • May–Hegglin anomaly • Wiskott–Aldrich syndrome

Acquired	• Immune-mediated destruction
	  • Immune thrombocytopenia (ITP)
	  • Systemic lupus erythematosus (SLE)
	  • Infection (HIV, hepatitis B)
	• Mechanical destruction
	  • Haemolytic-uraemic syndrome (HUS)/ thrombotic thrombocytopenic purpura (TTP)
	  • Disseminated intravascular coagulation (DIC)
	  • Congenital heart disease
	  • Giant haemangioma (Kasabach–Merritt syndrome)
	  • Hypersplenism

Thrombocytopenia in the neonatal period

Thrombocytopenia is relatively common in the neonatal period, occurring in a third of infants admitted to neonatal units. In most cases it is mild and is due to placental insufficiency (IUGR) or maternal hypertension and improves spontaneously in the first week of life. Thrombocytopenia developing after the first few weeks of life is mainly due to sepsis or necrotizing enterocolitis. In otherwise well term infants, the most common cause of severe thrombocytopenia is neonatal alloimmune thrombocytopenia (NAIT) (see Chapter 10, Perinatal medicine).

Thrombosis in children

Acquired risk factors

Thrombosis is uncommon in children. When it occurs, it is almost always associated with an underlying hypercoagulable state such as:

- Presence of a central venous line
- Malignancy
- DIC
- SLE
- Trauma
- Polycythaemia

In addition, chickenpox is an important cause of stroke in childhood. This occurs due to a reduction in the level of the natural anticoagulant Protein S, which increases the risk of thrombosis.

Inherited risk factors

An inherited deficiency in any of the natural anticoagulants can lead to an increased risk of thrombosis. This is known as inherited thrombophilia. The main causes of clinically important inherited thrombophilia are deficiencies of:

- Antithrombin – inhibits thrombin and factor X
- Protein C – inhibits factors V and VIII
- Protein S – enhances action of protein C.

Homozygous deficiency (loss of both copies of the gene) in any of these factors markedly increases the risk of thrombosis. Homozygous deficiency of protein C and protein S present in the neonatal period. Antithrombin deficiency does not usually present until adulthood. The role of heterozygous deficiency is less well defined in children but is likely to increase the risk of thrombosis only when other risk factors (e.g. surgery) are also present.

The most common inherited thrombophilia is caused by the presence of the factor V Leiden mutation, which prevents protein C binding to and inhibiting factor V. This occurs in up to 5% of the population and leads to a very mild increase in the risk of thrombosis.

Transfusion in children

Blood groups and red cell antigens

Red blood cells express a large number of antigens on their surface that are important for normal cell function. These antigens are significant when considering transfusion, as transfusion of donor red cells expressing an antigen which the recipient lacks may lead to the development of red cell antibodies. This can result in a transfusion reaction or, in women and girls, to the risk of haemolytic disease in their offspring.

Red cell antigens are organized into more than 30 blood group systems, the most important of which is the ABO system. The clinical significance of the ABO system stems from the fact that, unlike other systems, individuals naturally produce antibodies against the red cell antigens they lack (Table 23.12). Therefore, transfusion of an ABO-incompatible unit of blood can cause a severe, potentially fatal, acute transfusion reaction.

The other main red cell antigen system of clinical importance is the Rhesus system and, in particular, the RhD antigen. The majority of the Caucasian population (85%) is RhD positive. RhD is extremely immunogenic, which means if an RhD negative person is exposed to RhD positive blood, they are very likely to develop an antibody, which can cause transfusion

Table 23.12 The ABO blood group system

Group	Antigens	Antibodies produced	Compatible groups for transfusion	Frequency (%)
A	A	Anti-B	A, O	42
B	B	Anti-A	B, O	9
AB	AB	None	A, B, AB, O	3
O	None	Anti-A, Anti-B	O	46

Case history

Anaemia and jaundice at 12 hours of age

A term neonate is found to be jaundiced on the first day of life. The family has recently arrived from Somalia. It is the mother's second pregnancy; her first child was entirely healthy. Investigations at 12 hours reveal that the infant is anaemic with Hb 70 g/L and bilirubin 300 μmol/L. The mother's blood group is A RhD negative. The infant's blood group is A RhD positive.

What is the likely diagnosis and what is the pathogenesis of this condition?

Jaundice within the first 24 hours of birth suggests haemolysis. In this case, the mismatch between the maternal and infant blood groups suggests that this is haemolytic disease of the newborn (HDN) due to RhD incompatibility.

HDN occurs when the mother carries an antibody against an antigen on the red cells of the fetus. The most common antibody is anti-D although other antibodies can be seen including anti-C, anti-E and anti-Kell. Red cell antibodies develop during pregnancy when the mother is sensitized against fetal red cell antigen(s). This usually occurs due to small feto-maternal haemorrhages, particularly at the time of birth, but can also occur with miscarriage, amniocentesis or other invasive procedures. In subsequent pregnancies, red cell antibodies can then cross the placenta and bind to fetal red cells resulting in red cell destruction (haemolysis).

How would you treat the infant?

This infant requires immediate treatment with intensive phototherapy. The baby is likely to need an exchange transfusion to prevent excessively high hyperbilirubinaemia. Late anaemia (age 3–6 weeks) is common in RhD haemolytic disease of the newborn even where there was no significant anaemia in the first week of life.

How can this condition be prevented?

Pregnant women should have a blood group and antibody screen performed at booking to identify those who are RhD negative. Repeat antibody screening at 28 weeks of pregnancy of women found to be RhD negative is performed to identify sensitization during pregnancy. RhD-negative women who still lack anti-D antibodies in the second trimester should be given anti-D prophylaxis at 28–34 weeks' gestation to prevent sensitization. In addition, anti-D should be given to the mother after any invasive procedure (e.g. amniocentesis) and following birth.

If anti-D antibody is detected during pregnancy, the antibody level should be measured to predict the risk of developing HDN. The fetus is monitored by Doppler ultrasound, as intrauterine transfusions may be required if significant anaemia develops.

reactions and red cell alloimmunization in pregnancy (discussed below).

Red cell transfusion

Red cell transfusion is used for the correction of symptomatic anaemia. The volume of red cells transfused is based on the patient's weight and the desired increment in Hb:

$$\text{Volume to be transfused (mL)} = \text{Weight (kg)} \times \text{Hb increment (g/dL)} \times 4$$

Safe transfusion requires:
- ABO and RhD grouping of patient
- Antibody screen to identify antibodies in the patient's serum
- Selection of a compatible red cell unit
- Final crossmatch to ensure the unit is compatible.

Transfusion of other blood products

In addition to red cells, the most frequently transfused products are platelets and fresh frozen plasma (FFP).

Platelets are commonly used in patients who develop thrombocytopenia due to chemotherapy or in those with inherited platelet disorders. As they are suspended in a small volume of plasma, platelets must be compatible with the patient's ABO group.

FFP is prepared from plasma removed from fresh blood and stored at −30°C. It is most commonly used to correct clotting factor deficiencies when a recombinant form of the factor is unavailable.

Complications of transfusion

Although transfusion is extremely safe, complications do occur:

Acute complications:
- Infection: bacterial or viral (now very uncommon due to use of screened products)
- Hypocalcaemia (more common in neonates than in infants or children)
- Volume overload
- Citrate toxicity
- Rebound hypoglycaemia (high glucose levels from blood additives)
- Hyperkalaemia (from large volume transfusion)
- Transfusion-associated graft-versus-host disease (GvHD; if non-irradiated products given to those at risk)
- Haemolytic transfusion reaction:
  – Is due to the transfusion of an incompatible unit of red cells, particularly ABO incompatibility

- If severe, results in massive haemolysis, haemodynamic shock and renal failure
  - Treatment involves supportive management and full investigation into the circumstances of the reaction
- Transfusion-related acute lung injury (TRALI)
  - Due to leukocyte antibodies in plasma
  - Results in severe respiratory compromise
  - Treatment is supportive

Long-term complications:

- Alloimmunization: production of red cell antibodies by patients who receive a transfusion of donor cells expressing red cell antigens not present in the patient
- Iron overload

Further reading

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Max Davie, Jacqui Stedmon

CHAPTER

24

Child and adolescent mental health

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Understand the context of child mental health within paediatrics
- Understand the social, moral and cognitive development of children
- Be aware of the determinants of mental health
- Understand the 4Ps framework and how common emotional and behavioural problems may evolve
- Know about common emotional and behavioural problems, such as sleep problems, feeding problems, disruptive behaviour, eating disorders, chronic fatigue syndrome, recurrent unexplained somatic symptoms
- Understand the basis of the management of emotional and behavioural problems
- Be aware of the pharmacology of the main medications used in child mental health

Introduction

Why does children's mental health matter?

A child's emotional well-being is the single strongest predictor of adult life-satisfaction, greater than physical health, economic factors or educational level. Therefore, child mental health should be a key public health priority, and is fast becoming so.

Mental health disorders are common; since the 1960s there has been a fairly stable prevalence rate of around 10% in children under the age of 16 years. It is estimated that a further 10% have significant difficulties, yet are not clinically diagnosable. The rate rises to close to 40% in children and young people with co-existent physical health conditions. The risk is highest in young people with central nervous system disease. There are other known risk factors. Young people facing adverse life circumstances also have an increased prevalence of poorer physical and mental health. In the UK over the past 40 years, income inequality has spiralled, leaving an estimated 1 in 4 children living in relative poverty. Mental health conditions

also represent the single biggest cause of morbidity in adults and half have symptom onset before the age of 15. Mental health is everyone's business and needs to be tackled at grass roots level.

To take one very stark example, let us consider eating disorders. Eating disorders are now more common in children than meningococcal disease; its peak incidence at age 15 is markedly greater than a number of chronic illnesses including type 1 diabetes. Around half of patients with anorexia nervosa who will die of medical complications, and death rates in children in the UK are comparable with both asthma and diabetic ketoacidosis. Although it is a psychiatric diagnosis, the key medical aspects of care, especially those relating to being critically underweight, mean that they commonly present to paediatric services.

Why should paediatricians get involved in children's mental health?

Even with an optimally funded Child and Adolescent Mental Health Services (CAMHS) system, children with mental health problems will present to

paediatricians. Some 40% of paediatric outpatient attendances involve an emotional or behavioural element, and if one turns to recurrent abdominal pain, the rate of significant mental health problems rises to around 80%.

In community paediatrics, the overlap with mental health is unavoidable, especially as safeguarding and the assessment of neurodevelopmental conditions such as attention deficit hyperactivity disorder (ADHD) are at the core of community work.

Emotional and behavioural development

Since feelings, thoughts and actions are a source of mutual influence throughout life, the development of emotions and behaviours in children run in tandem, and both are mediated by the individual's stage of cognitive development. While it is important to understand the child's general intellectual abilities, the ability to think about others and to engage in reasoning are of greater relevance for formulating behavioural and emotional difficulties.

So how is cognitive development relevant to formulating emotional and behavioural difficulties in children? First, it is helpful to have a normative framework so that carers have a realistic expectation of how children think. For example, an egocentric toddler is not being wilfully selfish to upset his mother. Second, because there are qualitative differences in how children make sense of the physical world compared to adults, their feelings and actions may be triggered by misunderstandings. For example, a 5-year-old who has become upset and clingy since her (recently deceased) grandmother has stopped visiting may genuinely not understand that dead people cannot come back and that they no longer have thoughts and feelings. Finally, when talking about illness with younger children, showing rather than telling may get the message across better.

Cognitive development

Piaget proposed that cognitive development can be divided into phases, although we now recognize that these are not rigid and that the pace and patterns of cognitive development may vary significantly across children and cultural groups.

Below the age of two years, during the *sensorimotor stage*, infants' mental experiences are dominated by bodily sensations and a focus on their own actions as they begin to build up cognitive representations of an external world of objects. With the rapid acquisition of language during the *preoperational stage*, young children increasingly develop mental symbols to represent people, objects and actions in the physical world. Until 6–7 years, children's thinking is limited and they quite literally can only see things from their own cognitive viewpoint. With limited memory ability, they tend to focus on the here and now and will struggle to focus on more than one aspect of an event at any given time. Hence, children at this stage are egocentric and their intellect is characterized by attributing life-like qualities to inanimate objects, or imagining somewhat omnipotently that they can make something happen merely by thinking about it. They are overly swayed by how things appear and struggle to understand that invariant properties of objects (such as number, weight, mass and volume) remain unchanged even when the objects themselves are rearranged in some way. Hence, this stage is dominated by the child's immediate perception of the world around them.

Between the ages of 6–7 and 11–12 years, the *concrete operational stage*, children are rapidly gaining an understanding of basic concepts about causality, time, space and matter as they develop the ability to hold several ideas in mind at the same time and carry out mental processes on the content. Of course, in modern cultures, intellectual growth is facilitated through statutory education by teachers who are trained in child development and by access to the worldwide web. Piaget proposed that the capacity to manipulate abstract, hypothetical and symbolic information was not reached until adolescence. This final *formal operations stage* is characterized by the ability to solve problems using scientific methodology and to think rationally and logically.

Social and moral development

We know that infants are born with innate neurological pre-wiring to engage in social relationships. They are equipped at birth to make eye contact, to follow another's gaze, to mimic human facial gestures, commonly sticking out their tongue, and later to engage in turn-taking, such as games of 'peekaboo'.

The child's sense of self emerges from the way that other people react to them; we come to know ourselves through our interactions with others. For example, if a baby cries when a fun toy is withdrawn, a parent might respond by repeating the sequence, perhaps saying, 'Let's make that squeaky noise again' and laughing with their child. Alternatively, if a baby looks alarmed and cries at the toy, a parent might quickly put it away and soothe her instead. Both actions demonstrate that the parent is able to function reflectively to hold their child in mind, sometimes referred to as 'mind-mindedness'. The parent is also mirroring for the baby that she has been understood and that her feelings are meaningful to others.

Owning a sense of self is an important milestone for a child as this differentiates them from other people and confers a powerful sense of agency. In a classic experiment, it was shown that infants aged 18–24 months recognized themselves in a mirror. When a red spot was surreptitiously painted on their nose, at this age infants would see this in the mirror and touch it on their own faces, showing amusement or consternation. Younger infants do not respond in this way. Toddlers can begin to work out the intentions, feelings and beliefs of others so as to make sense of the social world around them. Psychologists often refer to this ability to understand the mental states of others as having 'a theory of mind', although, at least initially, children's empathic responses may be intuitive, rather than mediated by social cognition.

At around the same time as children develop a sense of self, they also demonstrate a capacity to infer what someone else is trying to do (i.e. their hidden intentions) and to use simple words to label their own mental states (the 'I want' and 'No' will be all too familiar to parents!). Over time, children develop a more sophisticated perspective, acquiring skills through interacting within their social environment, including playing with friends, and engaging with parents and siblings. By the time they reach 4 or 5 years of age, they are able to pass a classic 'false belief test', demonstrating the ability to take another's point of view when it is different from one's own. This can by demonstrated with the 'Sally–Anne test'. In a nutshell, the child observes a doll, Sally, hiding a marble in a box before going out to play. Another doll, Anne, comes along, takes the marble, and places it elsewhere, say in a cupboard. Sally returns and the child is asked where she will now look for the marble. Younger children wrongly assume Sally will think the same as themselves and go to the new hiding place. From the perspective of understanding children's emotional and behavioural development, having a theory of mind equips them to anticipate and make judgements about how their own actions and feelings reciprocally impact on others.

We now know that there are a number of factors that both facilitate and inhibit social development and will impact on children's emotional and behavioural development. Having parents who struggle to tune into their child's emotional world, perhaps because they themselves had difficult childhoods or are experiencing mental health problems, or are living with harmful relationships characterized by domestic violence, delays social cognition. In extreme cases of neglect, such as observed in Romanian orphans, there is evidence of lifelong impairment in structural brain development. Structural changes are more subtle in those children living in the UK who have been abused or maltreated. Deficits in language and cognition, social and communication skills and emotional regulation persist.

Historically, philosophers and theologians have debated whether infants are born with original sin that requires eradicating through strict discipline, or resemble blank slates that are environmentally shaped, or whether childhood is rather more a romantic age of innocence. Research reveals something more interesting; that given a safe and secure environment, infants are instinctively prosocial but this basic capacity for kindness can be attenuated or even reversed by adverse life circumstances, including abusive parenting.

Infants as young as 10 months demonstrate clear preference for a victim character rather than an aggressor. By 15 months, toddlers will pick up an object dropped by an adult, seemingly with no expectation of a reward apart from the mere act of being helpful. At the same age, in experimental situations, children demonstrate a sense of fairness, anger against unfairness and evident surprise at unkind behaviour. However, it seems that good experiences of parenting and a safe environment are significant factors in nurturing these innate prosocial behaviours. Furthermore, the development of altruistic empathy is neurologically linked to the self-regulation of behaviours, including the ability to tolerate waiting for a reward. It seems that such a deceptively simple milestone paves the way to success in adulthood across diverse domains in life, including future employment and intimate relationships. In the 1970s, a famous study was designed to test a child's ability to delay gratification. Children aged 4–6 years were sat close to one delicious treat, such as a marshmallow, and told that if they waited for 15 minutes they could instead have two of them to eat. When these children were followed up as adults, those who were better able to delay gratification at a young age were relatively more successful. Competence in inhibiting behavioural impulses for strategic gain also depends on emotional maturity and self-regulation and develops in tandem with acquiring a theory of mind. This yoking of emotional and behavioural development is biologically mediated through shared executive brain mechanisms involving the prefrontal cortex. Conceptually, perhaps having a theory of mind allows one to imagine a future self as well as thinking about the mental state of others.

Determinants of mental health

Why do some children run into trouble with their mental health, and not others? What implications are there for practice from the answer to this question?

One very influential text in this field is called *From neurons to neighborhoods*, and thinking about this image is a good start, but in fact we need to begin at a more basic level than the neuron.

Genetic influences

A small but important minority of children with mental health problems have these as part of either a chromosomal trisomy or a single gene disorder. Even here, however, while some difficulties may stem directly from the conditions, others will result from, for example, frustration caused by other developmental problems.

For instance, there is an increased incidence of behavioural problems in Down's syndrome. The popular view of them as happy-go-lucky, cheerful souls conceals the significant behavioural difficulties encountered by many of them, combined with parental responses to coping with a vulnerable child, as shown in Box 24.1.

Box 24.1 Behavioural problems in Down's syndrome

Wandering/running off

This is a common complaint related to cognitive immaturity, impulsivity and social naivety.

Stubborn/oppositional behaviour

At times, oppositional behaviour may be an individual's way of communicating frustration or a lack of understanding due to their communication/language problems. Children with Down's syndrome are often good at distracting parents or teachers when they are challenged with a difficult task.

Attention problems

Individuals should be evaluated for attention span and impulsivity based on developmental age and not strictly chronological age. Anxiety disorders, language processing problems and hearing loss can also present as problems with attention.

Obsessive/compulsive behaviours

This type of behaviour is seen more often in younger children with Down's syndrome. Increased levels of restlessness and worry may lead the child or adult to behave in a very rigid manner.

Autism spectrum disorder

Autism is seen in approximately 5–7% of individuals with Down's syndrome. The diagnosis is usually made at a later age (6–8 years of age) than in the general population.

Some of these difficulties may be inevitable, but for others there is potential for helpful early intervention. For instance, parents can be informed about the tendency of the children towards rigid behaviours, and take steps to help them cope, for example by early use of visual timetables, and careful preparation for transitions.

For most children with mental health difficulties, genetics exerts a 'gravitational pull', rather than determining the presence or absence of disorder. For instance, the heritability of ADHD is consistently estimated as around 80%, and yet the search for identifiable genetic changes to account for this figure has been largely fruitless. The same is proving to be true across child mental health.

Over and above the biological contribution of genetic information to final phenotype, environmental influences shape ongoing development. Some, but not all, of this influence is mediated by epigenetic mechanisms, but epigenetics is a mechanism, not a causative factor in its own right.

Environmental influences

Environmental influences can be classified by levels of description:

- Social/cultural
- Interpersonal
- Psychological
- Neurological
- Cellular

Take the example of domestic violence; clearly, this is a social phenomenon, and the normalization of violence against women plagues many cultures. Most research on the impact of violence focuses on the interpersonal, family level, via the effect on children of fear of one partner, and disorganized and confused responses to the other. However, the process also occurs at a neurological level, and we see evidence of effects on the limbic system. These brain level changes are in turn mediated by cellular changes, with neuroendocrine influences to the fore – exposure to violence seems to be associated with chronic cortisol elevation, and cellular damage.

What social influences affect children's mental health?

We know that disruptive behaviour, and the diagnoses for which disruptive behaviour is a required feature, are more often reported in deprived socio-economic groups. There may be a genetic influence even here, as the traits that lead to disruptive behaviour are also maladaptive in education and employment, so parents possessing these traits may find themselves

disadvantaged economically. On top of this, poverty robs the family of the resources, both financial and in terms of time, skills and emotional resilience, required to deal with disruption. Finally, deprived families have been found to have a more coercive parenting style, which is counterproductive (see Parenting, below).

The issue of electronic media is a current political and clinical hot topic, and the data quoted is likely to rapidly become out of date. There is an established link between more than 4 hours of *weekday* computer gaming (that is, after school) and low levels of well-being. However, it may be that unhappy children are escaping into gaming, as low levels of gaming are associated with higher levels of well-being than no gaming at all!

There does also appear to be a link between diagnosis of disruptive disorders (ADHD, autism spectrum disorder (ASD), conduct disorders) and diet, exercise and screen time. Again, this does not appear to be causal. Diet seems impossible to separate from broader socio-economic deprivation, as does exercise. Emerging evidence suggests that children with these disorders may seek out screen-based activities because these are easy to concentrate on, do not involve social failure or rejection, are perfectly structured and in many ways are highly predictable.

Substance misuse looms in adolescence, and appears to be both a consequence and cause of both poor subjective well-being and disruptive behaviour.

Sleep, both quality and quantity, is a vital support to emotional and behavioural resilience. Substance misuse, caffeine, use of screens late at night and anxiety can all impact on sleep, and can often be addressed with fairly simple interventions (see Further reading).

Answer 24.1

B. Having fun as a family and good sibling relationships.

According to the NatCen study, *Predicting well-being*, the answer is having fun as a family and good sibling relationships. This is important knowledge for paediatricians.

Attachment

Attachment theory is an influential framework in psychology, which suggests the development of a set of expectations during the first few years, based on the child thinking of his/her carer as a 'secure' base from which to explore the world. This kind of security is extended in later life to include friends, partners and the person's own memories and feelings. Parents who attune to their child's emotional and physiological states, and respond so as to reduce discomfort and promote pleasant feelings, tend to foster children's attachment and security.

A very small number of children seem unable to form attachment relationships, even in the absence of other developmental problems; this condition, attachment disorder, appears to have a strong genetic basis. Other problems with attachment seem more likely to stem from a poor 'match' between infant cues and carer responses.

Carers who are unresponsive, unpredictable or frightening can lead to a disorganized pattern of attachment, where the child cannot settle on a single attachment strategy, and is, in turn, unpredictable. This pattern of attachment is associated with later psychopathology of all types across the lifespan.

Of less certain long-term significance is the distinction between secure and insecure attachment styles in the child. This categorization is based on observation of the strategies used by children when they are being parted from their carer. Around 40% of children show 'insecure' behaviours, stemming either from the overexpression or underexpression of their distress at separation. These responses should not be regarded as 'abnormal' and are better understood as commonly occurring adaptive strategies used by children to elicit optimal protective behaviour from their carers, who themselves might not be so finely attuned to the emotional needs of others. While this distinction may not be crucial in determining psychopathology, it can be a useful way to think about particular cases.

As well as providing a secure base via attachment processes, parents and carers provide the child with opportunities for exploration and play, and feedback on their efforts. This innocuous-sounding sentence conceals a wealth of complication. Take language, for

Question 24.1

Well-being of children

What is the best determinant of a child's well-being, at a population level? Select ONE answer only.

A. All early childcare within the home and living away from inner cities
B. Having fun as a family and good sibling relationships
C. 'Nuclear' family structure and level of parental literacy
D. Parental income and quality of school attended
E. Quality of diet and opportunity for regular exercise

example: the job of parents is to provide motivation for speech; that is, something to talk about. They must then ensure that the child's attempts at language are listened to, which means being, as far as possible, available to respond briefly. Responses should encourage further attempts at communication, so parents should be encouraging even if the answer to a specific enquiry is 'no'. In conflict situations, parents need to encourage children to verbalize their feelings, as this will allow them to be processed and resolved. This is not the beginning of a parenting manual, but an example of how the very simple principles of good parenting play out in the complexity of everyday family life across domains of development.

The best data on children's subjective well-being was gathered in the 2013 NatCen study, *Determinants of well-being,* which surveyed a large cohort of seven-year-old children and their parents in the UK. It found that the most important determinants are social relationships. The children most likely to regard themselves as always happy were those who got on well with their siblings, had fun together with their family at weekends, and had lots of friends. They were also more likely not to bully others, and were less likely to be bullied themselves. Somewhat surprisingly, regular exercise was associated with, but did not predict, better well-being. Poor diet was not associated with worse well-being, but there seemed to be a link between very low levels of worry and consumption of junk food, seemingly suggesting that a little worry is actually good for us!

For adolescents, feeling supported and doing activities together, such as eating a meal, remain crucial, although the quality of peer relationships and lack of bullying become statistically significant.

Child abuse and neglect act at multiple levels to impact upon children's behaviour and well-being. The category is too broad to generalize the mechanisms, but attachment, self-image, nutrition and chronic stress all contribute. Of course, the child's own behaviour is an important determinant of their treatment by others, and so the causal influences are dynamic and reciprocal, not one-way.

Psychological characteristics

Children are not inert vessels into which we pour environmental influences. They have different temperaments, and the study of personality theory within psychology has identified many stable traits that vary between people. For children, individual differences in their emotional irritability, ease of temperament, locus of control, self-efficacy, novelty-seeking behaviour, self-esteem, anxiety and callous–unemotional traits, to name but a few, can influence feelings and behaviours. Again, the child's own individual make-up will reciprocally influence interactions with their

physical and social environments, potentially shaping pathways to problems or success in life.

A key feature of humanity is our capacity for both introspection and agency; so thoughts, beliefs and attitudes about ourselves influence emotion and behaviour. For example, we know that optimism in a child is a powerful tool for emotional resilience, and that optimism is promoted by positive, specific adult comments, and parental responsiveness. Every clinical encounter provides an opportunity to promote this resilience, for example by asking about strengths, talents, abilities, achievements, hopes, aspirations and wishes.

This is described further in the section on emotional and behavioural development, above.

Neurological level

The brain is the arena upon which causal influences play out, and so the neurological findings (scan, EEG) associated with mental health problems are best thought of as a description, rather than 'causes' of mental dysfunction.

Much attention has recently been focused on discovering reliable imaging or EEG changes to aid the diagnosis and management of neurodevelopmental disorders. This has been a frustrating search, as one might expect, given that these are behaviourally defined syndromes, and the connection between brain structure and behaviour is unlikely to be straightforward. Nonetheless, some recent work has suggested a reproducible finding in ADHD of reduced dopamine receptor availability in the thalamus. However, this is not a structural change, but an alteration in the distribution of biochemistry within the brain. This linkage between structure and cellular processes is likely to be a fruitful area for further research.

Cellular mechanisms

This is the level at which drug treatment acts, but as described in the section on psychopharmacology, below, the mechanisms are only superficially understood. Research on how environmental influences act at a cellular level is likewise in its infancy. Perhaps the best studied mechanism is the influence of cortisol on the developing brain.

Cortisol is secreted in response to physiological and psychological stress. Acutely raised cortisol does not seem to be harmful to the developing brain. It is chronically raised levels that appear to affect development, especially within the limbic system. This effect seems to occur both ante- and postnatally, with greatest impact occurring before 3 years. For most study populations, this is a modest effect, only subtly visible on imaging, but with important implications for childcare and safeguarding policy.

Nutrition is frequently emphasized as important for the developing brain, but the evidence for the influence of specific nutritional constituents (e.g. fish oils) is poor or non-existent. It seems that children are fairly resilient to a variety of diets, and that the most promising period for optimizing nutritional influence in brain development is that which precedes birth. Acutely, it matters whether the child has had breakfast if you want them to learn, but what they have eaten has greater long-term effect on their waistline than their IQ.

Conclusion

Children's emotions and behaviour are the result of a dynamic network of genetic and environmental influences. The temptation is therefore to shrug and say it is all too complicated to make sense of in paediatric practice. But a way of applying this section to everyday paediatrics is to construct a biopsychosocial grid, as shown below. Often this will lead naturally to fruitful areas of intervention, especially the 'resilience' row, often ignored but a key source of compensatory strengths.

Question 24.2

Developmental and emotional consequences of domestic violence

Which pair of mechanisms is most significant in driving the developmental and emotional consequences for children experiencing domestic violence? Select ONE answer only.

A. Disorganized attachment style and structural limbic change
B. Excess adrenaline in thalamus and local gang culture
C. Loss of father figure and diet poor in essential oils
D. Poor housing and genetic predisposition
E. Weak maternal parenting and repeated head trauma

Answer 24.2

A. Disorganized attachment style and structural limbic change.

Violence disrupts the attachment mechanisms, while also leading to chronic cortisol elevation; in turn this causes structural alteration in the limbic system. In 2012, Choi et al published evidence from MRI studies of the brain that showed significant abnormalities in the inferior longitudinal fasciculus of the left lateral occipital lobe in right-handed subjects who had witnessed domestic violence between the ages of 7 and 13. The inferior longitudinal fasciculus connects the occipital and temporal cortex and is the main component of the visual–limbic pathway that subserves emotional, learning and memory functions that are modality-specific to vision. This finding is consistent with the hypothesis that exposure to childhood maltreatment is associated with alterations in fibre pathways that convey the adverse experience to frontal, temporal or limbic regions.

Pathways to problems – how specific emotional and behavioural problems can evolve

There are as many pathways to emotional and behavioural difficulties as there are children with difficulties, so this section could be infinitely long. What we have chosen to do is look at problems that are more complex than those covered in the undergraduate textbooks, but not the province of mental health. We will cover complex feeding difficulties, sleep, disruptive behaviour and eating disorders as examples of the 4Ps approach to case formulation. This takes the narrative leading to the problem, and the context in which it continues, and tabulates it as shown in Table 24.1.

In the 4Ps approach, one looks across the biopsychosocial context in which the child lived prior to the problems (predisposing), then how the problems started (precipitating) and have been perpetuated, often by unhelpful responses by parents and others. Finally, it is vital to identify strengths that remain in the situation, as this is where your plan will come from! Examples of this are given below.

The biological and developmental aspects of the child's situation will be familiar territory to the paediatrician. At the psychological level, you will be noting emotions and thought patterns, either that the child has told you, or that you deduce from his or her behaviour and the accounts of others. The social level is noted for its breadth, spreading out from the mother–infant relationship to a relationship with the wider world of media and politics. Sometimes, this leads to extra columns being added to the grid.

Table 24.1 The 4Ps framework

	Biological/ developmental	Psychological	Social
Predisposing			
Precipitating			
Perpetuating			
Protective			

Example 1: Behavioural sleep problems resistant to first-line advice

Most parents presenting with young children with sleep problems are frustrated by the child's inability to settle to sleep alone, or by their frequent night wakings. We will not consider infant sleep, but concentrate on the pre-school child.

Social factors

Historically and cross-culturally, it is highly unusual to expect young children to sleep alone. Nonetheless, that is the UK norm, and it is achievable for most families.

Psychological factors

Going to sleep alone is a form of separation, and like all separations must be prepared for. If the child is in an anxious or fearful state, this will require very slow withdrawal of the protective adult. Usually, if the fear is external to the adult, e.g. of the dark, gradual withdrawal is effective, but where the fear is *of* the adult, or more commonly *about* the adult, e.g. in domestic violence, then more specialist input may be needed.

Sleep is also a habit, and habits form very strongly in pre-school children. If sleep is usually with an adult, or in the light, changes to this should be carefully applied one at a time. Likewise, if the physical situation (light, noise, presence of adult) is different between sleep onset and the (normal) awakenings that occur every 1–2 hours, then full arousal will often result.

There is an association between some forms of insecure attachment and sleep problems, and also maternal depression. The precise relationship is unclear, however, and probably varies from family to family.

Biological factors

Sleep is a biological phenomenon, and is therefore affected by biological mechanisms. Chronic symptoms, e.g. pain or gastrointestinal symptoms, may prevent sleep, but equally phenomena such as epileptic seizures can disrupt the diurnal rhythm. A far more common way to interfere with sleep initiation is to watch a back-lit screen close to bedtime. Such activities appear to suppress endogenous melatonin secretion, and thus the physiological 'cue' to sleep, and so are best avoided within an hour of bedtime.

Case history

Refusal to go to bed

Ahmed, 4, has a tantrum every night at bedtime. His health visitor has advised his mother to shut the bedroom door and ignore him, but it is not working. Table 24.2 shows his 4Ps framework.

This leads to some simple, hopefully helpful interventions:

- Stop screen time before bedtime
- Mother to seek counselling/treatment for depression
- Grandparents asked to help with domestic tasks so mother can spend time with Ahmed
- Gradual withdrawal of mother from bedroom at bedtime, following good 'wind-down'

Example 2: Complex feeding problems

Hayley was 4 years old and presented with oppositional behaviour around both eating and drinking for her parents, refusing anything apart from a very restricted diet of yoghurt and chocolate. Hayley's early medical history suggested mild cerebral palsy affecting swallowing responses in infancy and consequent feeding and weaning difficulties. She had repeated emergency admissions for severe dehydration due to refusing drinks.

A behavioural programme involving the use of time out and bed rest as negative reinforcers had back-fired and parents experienced themselves as persistently punishing Hayley's oppositional behaviour, which had generalized to disrupted sleep and daytime tantrums, to the point that they were concerned about family relationships, and found themselves arguing over how best to manage her.

See Table 24.3 for Hayley's 4Ps framework

Table 24.2 Use of 4Ps framework for Ahmed

	Biological/developmental	Psychological	Social
Predisposing	Preterm birth	Maternal anxiety	
Precipitating		Break-up of parents' relationship	Domestic violence
Perpetuating	Screen use (TV) in bedroom up until bedtime	Anxiety of mother	Mother unavailable due to depression
Protective	Healthy, good communicator	Good relationship with mother during the day	Family well-supported by grandparents

Table 24.3 Hayley's 4Ps framework

	Biological/developmental	Psychological	Social
Predisposing	Physical difficulties with swallowing	Insecure attachment associated with separations through hospitalization	Parents anxious about Hayley's uncertain medical condition, low self-confidence in their parenting skills
Precipitating		Anxiety about choking, and discomfort associated with eating	Transfer home from hospital, feels unsupported
Perpetuating	Discomfort associated with eating and drinking?	Usually wins and gets own way so oppositional behaviour is reinforced. Experiences time alone as further rejection, increasing emotional insecurity and angry oppositional behaviour.	Avoids outings and new situations as these have led to hospital admissions in past. Lack of consistency as parents lose confidence
Protective	Can eat some solids	Sociable, good at drawing	Loving parents, routine and structure at home

Helpful interventions might be:

- Abandon unhelpful behavioural intervention and make mealtimes fun.
- Encourage parents to help Hayley play and explore through introducing her to new activities.
- Help parents make sense of Hayley's current difficulties through understanding how ill health has shaped her experiences and relationships.
- Trigger multidisciplinary input to support school entry.

This case also illustrates how formulation paves the way for combining interventions that draw on a number of different models, including cognitive behaviour therapy and variants of systemic family therapy. 'Parent training ' is a common component of best practice in treating emotional and behavioural problems in children and may be carried out on an individual basis or in groups (e.g. in NICE guidelines for ADHD). Programmes are designed to help parents better understand their child, which is likely to promote parental 'mind-mindedness' and in turn lead to improved attachment security for the child.

Another lesson we can learn from Hayley's clinical history is that emotional and behavioural problems are often routed in very early patterns of interactions that over time have a spiralling effect. Early intervention can be very helpful. For example, expectant parents who are aware their child may be born with a specific genetic syndrome or disability may be more prone to prenatal anxiety and postnatal depression. Ongoing psychological support can reduce these symptoms, promote coping, maximize bonding and attachment security, and optimize brain development for the infant.

Since attachment security depends in part upon a parent's ability to respond appropriately at times when a child is physically hurt or ill, we can expect attachment style to shape children's illness behaviour. When caregivers respond sensitively, infants will signal distress in a direct manner, expecting their needs to be met. Children who present with medically unex-plained symptoms of pain may conform to the two patterns of insecure attachment styles. Developmentally, these children may have learned either to inhibit signalling pain and discomfort to parents because they were ignored or discouraged, or else to exaggerate signals of distress to gain the attention of preoccupied or inattentive parents. Either strategy involves bio-behavioural adaptation to the experience and expression of pain that might be a predisposing factor for stress-related illness. It is therefore always important to assess patterns of family interactions around unusual pain presentations.

Related difficulties may be set in motion when parents are overly focused on a child's physical state due to health anxieties during pregnancy, premature birth or early infancy. Children may implicitly learn that they are more likely to elicit a caring response from their parent when they are signalling physical discomfort rather than emotional distress. Hence, illness may become the family's currency for meeting one another's emotional needs. Again, pathways to problems will be complex.

Example 3: Why do young children develop disruptive behaviour?

There seem to be two main groups of children who develop disruptive behaviour. We will discuss those who develop relatively *early-onset* problems, for example between 3 and 7 years, as they are most likely to come into contact with paediatricians.

Social factors

There are associations with various socio-economic and demographic characteristics, such as teenage parents, poverty and parental mental health problems, but these seem to be mediated via a style of parenting marked by hostility towards the child and the other parent, lack of warmth and lack of positive involvement with the child. Often the parent interacts with

the child mainly when they are being 'naughty' and ignores them when they are behaving well. This serves to unconsciously encourage the disruptive behaviour, on the basis that negative attention is better than none at all. Multiple caregiver changes are an important association.

Psychological factors

There is an increased rate of 'callous–unemotional' behaviour. There is also far more negative attribution, by which neutral actions of others are interpreted as hostile.

Biological/developmental factors

These children have a higher rate of special educational needs (SEN), but particularly ADHD, memory and planning skills. Thus, the attitude of the school becomes crucial – a harsh, unsupportive school is likely to increase escalating behaviour.

Some biological features are more common in these children, for instance a lower resting heart rate, but the evidence is still emerging for consistent neurophysiological changes.

The search for candidate genes to explain disruptive behaviour has been fruitless, but there is some indication of a gene–environment interaction. Children with a variant of the monoamine oxidase A gene are at an increased risk of disruptive behaviour, but only if they also receive poor parenting.

Case history

Disruptive behaviour at school

Jared, 6, has been referred by his school for 'consistently choosing to disrupt lessons despite clear instructions from the head teacher'. See Jared's 4Ps framework in Table 24.4.

The helpful, simple interventions here would be:

- Encourage his mother to combine college with some parent training.
- Arrange for Jared to have an assessment of his SEN.
- Talk to his mother about involving others in the family who get on well with Jared.

Example 4: How do eating disorders evolve?

Eating disorder (ED) is an umbrella term encompassing both anorexia nervosa (AN) and bulimia nervosa (BN). AN is characterized by an abnormal and pervasive drive to lose weight, frequently in the context of profound and potentially dangerous levels of underweight. BN is characterized by abnormal weight-losing behaviours, in particular purging, in the context of binge eating, driven by a guilt cycle. Patients with AN tend to be underweight, and BN normal to overweight.

Social factors

The western ideal of beauty can be difficult for adolescents emerging from their childhood bodies to cope with, and when combined with adverse life events can encourage the development of ED. Links to particular events or family characteristics are not well-established, but there is a trend towards poor emotional communication in families.

Psychological factors

Perfectionism is commonly found as a pre-existing personality trait, but there do not seem to be any specific mental health difficulties that act as a preamble to ED. Distortions of body image and beliefs about the harmfulness of food are key in perpetuating behaviours.

Biological/developmental factors

Genetic studies on the inheritance are as yet inconclusive. Key to recognizing AN in children is an understanding of cognitive level of development. Many children with emerging AN will not be at a cognitive level to express weight and shape concerns, and presentation will be vague with unexplained weight loss. This is in contrast to BN, where a certain level of cognitive development is required in order to display the compensatory behaviours and thought processes that characterize the condition, and hence the older age of presentation.

The impact of ED in children and young people on brain development is unclear, though a small number

Table 24.4 Jared's 4Ps framework

	Biological/developmental	Psychological	Social
Predisposing	Paternal history of criminality		Poverty, teenage mum
Precipitating	Emerging SEN	Awareness of falling behind at school	
Perpetuating	Impulsive response to stress	Negative attribution	Harsh, critical parenting
Protective	Good social skills	Some positive relationships	Mother enrolling in college

SEN, special educational needs.

of studies have demonstrated sclerosis on MRI, especially in the hippocampal regions, which may recover with weight restoration. Ansel Key's post-war starvation studies in healthy volunteers (the 'Minnesota experiment') demonstrated that underweight can impact significantly on cognitive function in such a way as to mimic other mental health conditions. Indeed, underweight children can also behave differently, and this may include loss of hunger, further compounding eating problems, and even the displaying of autistic traits. The physiological changes of starvation, such as a lack of insulation leading to exercise compulsion, or constipation leading to feelings of 'fullness', can conspire with cognitive changes to produce a 'vicious cycle'.

> ### 👥 Case history
>
> **Palpitations and weight loss**
>
> Leonora, aged 14, attends the accident and emergency department with palpitations and weight loss, and is admitted to the paediatric ward. A diagnosis of anorexia nervosa is made.
>
> See the practice points in dealing with young people with eating disorders in Box 24.2 and Leonora's 4Ps framework in Table 24.5.

> ### Box 24.2 Practice points in dealing with young people with eating disorders
>
> Management of this life-threatening condition should be by reference to published guidance (e.g. Junior MARSIPAN. *Management of really sick patients with anorexia nervosa.* London: Royal College of Psychiatrists), but you can help her in the following ways:
>
> - Show humanity and your own fallibility – being surrounded by 'perfect' professionals may not be helping.
> - Discuss what you know about starvation openly with her when she is ready to listen.
> - Actively encourage the family to understand and empathize with her, while remaining realistic.

The physical mind

Disorders of emotional and behavioural function are inextricably linked with brain disorders. The evidence for this confluence is compelling; while having any chronic illness leads to an increase in mental health difficulties (from 10% to 20% on most estimates), this rises to 40% in some studies of children with brain disorders. In addition, there are a number of conditions with both physical and psychological symptoms, and presentations that only make sense if the emotional component is recognized. In this section, we will consider, as an example of the first category, chronic fatigue syndrome, and for the latter, functional abdominal pain. However, the points made can be applied widely throughout paediatric practice.

In discussing these conditions, we will be extending application of the biopsychosocial model and providing a further rationale for its application.

Conditions which combine physical and psychological symptoms: chronic fatigue syndrome

Is fatigue a psychological or physical phenomenon? It seems obvious from common experience that the answer is 'both', and the list of common symptoms in chronic fatigue syndrome (CFS) bears this out (Table 24.6).

There is a genetic component to susceptibility to CFS, as demonstrated by twin studies. There is a female preponderance which appears after 13 years of age, but the reason for this is unclear.

There is also an intriguing association with family adversity of all kinds during pregnancy and the child suffering CFS. This could be explained in a number of ways, including epigenetic effects *in utero*, ongoing adversity, neuroendocrine programming, or, more likely, a combination of these and other processes.

The link with pre-existing anxiety and depression is controversial, but there does seem to be an excess of symptoms when looked at retrospectively. What is certain is that rates in CFS are far in excess of similarly disabling non-brain disorders, suggesting a degree of common causality between fatigue and mood disorders.

Table 24.5 Leonora's 4Ps framework

	Biological/developmental	Psychological	Social
Predisposing		Perfectionist personality	Family very ambitious for Leonora
Precipitating	Onset of puberty – period of weight gain	Grief over loss of friend in car crash	Transition to large secondary school
Perpetuating	Effects of starvation on cognition	Anorexic-type cognitions	Some contact with 'pro-anorexia' groups
Protective	Bright, emotionally attuned before ill	Insight developing into her situation	Family highly committed

Table 24.6 Common symptoms of chronic fatigue syndrome

Symptom	Notes
Difficulty sleeping	Insomnia, hypersomnia, unrefreshing sleep, disturbed sleep–wake cycle
Muscle and/or joint pain	Multisite and without evidence of inflammation
Headaches	
Painful lymph nodes	Without pathological enlargement
Sore throat	
Cognitive dysfunction	Difficulty thinking, inability to concentrate, impairment of short-term memory, difficulties with word-finding, planning/organizing thoughts and information processing
Physical or mental exertion makes symptoms worse	The 'boom and bust' cycle
General malaise or 'flu-like' symptoms	
Dizziness and/or nausea	
Palpitations	In the absence of identified cardiac pathology

(From Crawley E. The epidemiology of chronic fatigue syndrome/ myalgic encephalitis in children. Arch Dis Child 2014;99:171–174 doi:10.1136/archdischild-2012-302156, with permission. © BMJ)

When it comes to intervention, this biopsychosocial convergence of causes and symptoms explains why effective interventions have been found across both physical and psychological therapies, and that interventions aimed at a single putative cause (e.g. viruses) have failed.

The case of CFS is a good illustration of the narrative outlined under determinants of mental health, in that these problems defy categorization, and that even known associations should be regarded as levels of description, rather than causes *per se*.

Conditions which only make sense once the emotional component is addressed: functional abdominal pain

Functional abdominal pain (FAP) is presumed when significant recurrent pain occurs with no identifiable pathology.

All pain is a brain process, fed into by sensory afferents, but essentially experienced as a result of processes within the brain. The amount of input required to stimulate this pain system is a function of pain sensitivity. The determinants of this sensitivity, like the determinants of mental health more widely, can be understood at several levels.

Genetics

There is some evidence for a temperamental sensitivity, in that young children displaying early problems of dysregulation (poor sleep, tantrums, feeding difficulties) have a greater chance of later functional pain syndromes emerging.

There are some correlates detectable on functional brain imaging, which show a less organized response to pain, and the mesenteric nervous system shows unusual features in children and adults with functional disorders, such as pain being referred to different dermatomes, and an abnormal paracrine response to distension.

At a psychological level, according to Borkum, 'pain sensitivity is an adaptive process affected by expectation, mood, coping, operant conditioning, and the preconscious allocation of attention'. The important point is that sensitization seems to be largely sub or preconscious, and crucially dependent on mood. In some studies, 80% of children with recurrent abdominal pain suffered clinically significant anxiety.

Of course, it is not the case that these factors act independently to produce pain sensitivity; there are important interactions between them. For instance, the neurobiological processes of anxiety seem to act upon the gut to make it more reactive (a process known since the 19th century), thus increasing the input into the pain system and encouraging greater anxiety, and so on around a vicious cycle. Management should aim to break this cycle, and return the pain system to a less activated state. Pharmacological, psychological, lifestyle and dietary interventions all have a potential role in this process, dependent on evidence base.

Similar arguments to those involved in CFS and functional abdominal pain can be applied to a variety of clinical situations, such as: the child whose fear of defecation perpetuates constipation; where poor glucose control affects the mood and adherence of a young person with diabetes; when the neurophysiological changes of epilepsy predispose to ADHD. The key is to keep in mind the biopsychosocial model of illness, and remain neutral as to the modality of intervention, as long as that intervention is effective.

Management of emotional and behavioural problems – the scientific basis and evidence

Social/environmental

When children and young people across Plymouth, UK, were asked what they believe makes them

mentally well, their 'mental health 5-a-day' were: playing, friends, family, music and pets. This suggests that children do know what is good for them, but many environments do not support or facilitate parents to provide the basic components for achieving fundamental well-being. There is a growing public health agenda to promote psychological well-being through intervening at a community level, for example making use of green space and open water for activities, creating safe play areas, connecting relational networks to support and mentor vulnerable groups and many more creative arts projects. Although this is not a level of intervention that many paediatricians will be delivering, health and social care professionals should have a role in influencing policy to improve children's mental health and well-being through social and environmental change.

Parenting

There is a vast market in courses/books/websites to help parents who are struggling with their children's behaviour. Fortunately, they are all founded on the same core principles, which are summarized below. What one is essentially doing is implementing new habits, forming new structures of reward and consequences to make the organization (family) run more smoothly and improving interpersonal relationships. (It is a process that should be familiar to anyone working in the NHS, who will also understand its difficulty!)

Positivity

In order for behavioural management to be effective, it needs to be based on a 'good enough' relationship. At some level, the child needs to care about the parent's feelings, and also feel good about themselves, to cope with the changes the parent wants.

Promoting the emotional security of the relationship through shared activities is useful, so any shared activity is worthwhile, but play is paramount for younger children. Play led by the child for a short (10 minute) period is advised, but any play where the adult attention is on the child is useful.

'Catching them being good' and noticing when they have made small positive steps is a powerful tool. Targeted praise is important. Vague, general praise ('Aren't you a good boy') has been shown to be worse than none at all, whereas specific praise ('I like how you did X') is beneficial.

Responsivity

Much attention is focused on children's screen time, but it is perhaps more important that parents limit the time they are unavailable to their children due to phone conversations, social media, etc. Unlike most household tasks, these cannot be combined with conversation with the child. Parents must learn to distinguish between listening to the child respectfully and granting the child's every wish, as learning to tolerate a degree of frustration is an important step in emotional development.

Structure

A routine is important for children to feel safe and reassure them that the adults are in control. This can be very mundane, like a list of tasks involved in getting ready in the morning, or fun, like a weekly film night.

There need to be rules, binding upon the adults and children. These need to be simple, unambiguous, and (initially) few, perhaps two or three. These rules should specifically target unwanted behaviours (e.g. 'Don't hit', rather than 'Be good'). Patterns of behaviour take a long time and much effort to change, using positive and negative encouragement and the power of habit, so sometimes it is more productive to target only one behaviour at a time to start off with.

Planning for situations does not require strategic genius. Parents know the situations where children have trouble, so before they enter a supermarket, for example, it is useful to stop, and calmly tell the child what is expected, what is not allowed, and what the consequences of positive and negative behaviour will be.

Consistency

None of the above will have any effect unless parents are consistent, in several ways:

- Consistency over time
- Consistency across all parents and carers
- Consistency across settings and contexts

Rules cannot be dependent on parents' moods or energy levels. Occasional rule lapses act as 'intermittent reinforcement', shown to be the single most powerful way to ensure that the behaviour that is being targeted continues with a vengeance.

Patience

This is perhaps the most important element, yet often overlooked by parenting manuals selling a quick fix. Behavioural management works, but takes time, and there is often an 'extinction burst' of increased unwelcome behaviour before things start to improve, as the child reacts against the new boundaries. Parents need to be prepared for this.

As well as patience across weeks, parents need patience across hours, to be able to abandon a shopping trip, wait out a tantrum, or stay calm in the face of sibling conflict when shouting would, in the short term, be quicker.

These principles can be applied to any behaviour, albeit with modifications. See Further reading for details.

Family therapy and systemic intervention

There is a strong evidence base to support family therapy and systemic interventions for child-focused problems, including: sleep, feeding and attachment problems in infancy; child abuse and neglect; childhood behavioural difficulties (including ADHD, conduct, delinquency and drug abuse); emotional problems (including anxiety, depression, grief, bipolar disorder and suicidality); and eating disorders and somatic problems (including enuresis and encopresis, recurrent abdominal pain, difficult asthma and diabetes). There are some key concepts of the model. 'Symptoms' are not seen as residing within one individual but are instead a product of the interactional dynamics between people, depending on how one and another's actions are ascribed meanings. This may seem counterintuitive to a medical model, where biological diagnoses and treatment are rightly premised on linear notions of 'cause and effect'. Instead, systemic practitioners look for circularities whereby problems are maintained by unhelpful cycles of feedback that have a tendency to escalate.

It is also important to understand triadic relationships. In families, the concept of 'triangulation' can be used to describe a situation where a child is caught in the conflict between parents. This happens when parents cannot talk about, or resolve, a couple's dispute between themselves and displace the unresolved conflict into disagreement about their child.

Individual psychological therapy

Cognitive behaviour therapy (CBT) is the treatment of choice for a wide range of emotional and behavioural problems in children and adolescents. It has scientifically proven effectiveness for the treatment of generalized anxiety and specific phobias, depression, obsessive compulsive disorder, sexual abuse and trauma,

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Case history

Chronic illness

Charlotte, aged 5 years, has developed a chronic illness and is having sleepless nights. With this stress, her parents are having marital difficulties. With no time for themselves, they argue about how best to manage Charlotte. Dad thinks Charlotte is being very naughty and Mum is too soft with her. Mum thinks Charlotte is unwell and feels sorry for her; Dad doesn't understand. Both take up increasingly polarized positions, since no one attempted solution is working. Finally, family therapists look for ways to understand the problematic situation in order to 'reframe' it in a positive light. For example, here both parents clearly love Charlotte very much and are willing to do their best for her, even if this means they must put their marriage on hold for the time being. Of course, such positive connotations must always be authentic and so would not be appropriate when there are safeguarding concerns. Family therapists also listen to the narratives and meanings that people bring to account for family life and are aware of how patterns of parenting can be transmitted across generations.

There are many different schools of family therapy utilizing a variety of theories and techniques, but these core ideas remain central.

Case history

Pain resulting in avoiding attending school

Liam is 14 years old and experienced severe bullying when starting secondary school, leading to an anxiety-related somatoform pain condition that often stopped him attending school. As a result of being bullied, he might have the unhelpful thought that 'boys don't like me, they will hurt me'. This leads him to feel anxious about going to school and to change his behaviour to stay at home indoors as much as possible. CBT also draws on principles of learning theory. Liam feels relieved at avoiding social situations and this pleasant feeling reinforces and maintains his current behaviours. Within this model, avoidant behaviour is often a factor in perpetuating the problem, since it is both rewarding and prevents alternative possibilities from being tested. Interventions in CBT focus on changing unhelpful patterns of thinking by challenging faulty logic (thought challenging), usually in combination with setting behavioural goals that reduce anxiety over time and provide tangible evidence that supports new and more helpful ways of thinking about oneself. For example, with Liam, we might draw up a hierarchy of situations graded from the least to most difficult involving meeting boys of his own age and agree an achievable goal. The first step might involve Liam inviting some old friends over to play computer games. Liam would be taught strategies to help him relax (anxiety management), and might rehearse in imagination and using role-play what he could do to prepare for success. Once achieved, Liam's view of himself can be modified in the light of new evidence to 'my friends like me and I can have fun', preparing him for the next step.

post-traumatic stress disorder, pain management and CFS. It is specified in the NICE guidelines for many of these conditions. However, most studies included in systematic reviews are based on a wide age range, from 7–18 years, and much less is known about the effectiveness of CBT for younger children. Furthermore, CBT may be more effective when delivered in combination with other interventions, such as parent training and medication.

CBT is based on the idea that how we think about ourselves shapes what we do and how we feel; hence, thoughts, feelings and actions are causally linked. CBT also draws on the 4Ps framework to map any presenting problem (the 5th P!).

e-Therapies

Given the large numbers of young people likely to benefit from mental health interventions, electronically-mediated therapy presents a promising way forward, using contemporary and engaging new products. A review by MindEd (see Further reading) published online suggests that the current evidence base for the effectiveness of e-therapies is weak, primarily due to the paucity of methodologically high quality studies. The most promising results were found for the treatment of depression and anxiety. Young people themselves viewed individual autonomy and active engagement with e-therapies favourably, but wanted their quality to be endorsed by the medical profession.

Psychopharmacology

General points

Where evidence exists for efficacy, this is usually in the improvement of specific symptoms, rather than overall well-being. For example, ADHD medications are good at improving core symptoms such as hyperactivity, but less good at improving engagement in class or relationships at home. This is the main reason why medication should always be given as part of a multimodal care package.

Monitoring for wanted and unwanted effects is also a multi-agency effort. Very often parents and teachers have a quite different perception of medication effects, and only by triangulating these views can a balanced overview be taken.

It is difficult to generalize about appropriate dosing. Some children and families tolerate side effects in order to control intolerable symptoms and behaviours, while for others, it is just important to 'tip the scales' with a low dose, to allow psychosocial intervention more traction.

ADHD medications

Methylphenidate and *atomoxetine* are described in Chapter 5, Developmental problems and the child with special needs.

Atypical antipsychotics are marketed as safer alternatives to older antipsychotics, and they are certainly less prone to produce tardive dyskinesia. However, the adverse metabolic effects, via hyperprolactinaemia and weight gain, are significant, and sedation and cognitive slowing are often a cause of complaint.

The drugs have been shown to have positive short-term effects on irritability, hyperactivity and disruptive behaviour in autism and learning disability, but longer-term data is sparse. The advantages decay quickly over time.

Anti-epileptic drugs

This is a vast subject. Fortunately the messages are simple:

- There is no justification for starting an anti-epileptic drug (AED) in a child without epilepsy in order to improve their behaviour.
- Sedating AEDs, such as valproic acid and carbamazepine, possess anxiolytic, antimanic, and sleep-promoting benefits, but may cause fatigue, impaired attention, and mood depression.

Activating AEDs, such as felbamate and lamotrigine, may possess antidepressant and attention-enhancing efficacy, but may cause anxiety, insomnia, and agitation. AEDs are described in detail in Chapter 28, Neurology.

Chapter summary

Children's mental health is clearly not only important but also part of the responsibility of paediatricians (Box 24.3). It is not mysterious or magical; it requires a patient, reflective approach and a breadth of vision beyond both the biology and diagnosis, and the illness, which can be disorientating as well as exhilarating. However, mental health is and will always be integral to paediatrics, and skills and knowledge in this area will undoubtedly make you a better clinician.

The role of the paediatrician needs to be wider than detection and referral, partly because of the intertwining of the physical and mental aspects of multiple conditions, and partly because so many mental health illnesses are at the 'sharp end' of a spectrum of difficulties which contain huge numbers of children with difficulties that do not quite meet diagnostic criteria, but which are undoubtedly significant for the child and family.

Box 24.3 How can paediatricians help children's mental health?

Paediatricians can help in the following ways:

- In public health, by ensuring that emotional well-being is considered in policy.
- In acute paediatrics, by taking a biopsychosocial approach from the beginning of the assessment process.
- In functional conditions, treating children and families with understanding, and with a flexible approach to intervention.
- In chronic disease, to understand the impact of psychological factors on adherence and outcomes, and adjust management accordingly.
- In community paediatrics, to adopt a holistic approach incorporating all aspects of development, helping parents to understand behaviour and make sense of family relationships.
- In emergency care, by recognizing that around one third of children (and their parents) who are admitted to ICU are traumatized and 1 in 10 go on to develop post-traumatic stress disorder.
- In all aspects, to detect serious mental distress and refer appropriately to specialist CAMHS.
- In all contacts with families, to model open listening, optimism and positivity.
- Encourage families to engage in social activities together, as a powerful driver of well-being.

Further reading

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Nicole Y Z Chiang, Timothy H Clayton

Dermatology

Embryology

Understanding the development of human skin offers an opportunity to study the structure and function of the skin in detail. It also helps to further the understanding of genetic skin diseases.

Embryogenesis of the skin

The skin is divided into two distinct layers: the epidermis and dermis. Both layers are composed of various cell types that are derived from the ectoderm and mesoderm.

Epidermal development

The ectoderm that covers the developing embryo is initially a single-layered epithelium, the surface ectoderm (Fig. 25.1A). This layer proliferates and forms a layer of surface epithelium, the periderm (Fig. 25.1B), which covers the developing epidermis until the cornified cell layer is formed. The embryonic epidermis begins to stratify at approximately 8 weeks' estimated gestational age (EGA), and is followed by cornification (composed of 'dead' keratinocytes held together by proteins and lipids). Until about 19 weeks' gestation, the fetal skin is highly permeable and early in gestation, amniotic fluid volume is mostly determined by fetal surface area. At 19 weeks, keratinization occurs and the skin becomes impermeable. When differentiation is complete, the periderm detaches from the underlying epidermis, and its remnants form the

vernix caseosa (greasy coat that protects the skin *in utero* from the amniotic fluid). The epidermis is morphologically similar to adult skin by mid third trimester (Fig. 25.1C). However, it does not acquire full barrier function until a few weeks after birth.

Melanocytes are derived from the ectoderm. They migrate from the neural tube to the epidermis, and are not fully functional until the second trimester. Active melanocytes are present throughout the dermis during embryonic development, and most migrate to the epidermis or undergo apoptosis by the time of birth. When the melanocytes fail to reach their proper location in the epidermis and are entrapped in the dermis at the time of birth, this leads to the presentation of congenital dermal melanocytosis (Mongolian blue spot), the common blue-grey birthmark which slowly resolves spontaneously with time.

Skin conditions that are a result of genetic abnormalities in the epidermis and/or its appendages often follow a distribution pattern (Fig. 25.2, Table 25.1) representing the migration pathways of epidermal cells during embryonic development. The pattern follows Blaschko's lines (described by the German dermatologist, Alfred Blaschko) and represent a manifestation of cutaneous mosaicism. Cutaneous mosaicism occurs when two or more genetically different populations of cells exist side by side within the skin. They have typical patterns: V-shaped on the upper spine, S-shaped on the abdomen, linear on the arms and legs, spiral on the scalp and vertical in the mid-face. Many congenital and acquired skin conditions can

follow Blaschko's lines (see Table 25.1). An example of this is an epidermal naevus, which occurs as a result of a defect in ectoderm, leading to an overgrowth of the epidermal keratinocytes. It presents at birth or in early infancy, often with a localized, linear, warty, hyperpigmented plaque. Hypomelanosis of Ito (naevoid hypopigmentation) on the other hand, presents with hypopigmented streaks that follow Blaschko's lines. Both conditions must be differentiated from incontinentia pigmenti, which is a neurocutaneous disorder syndrome due to a defect in the NEMO gene. This condition presents typically in the newborn with blisters that also follow Blaschko's lines. The blisters then resolve and reveal hyperkeratotic, warty plaques, followed by increasing pigmentation at 2–6 months of age. The hyperpigmented brown streaks later fade into atrophic hypopigmented streaks in later childhood. These conditions may have associated extracutaneous manifestations, e.g. epidermal naevus, incontinentia pigmenti and hypomelanosis of Ito are associated with central nervous system, heart, eye, skeletal system and dentition defects, McCune–Albright syndrome is associated with bone and hormonal abnormalities, and focal dermal hypoplasia is associated with eye, musculoskeletal, renal, gastrointestinal, cardiac and neurological abnormalities. The mode of inheritance needs to be ascertained in order to provide appropriate genetic counselling for family members.

Table 25.1 Patterns of cutaneous mosaicism

Pattern of cutaneous mosaicism	Clinical example
Narrow bands of Blaschko	Incontinentia pigmenti, epithelial naevi, e.g. inflammatory linear verrucous epidermal naevus, hypomelanosis of Ito
Large bands of Blaschko	McCune–Albright syndrome
Chequerboard pattern	Becker naevus, vascular malformation (port wine stain)
Phylloid pattern (leaf-like)	Mosaic trisomy 13
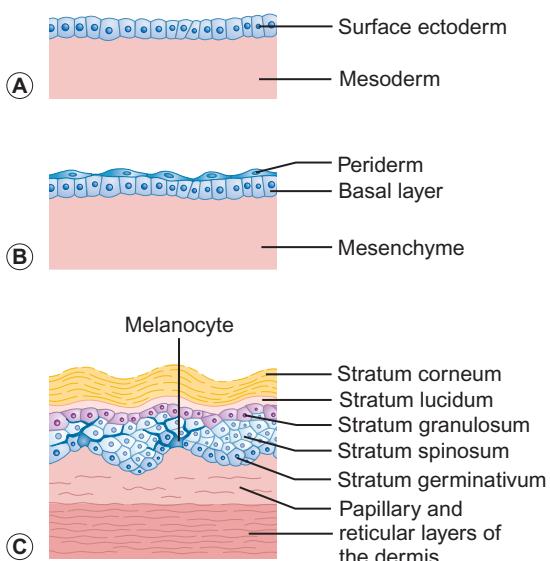
Fig. 25.1 Embryological development of the skin. A. 4 weeks. B. 8 weeks. C. Newborn infant. *(From Moore KL, Persaud TVN, Torchia MG. Before we are born, 8th edition, Saunders 2013, with permission.)*

Case history

Skin conditions which follow Blaschko's lines – Example 1

A baby boy presented with linear streaks on his buttocks and thighs. They were present at birth, and gradually became thickened and warty (Fig. 25.3).

What is this condition?

This is an epidermal naevus, an overgrowth of epidermal keratinocytes. Mutations associated with an epidermal naevus are present only in the cells of the naevus, not in the normal surrounding skin cells (cutaneous mosaicism). They are treated with emollients.
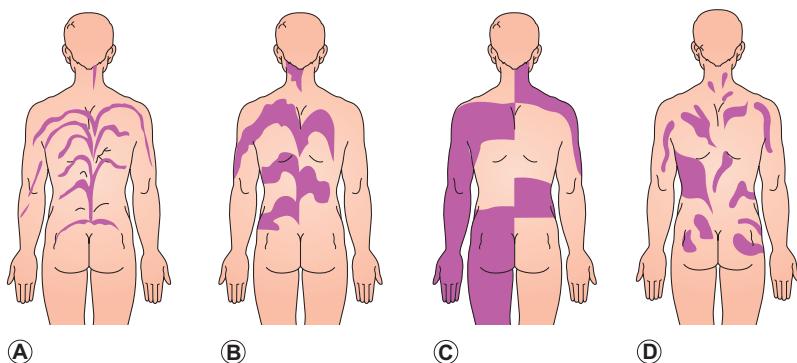
Fig. 25.2 Various patterns of cutaneous mosaicism. A. Narrow bands of Blaschko. B. Large bands of Blaschko. C. Chequerboard pattern. D. Phylloid pattern. *(From Schachner L, Hansen R. Pediatric dermatology, 3rd edition, Mosby 2011, with permission.)*

Fig. 25.3 Thickened and warty streaks over the thigh.

Fig. 25.4 Congenital hairless patch. *(Courtesy of Professor Julian Verbov.)*

Fig. 25.5 Collodion baby. *(Courtesy of Dr Ian Coulson.)*

stratum corneum) (Fig. 25.5). The membrane is shed over the first 2–3 weeks of life. In the majority of cases, the shedding will then reveal a phenotype of ichthyosis, a cornification disorder due to a genetic abnormality resulting in persistent dry and scaly skin.

Case history

Skin conditions which follow Blaschko's lines – Example 2

A 3-year-old girl presents with a hairless patch on her scalp. It was present at birth but has become more prominent (Fig. 25.4).

What is this condition?

This is a sebaceous naevus, an overgrowth of the entire skin component (epidermis, sebaceous glands, hair follicles, apocrine glands and connective tissue) due to a genetic abnormality. It typically presents as a brown/orange hairless patch on the head, which becomes warty during puberty. There is a small risk of tumour development later in life. Surgical treatment is recommended in late adolescence. The differential diagnosis includes aplasia cutis.

Question 25.1

A baby with linear streaks

A newborn male infant was found to have linear streaks on his forearm extending to his hand that were present since birth. These streaks were warty, inflamed and very itchy. Which layer of the skin is most likely to be affected? Select ONE answer only.

A. Dermis
B. Dermal–epidermal junction
C. Epidermis
D. Subcutaneous fat
E. All of the above

Answer 25.1

C. Epidermis.
    This child is likely to have a type of epidermal naevus (EN) called inflammatory linear verrucous epidermal naevus (ILVEN). Like other types of epidermal naevus, it tends to follow Blaschko's lines. It is due to a defect in the ectoderm which results in an overgrowth of epidermal keratinocytes.

Genetic abnormalities that result in a more global abnormal epidermal differentiation and barrier formation can give rise to the presentation of a 'collodion baby' (baby born encased in a taut, shiny, transparent membrane that is formed by aberrant

Dermal development

The origin of the dermis depends on the body site. The face and anterior scalp are derived from the neural crest ectoderm, whereas the extremities and trunk arise from the mesoderm. Dermal fibroblasts are developed under the epidermis by 6–8 weeks' gestational age. These fibroblasts synthesize collagens and microfibrillar components. By 12–15 weeks, the distinction between papillary dermis and reticular dermis is formed. By the end of the second trimester, the dermis shifts from a non-scarring to a scarring form of wound repair.

The dermal–epidermal junction (DEJ) provides adhesion between the basal keratinocytes and the dermis, as well as resistance against shearing forces on the skin. Mutations in genes that encode the components of the DEJ can result in skin fragility and blister formation.

Case history

A defect in the dermal–epidermal junction (DEJ)

A newborn male infant presents with fragile skin and blister formation following minor trauma since birth. The blisters gradually became more widespread.

He is likely to have a form of epidermolysis bullosa (EB), a group of genetic disorders that result from mutations in genes that encode molecules in the DEJ. It is characterized by blisters on the skin and mucous membranes. The blisters often occur at sites of friction and minor trauma, such as the feet and hands. Treatment is symptomatic; the primary aim is to protect the skin and prevent secondary infection and deformity.

Strawberry birthmarks (infantile haemangioma) (Fig. 25.6) are thought to be a result of proliferation of endothelial cells and mutations in genes that encode for vascular endothelial growth factor (VEGF) and other pathways that affect the vascular development. They usually present shortly after birth (unlike vascular malformations – malformed dilated blood vessels in the skin, which are usually present at birth). Infantile haemangiomas are common in the head and neck area, and usually proliferate in the first 6–9 months. This is followed by spontaneous involution over several years and therefore active non-intervention is advised. However, treatment should be considered for lesions which are large with potential for disfigurement, ulcerating, threaten vital function, e.g. vision, hearing, breathing or feeding, or cause high-output cardiac failure. Until recently, steroids (topical, intralesional and oral) were the mainstay of treatment. However, the serendipitous discovery of a non-selective oral beta blocker as an effective treatment has

Fig. 25.6 Infantile haemangioma.

revolutionized its management. Oral propranolol has become the treatment of choice for complicated lesions. The exact mechanism for its action is not completely understood, but is postulated to inhibit angiogenesis and recruitment of endothelial progenitor cells as well as inducing apoptosis. More recently, topical beta blockade in the form of eye drops (usually used for glaucoma) applied directly to the lesions has been shown to be effective.

A number of genes are involved in the formation and migration of neural crest cells. Genetic mutations causing defects in the neural crest can lead to the development of neurocutaneous syndromes (i.e. disorders that affect the skin and are associated with CNS and other abnormalities). Examples of neurocutaneous syndromes include tuberous sclerosis, neurofibromatosis and Sturge–Weber syndrome (Table 25.2).

Recent scientific advances which have improved clinical practice – infantile haemangioma

For years, management of infantile haemangiomas consisted of active monitoring, surgery, steroids, interferon or vincristine.

In 2008, the serendipitous observation of the efficacy of beta-blocker therapy for clearing infantile haemangiomas in 11 infants was reported by Léauté-Labrèze et al. Since then, the use of propranolol for infantile haemangiomas has been reported in over 200 publications and it has become the first-line therapy for haemangiomas requiring treatment.

Table 25.2 Neurocutaneous syndromes

Disorder	Inheritance pattern	Clinical features
Tuberous sclerosis	Autosomal dominant (50% have new mutations) (see Chapter 9, Genetics, for more details)	Neurological abnormalities (e.g. seizures and cognitive impairment) associated with characteristic skin changes: • ash-leaf or hypopigmented patches • adenoma sebaceum (small red or yellow papules on the face, especially perinasal) • fibromatous nodules (nodules on the forehead and scalp) • periungual fibromas • shagreen patches (orange peel-like skin)
Neurofibromatosis	Autosomal dominant (see Chapter 9, Genetics, for more details)	Bony and/or neurological abnormalities, associated with characteristic skin changes: • café-au-lait spots (round or oval coffee-coloured macules) • dermal neurofibromas (small nodules)
Sturge–Weber syndrome	Autosomal dominant	Neurological and/or eye abnormalities, associated with port wine stain (capillary vascular malformation affecting the trigeminal nerve area) on the eye or forehead areas

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Recent scientific advances which have improved clinical practice – mTOR inhibitors for tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is a multisystem disease caused by inactivating mutations in the *TSC1* and *TSC2* genes that lead to dysregulated mTOR (mammalian target of rapamycin) activity. Hyperactive mTOR causes unchecked cell growth, proliferation, metabolism and angiogenesis, all of which can give rise to tumour growth, which may affect many organs.

mTor inhibitor medications (e.g. serolimus) are now being used as targeted therapy, including for subependymal giant cell astrocytomas (SEGAs) and the renal equivalent, angiomyolipoma.

Development of skin appendages

The development of the skin appendages (hair, nails, eccrine, apocrine and sebaceous glands) begins during the first trimester and matures in the second trimester. The epidermis is thought to convey signals to the

Case history

Abnormalities in the development of skin appendages

A 2-year-old boy presents with a firm rubbery nodule on his right eyebrow.

This child is likely to have a dermoid cyst, which, despite its name, is an overgrowth of epidermis and adnexal structures such as sebaceous, eccrine and apocrine glands due to a defect in the skin development in fusion lines. It typically presents as a firm rubbery nodule at birth, or by 5 years of age. It can be associated with a pit or sinus tract to underlying structures. Imaging may be required before surgical excision (plastic surgery).

dermis to initiate appendage formation. Abnormalities in epidermal development and the associated signalling pathways can result in skin appendage abnormalities.

Anatomy of the skin (Fig. 25.7)

Epidermis

The epidermis is a stratified squamous epithelium. It has four or five layers:

- Stratum corneum, an outer layer of dead cells and keratin, which presents a barrier to bacterial and environmental toxins
- Stratum lucidum (only palms and soles)
- Stratum granulosum
- Stratum spinosum
- Stratum basale (basal cell layer)

The skin epithelium changes and becomes super-specialized as the cells migrate to the skin surface, forming a squamous shape (elongated flattened cells). This is achieved by filling of the cytoplasm with proteins, especially keratin, and cross-linking these polymer fibres into strong stable networks. The squamous shape means the skin is resistant to mechanical trauma and allows shedding without disruption of the whole surface. The epidermal cells, known as keratinocytes, are held together by organelles called desmosomes. Desmosomes are cell adhesion structures that are especially prominent in the epidermis and mucous membranes. The basal cell layer is the source of new epidermal cells, and rete pegs ensure attachment of the dermis to the epidermis via the basement membrane (the multi-layered structure forming the DEJ).

The epidermis consists of four major cell types:

- Keratinocytes – produce keratin and lipids as a protective barrier, daughter cells move to the
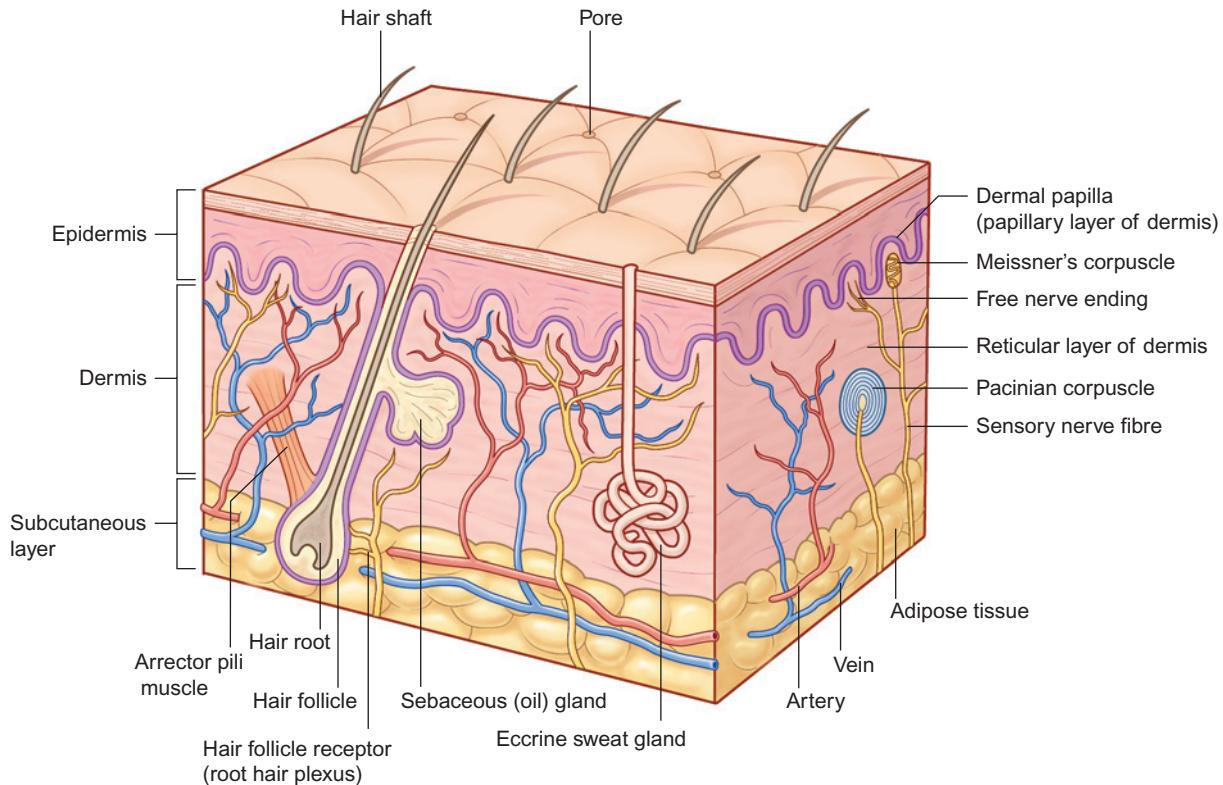
Fig. 25.7 **Anatomy of the skin showing the epidermis, dermis and adnexal structures.** *(From Naish J, et al. Medical Sciences 2e, Saunders 2014, with permission.)*

surface to form the cornified layer (stratum corneum)

- Melanocytes – produce melanin, which gives pigment to the skin and protects the cell nuclei from ultraviolet (UV) radiation-induced DNA damage. UV-induced DNA damage and/or its repair produce initiating signals that induce an increase in melanogenesis (production of melanin) after UV irradiation. Melanogenesis occurs in specific ovoid organelles, known as melanosomes, which are produced in dendritic melanocytes. Each melanocyte is associated with about 36 keratinocytes and one Langerhans cell (epidermal melanin unit). Melanin synthesized within melanosomes is transported via dendrites to adjacent keratinocytes, and accumulate within keratinocytes and melanocytes in the perinuclear areas. Melanin serves as a physical barrier that scatters UV radiation, and reduces its penetration through the epidermis.
- Merkel cells – contain specialized nerve endings for cutaneous sensation
- Langerhans cells – present antigens and active T-lymphocytes for immune protection

The epidermal turnover time (migration of cells from stratum basale to stratum corneum) is approximately 30 days.

Dermis

The epidermis is supported and nourished by a thick layer of dense tissue underneath, the dermis. The dermis consists of a fibrous component (mainly collagen, and elastin) and ground substance (glycosaminoglycans), which are produced by fibroblasts. Collectively, they provide structural stability and elasticity to the skin.

The dermis consists of two layers: papillary dermis and reticular dermis. It also contains vascular plexus supplied from vessels within the subcutaneous fat, and an extensive lymphatic and nerve system.

The efferent system controls the cutaneous vasculature and its appendages, whereas the afferent system provides appreciation of cutaneous sensation.

The dermis is attached to the underlying tissues by a layer of loose tissue called the hypodermis or subcutaneous layer, which contains variable amounts of adipose tissues.

Adnexal structures

Sebaceous glands produce sebum via hair follicles (collectively called a pilosebaceous unit). They are most concentrated on the face and scalp. They are stimulated by androgens and become active at puberty.

In general, sweat glands are divided into eccrine and apocrine glands. Eccrine glands are mostly concentrated on palms, soles, axillae and forehead. They regulate the body temperature. Apocrine glands are mainly found in axillae and perineal regions. They open into pilosebaceous follicles and produce body odour.

The hair is made up of modified keratin. The hair cortex is produced from medulla within the hair bulb. The cortex contains densely packed keratin and is surrounded by a single layer of cells called cuticle. The hair colour depends on the amount of melanin in the cortex.

There are three main types of hair:

- Lanugo: fine long hair on the fetus
- Vellus hair: fine short hair on all body surfaces
- Terminal hair: coarse long hair on the scalp, eyebrows, eyelashes and pubic areas. There are three phases in a hair cycle – growth phase (anagen) which lasts several years; short involutional phase (catagen); and resting phase (telogen), which lasts several months.

Most infants at term have a full scalp of terminal hair. However, shortly after birth, infants undergo a brisk period of shedding, where the pattern of synchronous hair growth shifts to the dyssynchronous hair growth of a normal adult. In an adult, approximately 85–90% of hairs are in the anagen phase, 10–15% in telogen and fewer than 1% in catagen.

Congenital and hereditary hair disorders tend to present with abnormal pattern of hair growth or shaft morphology. Localized patches of hair loss (alopecia) may be a result of vascular compromise secondary to perinatal trauma, hamartomatous malformation, the development of naevi such as epidermal naevus and sebaceous naevus, or aplasia cutis. Generalized sparse hair may suggest an inherited structural hair defect or genodermatosis.

In general, hair disorders can be broadly categorized into focal or diffuse, congenital or acquired and scarring or non-scarring (Table 25.3).

Nail

The nail is made up of a nail plate (hard keratin) which arises from the matrix beneath the proximal nail fold. The nail plate rests on the nail bed, which contains blood capillaries that gives the pink colour of the nails. A white, crescent-shaped lunula extends from under the proximal nail fold. The lateral borders of the nail plate are enveloped by the lateral nail folds. The skin underlying the free end of the nail represents the hyponychium.

Congenital and hereditary disorders often present with absence, hypoplasia (incomplete development), or dysplasia (abnormal development) of the nails. Congenital malalignment of the big toenail represents a lateral deviation of the nail plate from the longitudinal axis of the distal phalanx. As a result of repeated trauma, this congenital abnormality causes thickened nail plate, onycholysis (separation of the nail plate from the nail bed) and discoloration of the nail. With time, this can lead to an ingrowing painful toenail. Spontaneous improvement occurs in some patients. In ectodermal dysplasia, nails may be brittle, abnormally shaped, thickened, discoloured or absent. In pachyonychia congenita (an autosomal dominant disorder of keratinization), the nails usually appear packed and thickened (hyperkeratotic) and frequently discoloured.

Acquired disorders tend to present with dystrophic (distortion and discoloration of nail-plate structure) nails due to trauma or inflammatory processes that affect the nail matrix, nail bed or surrounding tissues. Traumatic nail injury constitutes 90–95% of all nail abnormalities in children. Inflammatory disorders such as psoriasis may damage the nail matrix and frequently cause coarse pits in the nail plate. Psoriasis affecting the nail bed causes onycholysis, oil-drop discoloration and subungual hyperkeratosis. Eczema also causes inflammation of the nail matrix, which leads to pitting, Beau's lines and transverse ridges of the nail plate. Children with alopecia areata are often found to have nail pitting.

Paronychia (inflammation of the nail fold due to infection or injury) is also a common acquired nail disorder in children. It typically presents with red, tender swelling of the proximal or lateral nail fold and is usually associated with pus formation. Acute paronychia is often due to *Staphylococcus aureus* or herpes infection. Chronic paronychia is usually caused by a mixed infection of bacteria (particularly Gram-negative bacteria) and yeast (*Candida* species). Onychomycosis (dermatophyte fungal nail infection), which is a common cause of nail dystrophy in adults, is unusual in children and mostly occurs in the toenails. Onychomycosis of the fingernails may represent underlying immunodeficiency. The finding of nail abnormalities may also represent an underlying systemic disease (Table 25.4).

Physiology of the skin

The key functions of the skin include:

- Protection against environmental insults
- Regulation of body temperature
- Provision of cutaneous sensation
- Synthesis of vitamin D
- Immunosurveillance
- Appearance and cosmesis

Table 25.3 Hair disorders

Diffuse hair loss	
Congenital non-scarring	**Congenital hypotrichosis** Most are inherited in an autosomal dominant pattern and there is usually no internal abnormality. Ectodermal dysplasias are genodermatoses that are characterized by absent or inadequate development of one or more of the epidermal appendages (i.e. hair, sweat glands, sebaceous glands, nails and teeth). **Hair shaft anomalies** Genetic syndromes are commonly associated with hair shaft anomalies. Examples include: a. Netherton syndrome – an autosomal recessive condition of ichthyosis associated with bamboo hair (a ball-and-socket hair shaft), erythroderma, and atopy. b. Menkes kinky hair syndrome – an X-linked recessive disorder of copper metabolism, causing microcephaly, brittle silvery hair, pale skin and neurological abnormalities.
Acquired non-scarring	**Telogen effluvium** An excessive loss of telogen hair, which can be physiological in the newborn, or triggered by illnesses, stress, surgery, iron and protein deficiency. **Anagen effluvium** An abrupt loss of anagen hairs, triggered by radiotherapy (can cause scarring), systemic chemotherapy and any toxic agents.
Focal hair loss	
Congenital scarring	**Aplasia cutis** An eroded area on the scalp, which presents at birth and heals over time as a patch of scarring hair loss. It can be associated with or without developmental anomalies. **Naevus sebaceus** As described above – a type of epidermal naevus, which presents early in life as a waxy hairless rough plaque on the head and neck area. **Inflammatory skin disorders** An example of this is morphoea (localized scleroderma) on the frontal scalp, which may present as a shiny plaque of firm skin with scarring hair alopecia.
Acquired non-scarring	**Alopecia areata** A chronic, autoimmune disease presenting usually with focal smooth patches of hair loss on the scalp or other hair-bearing areas (eyebrows/lashes typically). It may be associated with other autoimmune conditions such as thyroid disease. The majority of children achieve full regrowth of hair within 1 year. **Tinea capitis** A common cause of patchy hair loss in children, especially in developing countries. It represents fungal infection of the scalp by dermatophytes (most commonly *Trichophyton tonsurans* in the UK). Positive culture requires systemic antifungals. **Trichotillomania** A compulsive habit to pull out the hair. Results in a bizarre pattern of hair loss with twisted and broken-off hairs found on an otherwise normal scalp.

Table 25.4 Nail changes and associated systemic diseases

Characteristic nail findings	Description	Systemic disease
Clubbing	Thickening of the soft tissue beneath the proximal nail plate, which results in widening of the angle (>180°) between the nail plate and the proximal nail fold (normal <160°)	This can be due to hereditary (primary hypertrophic osteoarthropathy) or acquired causes, such as arteriovenous malformations, lung disease, congenital heart disease, liver cirrhosis and inflammatory bowel disease.
Koilonychia (spoon nail)	Concavity of the nail plate caused by thinning and softening of the nail plate	Iron deficiency anaemia, may occur congenitally, or in association with Raynaud's phenomenon (episodic reduction in blood supply to the fingers and/or toes in response to cold).
Beau's lines	Horizontal depression across the nail plate of all the nails	Disturbance in nail growth as a result of systemic illness.
Splinter haemorrhages	Small thin longitudinal lines under the nail plate due to rupture of nail bed capillaries	Trauma and nail psoriasis are the commonest causes. Systemic causes include infective endocarditis (usually proximal splinter haemorrhages) and connective tissue disease.
Pitting	Punctate depressions in the nail plate	Most commonly due to psoriasis and atopic dermatitis. Systemic causes include connective tissue disease, alopecia areata, sarcoidosis and incontinentia pigmenti.
Onycholysis	Separation of the nail plate from the nail bed	Usually occurs in children as a result of trauma. Also can be due to psoriasis, onychomycosis and thyroid disease.

Question 25.2

Skin infection in newborn infants

Which of the following statements are true (T) and which are false (F)?

Newborn children are more susceptible to skin infections than older children because:

A. Neutrophil function is reduced in the first month of life
B. Sebum production is at its lowest at birth
C. Skin pH is less acidic than older children and adults
D. There is an increased density of collagen fibres
E. They are unable to sweat

Answers 25.2

A. False; B. False; C True; D. False; E. False.

Although they are unable to sweat, it should not influence risk of infection.

The key comparative anatomical and physiological features of skin in the premature, newborn and adult skin are shown in Table 25.5.

Clinical evaluation

History

Below are the key points to consider when taking a dermatological history:

- Initial appearance, duration and evolution of rash/lesion
- Associated symptoms and systemic illness
- Aggravating or relieving factors
- Previous history of skin diseases
- Previous and current treatments for the skin
- Birth history, growth, immunization records and diet
- Previous medical issues
- Social history or concerns
- Family history of atopy, skin diseases and genetic disorders
- Medication and known allergies

Examination

A systematic approach should be used when examining the skin, mucous membranes, hair and nails. When examining the skin, observe and feel the

Table 25.5 Key comparative anatomical and physiological features of skin in the premature, newborn and adult skin

	Premature	Newborn	Adult
Skin thickness	0.9 mm	1.2 mm	2.1 mm
	Significance: Premature and newborn infants have thinner skin and are more at risk of transepidermal water loss and cutaneous absorption of topical agents compared to adults.		
Skin surface pH	6.2–7.5	5–5.5	5–5.5
	Significance: Premature skin has a less acidic pH and is more at risk of impaired barrier function and skin infections than newborn and adult skin.		
Melanocytes	Few melanosomes	Fewer melanosomes than adult	Well-developed melanosomes; melanin production varies with skin type
	Significance: Premature and newborn infants have fewer melanosomes to protect against UV damage and are therefore more at risk of photosensitivity compared to adults.		
Dermal–epidermal junction (cell attachments)	Flat, no rete ridges; fewer cell attachment structures compared to adults	Rete ridges start to form	Well-developed rete ridges and cell attachment structures; large number of antigens expressed
	Significance: Premature infants have fewer cell attachment structures and more fragile skin compared to newborns and adults.		
Dermis	Marked reduction of collagen and elastic fibres	Reduced collagen and elastic fibres compared to adults	Normal amounts of collagen and elastic fibres
	Significance: Due to reduced collagen and elastic fibres, there is reduced elasticity, and increased risk of blistering in premature infants and newborns compared to adults.		
Sebaceous gland	Increased activity compared to newborns	Similar activity to adults, then gradual decline until puberty	Normal activity
	Significance: Sebum production falls a few weeks after birth, and this causes impaired barrier protection, reduced lubricant and reduced immunosurveillance compared to adults.		
Eccrine glands	No activity	Reduced activity	Normal activity
	Significance: Absent or reduced activity of eccrine glands in premature infants and newborns causes impaired thermoregulation compared to adults.		

skin. Particular attention should be paid to the following:

- Pattern of distribution, e.g. flexures, extensors, sun-exposed site, generalized, localized
- Organization/configuration of lesions, e.g. linear, dermatomal, annular
- Surface, colour, border and textural changes
- Morphology of skin lesions (Table 25.6)

Investigations

Skin swab

A skin swab should be taken for microbial culture if there is an exudative or discharging wound, associated tenderness, oedema and/or surface crusting to exclude a skin infection. A viral swab for viral culture and PCR should be taken if there is a group of blisters or eroded papules to exclude a secondary viral infection.

Case history

Vesicles and eczema

A 5-year-old boy presents with painful vesicles and crusted papules on his face. He has a known history of eczema.

The diagnosis is likely to be herpes simplex virus infection (eczema herpeticum). This is a potentially life-threatening skin infection that typically presents with painful skin, vesicles and crusted papules on a background of eczema. There may also be secondary bacterial skin infection. A skin swab for virology and bacteriology will be helpful to confirm the diagnosis and guide appropriate management, although antiviral therapy should be started immediately.

Skin scraping, hair or nail clipping

A skin scraping, hair or nail clipping is recommended to confirm the diagnosis of a fungal infection before treatment with systemic antifungals is given. Causative organisms can be divided into three groups: dermatophytes, *Candida* species and lipophilic yeasts.

Case history

Itchy and scaly scalp

A 10-year-old Afro-Caribbean boy presents with an itchy and scaly scalp. On examination, there are discrete areas of patchy hair loss, associated with significant scaling and crusting. His brother also has a similar condition.

This is likely to be a fungal scalp infection – tinea capitis. Skin scrapings should be taken by a scalpel or sterile toothbrush from the scaly patch for mycology to confirm the diagnosis. Treatment with systemic antifungals is required.

Table 25.6 Morphology of skin lesions

Primary skin lesions (arise *de novo* in the skin)	
Macule	A small flat area of altered colour or texture Example: a café-au-lait macule of tuberous sclerosis
Patch	Larger flat area of altered colour or texture Example: a depigmented patch of vitiligo
Papule	A small raised lesion Example: inflammatory papules of acne
Plaque	A larger raised lesion Example: a scaly plaque of psoriasis
Nodule	A larger raised lesion with a deeper component (involvement of dermis or subcutaneous fat) Example: a nodular lesion of erythema nodosum
Vesicle	A small clear blister Example: a fresh vesicle on an area of rubbed skin in epidermolysis bullosa
Bulla	A large clear blister Example: a large bulla of local skin trauma
Wheal/weal	A transient raised lesion due to dermal oedema Example: an erythematous wheal of urticaria (hives)
Pustule	A pus-containing blister Example: a pustule adjacent to the toenail with acute paronychia
Secondary skin lesions (evolve from primary lesions or from scratching of primary lesions by the patient)	
Excoriation	Scratch mark, loss of epidermis following trauma Example: multiple excoriations during flare of atopic dermatitis (sign of acute rubbing)
Lichenification	Roughening of skin with accentuation of skin markings Example: background of lichenification on the skin of long-standing atopic dermatitis (sign of chronic rubbing)
Scales	Flakes of dead skin Example: confluent areas of scales on the scalp of cradle cap
Crust	Dry mass of exudates consisting of serum, dried blood, scales and pus Example: crust formation on a background of erythema in impetigo (bacterial skin infection)
Scar	Formation of new fibrous tissue post-wound healing Example: multiple scars seen with acne
Erosion	Loss of epidermis and dermis (heals with scarring) Example: multiple erosions at sites of trauma in epidermolysis bullosa
Ulcer	Loss of epidermis and dermis (heals with scarring) Example: an ulcerating haemangioma

Skin prick testing

Skin prick testing is used to investigate type 1 (immediate/IgE-mediated) hypersensitivity reaction allergens in patients with atopic eczema, suspected food allergy and contact urticaria. The relevance of

skin prick testing should always be interpreted in conjunction with the patient's history. This is described in detail in Chapter 16, Allergy.

Skin biopsy

A skin biopsy is performed when there are uncertainties about the clinical diagnosis, to exclude or investigate an evolving condition, or if there is poor response to therapy. It involves removing a sample of tissue from the affected area. It is particularly useful in the diagnosis of vesiculobullous diseases (e.g. epidermolysis bullosa) and skin lesions. The specimen can be processed for routine histology, direct immunofluorescence and for microbial tissue culture. General anaesthesia is rarely required for small skin biopsies. It is essential that specialist paediatric nurses and play therapists help to distract the children, who are often able to tolerate the procedure if topical anaesthetics, such as EMLA™ (eutectic mixture of local anaesthetics, 2.5% lidocaine and 2.5% prilocaine) or Ametop™ (3% amethocaine gel), are applied before infiltration with local anaesthesia. Types of biopsy are shown in Box 25.1.

Treatment

Principles of therapy

In general, the principles of skin treatment in paediatric patients are similar to those in adults. However, as only a few agents have been specifically designed or tested for paediatric use, topical therapy is generally the preferred choice of therapy. Topical therapy allows the medication to be delivered directly to the skin, with reduced risk of systemic toxicity.

Topical therapy

When a topical treatment is prescribed, it is important to specify the base (ointment, cream, gel, lotion and foam), quantity, site and frequency of application.

Emollients, soap substitutes and bath additives

Emollients are bland substances that hydrate the skin. They are occlusive to varying degrees and reduce transepidermal water loss. Emollients are indicated not only in dry skin but also in inflammatory skin conditions. They can also be used as bath additives and soap substitutes to soothe dry, flaky and itchy skin.

In general, ointments are occlusive and allow for high transcutaneous penetration of the active drug. They are also bacteriostatic and contain less preservatives and additives. However, they are messy to use, can potentially cause folliculitis (if applied against the direction of hair growth) and pose a fire hazard (e.g. emulsifying ointment or 50% liquid paraffin in white soft paraffin). Creams are suspensions of oil in water. They are less messy to use but can occasionally be sensitizing due to preservatives and additives. Lotions are powders suspended in water, whereas gels are often an alcohol–water mixture. Both are useful for large and hairy areas such as the scalp. However, they tend to be drying and are not suitable for dry, scaly conditions such as atopic dermatitis.

Topical antibiotics

Bacterial skin infections are common in young children and are often seen coexisting with a flare of atopic dermatitis. Mild to moderate skin infections can be treated with a topical antibiotic agent. Topical fusidic acid can be effective for the treatment of skin infections that are due to *Staphylococcus*. However, bacterial resistance to fusidic acid has increased in recent years, and its use should therefore be limited to 1–2 weeks.

Topical mupirocin is another topical antibiotic which is effective for skin infections caused by *Staphylococcus aureus*, *Streptococcus pyogenes* and other Gram-positive organisms. Resistant strains are also being recognized. Its use should be limited and it should only be prescribed when clinically indicated.

Topical antifungals

Topical antifungals such as clotrimazole and miconazole are effective for superficial fungal infections of the skin and napkin dermatitis. However, they are not effective for fungal infections affecting the hair and nails.

Topical steroids

Topical corticosteroids have anti-inflammatory properties and are indicated for acute and chronic inflammatory dermatoses. Broadly speaking, there are four strengths of topical steroid: mild (hydrocortisone),

moderate (betamethasone valerate cream 0.025%, clobetasone butyrate 0.05%), potent (betamethasone valerate 0.1%, mometasone furoate 0.1%) and very potent (clobetasol propionate 0.05%, diflucortolone valerate 0.3%). Potential local side effects with chronic use of topical steroids include striae, petechiae, telangiectasia, skin atrophy and steroid-induced acne. These side effects are correlated with the length of use and potency of topical steroid. Systemic side effects with topical steroids are generally rare. It is advised to:

- Only use low potency steroids in skin fold areas
- Use mild topical steroids initially and step up to stronger preparations if no response
- Avoid prolonged use of very potent topical steroids
- Avoid the use of topical steroids on the periorbital region
- Avoid the use of occlusion with topical steroids
- Limit applications to up to twice a day, limit duration of therapy, and consider an alternative steroid-sparing agent (e.g. topical calcineurin inhibitor) as maintenance therapy

Steroid phobia and inadequate explanation is a common cause of treatment failure. The use of fingertip units provides a rough guide to the application of an appropriate amount of topical steroids. One fingertip unit (FTU) weighs approximately 0.5 g and corresponds to the palmar surface of the distal phalanx of an adult index finger. It should treat an area of skin in a child equivalent to the size of two adult palms with the fingers together.

Topical calcineurin inhibitors

Topical calcineurin inhibitors (e.g. tacrolimus 0.03% and 0.1%, and pimecrolimus) have immune-modulating and anti-inflammatory properties. They are often used as steroid-sparing agents in the maintenance phase of treatment for atopic dermatitis. As they do not cause skin atrophy, they can be used safely on the face and skin folds.

Wet wraps and bandages

Wet wraps can be used for short periods in infants and children with flares of atopic dermatitis that have not responded to standard treatment. The wraps enhance the effects of topical treatment, provide a cooling effect and prevent damage to the skin by scratching. Topical treatments are applied underneath the wet tubular dressings, followed by dry tubular bandages on top. The wraps can be left overnight or longer if tolerated. Wet wraps should be avoided on infected skin.

Laser therapy

Laser (light amplification by stimulated emission of radiation) therapy is commonly used in paediatric patients for the treatment of port wine stains and congenital pigmented lesions.

Port wine stains are capillary vascular malformations of developmental origin characterized by permanent macular erythema. They affect 3 in 1000 newborn infants. Involvement of a trigeminal nerve distribution or the periorbital region may warrant further investigations to rule out Sturge–Weber syndrome and glaucoma. Pulsed dye laser (PDL) generates pulsed emissions of light of high intensity (at wavelengths between 577 and 600 nm). These are at wavelengths preferentially absorbed by oxyhaemoglobin of red blood cells within the dilated superficial blood vessels, which leads to selective thermal damage to the blood vessels. In general, children under the age of 5 years require general anaesthesia as the procedure is painful. Older children may be able to tolerate the treatment with topical anaesthetics. Most children will require between four and six treatments over a period of 2 years. Younger children, pink (rather than purple) lesions, and lesions at certain sites such as lateral face, forehead and neck tend to respond better to treatment. Pulsed dye laser therapy is generally safe and has minimal side effects, which include post-inflammatory pigmentary changes, blistering, crusting, post-laser purpura (which settles after 5–10 days) and infections (rare).

Q-switched lasers such as Q-switched ruby (694 nm), Q-switched alexandrite (735 nm) and Nd:YAG (1064 nm) are potential treatment options for large congenital melanocytic naevi as they absorb melanin, a major chromophore of the epidermis. However, the decision for laser treatment should be balanced against the long-term unknown effects on the residual naevomelanocytes.

Congenital disorders

Ichthyoses

Ichthyoses are disorders of cornification which present clinically as dry, rough, and 'fish-like' scales (Table 25.7). They can be inherited or acquired. There are at least 20 forms of ichthyosis to date and all exhibit impaired barrier function with increased rates of transepidermal water loss (even though the stratum corneum is thicker).

Table 25.7 The main subtypes of ichthyoses

Diseases	Inheritance/genetic defect	Clinical features	Treatment
Ichthyosis vulgaris	An autosomal dominant condition due to mutations in the *FLG* gene (filaggrin), which encodes profilaggrin (a keratohyalin protein which attracts water into the corneocyte and is required for the hydration of stratum corneum). *FLG* defect is also seen in individuals with atopic dermatitis.	Most common and mildest form of generalized ichthyosis. Features are not present at birth, but usually manifest within the first year of life. Prominent scaling mainly over the extensor surfaces of the legs and palmoplantar aspects (hyperlinear palms and soles). Flexural areas are spared. Scaling is often improved in warm, humid climate. The condition is associated with atopic dermatitis.	Regular emollients. Preparations containing mild keratolytic agents, such as urea or lactic acid, are often preferred over other aggressive agents. The use of vitamin D analogues and topical/systemic retinoids are not indicated, and can potentially aggravate or reveal atopic dermatitis.
Lamellar ichthyosis	An autosomal recessive condition, most commonly due to mutations in the *TGM1* gene (transglutaminase 1), which plays a key role in the formation of the cornified cell envelope in the epidermis.	Often presents as a collodion baby at birth. Widespread scaling (often dark) with flexural involvement. Nail dystrophy and hyperkeratosis of the palms and soles are common. Heat intolerance due to impaired sweating is a common complication. Ocular complications such as ectropion and conjunctivitis may occur.	Regular use of emollients, such as petrolatum and/or lanolin-based emollients. Topical keratolytics, such as 20% propylene glycol and 5% lactic acid, can be helpful. Systemic retinoids are of great benefit, but the risks of retinoids (especially teratogenicity) in this age group need to be balanced and discussed.
Epidermolytic hyperkeratosis (Congenital bullous ichthyosiform erythroderma)	An autosomal dominant condition, due to mutations in the keratin 1 or keratin 10 genes, which produce keratin filaments that provide mechanical durability to the epidermis.	Skin is moist and red at birth. May present with widespread blisters at birth. Following birth, blistering becomes less frequent and hyperkeratosis develops. Scaling is worse over the flexural areas.	Regular use of urea-containing emollients. Use of systemic retinoids may worsen the blistering.
Recessive X-linked ichthyosis	A recessive X-linked condition due to mutations in the *STS* gene (steroid sulphatase), which is localized to the distal short arm of the X chromosome. The absence of steroid sulphatase causes a shift in lipid composition in the stratum corneum, and affects epidermal barrier function.	Commonly presents within the first weeks of life as generalized scaling. The face, antecubital and popliteal fossa are usually spared. The palms and soles are usually not affected. Nails are usually normal. Most patients improve during summer and in more humid climate. May be associated with testicular maldescent and ocular opacities.	Regular use of emollients. Topical retinoids may be helpful. The use of oral retinoids is usually not warranted.
Harlequin ichthyosis	An autosomal recessive condition due to mutations in the *ABCA12* gene which result in keratinocytes with abnormal or empty lamellar bodies and stratum corneum retention.	Most infants are born prematurely with thick scales covering the entire body. There is usually marked ectropion and eclabium. The nose, ears and digits are usually deformed. Affected neonates may not survive beyond a few days.	Neonates need to be admitted to intensive care with monitoring of body temperature and fluid balance. Nutritional requirements are increased due to protein and heat losses. Assisted ventilation may be required until the restrictive scales are shed. Occlusive ointments (petrolatum) are recommended to all skin. The use of retinoids is controversial.

Epidermolysis bullosa

Epidermolysis bullosa (EB) is a severe, inherited blistering skin disorder characterized by extremely fragile skin and recurrent blister formation, resulting from minor trauma. There are three major types of EB, depending on the site of blister formation within the skin: EB simplex, EB junctional and dystrophic EB. EB simplex is the commonest type of EB. Almost all cases of EB simplex are autosomal-dominantly inherited, due to mutations in the keratin 5 or 14 genes, which provide strength and resilience to the epidermis. As a result, blisters form within the epidermis and heal without scarring. Patients with EB simplex often have mild symptoms with recurrent blisters limited to hands and feet. The nails and mucosal surfaces are usually not affected.

Junctional EB (JEB) is an autosomal recessive condition due to mutations in the laminin 332 or collagen XVII genes, which play an important role in attaching the epidermis to the underlying structures. As a result, blisters form within the DEJ. Patients with JEB often present with generalized blistering at birth. Blisters often heal with atrophic scar formation. There is usually mucosal, nail and teeth involvement. The condition can be lethal.

Dystrophic EB is due to mutations in the collagen VII gene, which result in blister formation in the upper dermis. It can be inherited in an autosomal dominant or recessive pattern. Dominant dystrophic EB presents with widespread blistering at birth. Blistering becomes localized to friction sites over the years. Milia (small white spots) often form at sites of previous blisters. Recessive dystrophic EB (RDEB) may present with widespread blistering at birth or mild disease. Severe blistering leads to scarring and deformity. Involvement of the gastrointestinal tract results in oesophageal strictures and faltering growth. Many children require gastrostomy feeding. Patients with RDEB are at risk of chronic wounds and skin cancer (squamous cell carcinoma) development. With mucosal involvement, patients are also at risk of other systemic complications such as nutritional impairment, which can lead to iron deficiency anaemia, failure to thrive and osteoporosis.

The diagnosis of EB often requires a skin biopsy with genetic testing. The management of EB is extremely challenging and requires a multidisciplinary team led by an expert in EB. In terms of local skin care management, fresh blisters should be popped with a sterile needle, and non-adherent dressings (instead of adherent dressings) should be used. Children need to be regularly reviewed and screened for systemic complications and be managed accordingly. The affected family needs to be provided with genetic counselling and support.

Further information on EB can be found on the DEBRA international website (see Further reading).

Inflammatory disorders of the skin

Atopic dermatitis (eczema)

Atopic dermatitis is a chronic inflammatory skin condition mainly of childhood. It is the most common type of dermatitis, and affects 1 in 5 children in the UK. Children presenting with eczema will often have a strong personal or family history of atopic disorders (e.g. eczema, asthma and hay fever; see Chapter 16, Allergy). Clinically, atopic eczema presents as dry red itchy skin. It often presents on the face in infancy (cheeks), and gradually spreads to the trunk and limbs (predominantly flexural involvement).

infantile seborrhoeic eczema (predominantly scalp involvement with greasy, scaly and crusty rash) and infantile acne (non-itchy papules and pustules rather than dry red patches).

What is the most likely underlying genetic abnormality?

The most likely genetic mutation is in the filaggrin gene (FLG), which encodes a protein that aggregates keratin filaments during terminal differentiation of the epidermis (filaggrin, filament aggregating protein). This mutation has been shown to be a major predisposing factor for atopic dermatitis.

What is your initial management plan?

The initial management plan should include informing the parents about the condition and the avoidance of potential triggers. Common triggers for eczema include skin irritants (e.g. detergents, soaps, perfume and wool clothing), pets, house dust mites, stress, extremes of temperature, cigarette smoke and infections. Management of eczema should also include treating the skin dryness and skin inflammation. Soap substitutes and regular emollients will help to maintain skin hydration. Topical anti-inflammatories, including topical steroids and topical calcineurin inhibitors, are helpful to treat skin inflammation. In severe cases, oral steroids, phototherapy and oral immunosuppressants may be considered.

What is Mark at risk of developing due to his skin condition?

Repeated scratching can lead to post-inflammatory pigmentary changes, lichenification, and even scarring. Atopic skin is also more susceptible to infections due to impaired skin barrier function and reduced cell-mediated immune response.

Recent scientific advances which have improved clinical practice – atopic dermatitis

Although topical and systemic corticosteroids are the most effective therapy for managing skin inflammation in atopic dermatitis, they can cause local and systemic side effects with long-term use.

Tacrolimus is an immunosuppressive agent used typically in transplant patients to prevent organ rejection. In 1994, Nakagawa et al first reported the efficacy of topical tacrolimus for atopic dermatitis in an open trial of 50 patients. Since then, several randomized controlled trials have confirmed the efficacy of topical tacrolimus for atopic dermatitis. Due to its effect in inhibiting T-cell activation and thereby suppressing the inflammatory response, it is now considered an effective steroid-sparing agent for atopic dermatitis that does not cause skin atrophy.

Fig. 25.8 **Excoriated red weepy patches on the face.** *(From Levene M. MRCPCH Mastercourse 2007. Elsevier, Churchill Livingstone, with permission.)*

Psoriasis

Psoriasis is a chronic immunological skin condition that occurs in adults and children. It is characterized by skin hyperproliferation, and can be associated with joint and nail disorders. It affects 1–2% of British, Europeans and North Americans. Psoriasis in children may resolve within months of presentation (especially guttate psoriasis), or persist into adulthood. Early-onset large-plaque psoriasis tends to be persistent and challenging to treat. It has a strong genetic component, with the HLA-Cw6 gene being the most common association. Clinically, it presents with symmetrical, well-defined, red plaques with thick silvery scales, which reveal tiny bleeding points when the surface is scraped (Auspitz sign). The affected areas are usually asymptomatic. The commonly affected sites include the scalp and extensor surfaces. Psoriasis may also affect the genitalia. Some 20% of patients with psoriasis have arthropathy and a third have nail changes. The main nail changes are: pitting, onycholysis (separation of the nail plate from the nail bed) and subungual hyperkeratosis. Various patterns have been described, but guttate, facial and flexural psoriasis are particularly common in children.

Acne

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit. It is a multifactorial disease that is dependent on hereditary, environmental and hormonal factors. It usually starts in puberty, when the androgen levels, growth hormones and insulin-like growth factors are elevated. It is characterized by the presence of non-inflammatory lesions (comedones), inflammatory lesions (papules and pustules) and post-inflammatory pigmentary changes. Acne tends to affect areas that have high levels of seborrhoea, such as the face, chest and upper back. *Propionibacterium acnes (P. acnes)* is a Gram-positive, anaerobic bacterium which plays a major role in inflammation. *P. acnes* produces a number of enzymes and metabolites that directly damage the host tissue, and stimulates production of pro-inflammatory cytokines and neutrophil recruitment. Acne patients have been shown to have increased numbers of *P. acnes*, and reduction of *P. acnes* numbers by antimicrobial agents correlates with clinical improvement of acne. Four pathogenic factors have been described to cause acne and they include: comedogenesis due to follicular hyperkeratinization, sebaceous hyperplasia and increased sebum production, hypercolonization of *P. acnes*, and inflammation. Severity of acne can generally be graded into mild (usually comedogenic type), moderate (usually papulopustular type) and severe (usually nodulocystic type or with evidence of scarring).

First-line treatments for mild acne are benzyl peroxide, salicylic acid, topical retinoid (e.g. adapalene), azelaic acid and topical antibiotics (e.g. clindamycin). Benzyl peroxide reduces the levels of *P. acnes* but can stain the clothing and bedding. Salicylic acid is keratolytic but is generally not as effective as other topical agents. Topical retinoids prevent the formation of new comedones. Azelaic acid inhibits the growth of *P. acnes* and normalizes the follicle. Topical antibiotics inhibit the growth of bacteria and have mild anti-inflammatory actions. Systemic treatments such as oral antibiotics and oral anti-androgens are used for moderate severity of acne. Oral retinoids (isotretinoin) are the most effective treatment for severe acne as it modifies all four pathogenic factors. However, there are several side effects including teratogenic, cheilitis, dryness, increased photosensitivity, musculoskeletal complaints, pseudotumour cerebri, hypertriglyceridaemia, hypercholesterolaemia, hyperostosis at sites of tendon closure, and the potential risks of depression, suicidal ideation, suicide and possibly triggering inflammatory bowel disease. Most side effects are dose-dependent and reversible. For this reason, patients will need regular blood and clinical monitoring, and female adolescents must use oral contraceptives for at least one month before they can be started on the treatment.

Acne variants

Neonatal acne is common on the cheeks of newborns. The onset is usually 3 weeks post-partum and it lasts for about 3 months. Typical lesions include papules and pustules (comedones are less common). This is due to activated sebaceous glands during the last trimester of intrauterine life, which regress by the third postnatal month. It is usually self-limiting and no treatment is needed. Benzyl peroxide, azelaic acid and topical antibiotics can be used if needed.

Infantile acne is rare and usually begins after the third month of life. It appears mainly on the cheeks and lasts for about 2 years. Typical lesions can range from comedones, papule and pustules, to nodules and scars. It may be due to elevated luteinizing, follicular-stimulating and testosterone hormones. Treatment options are similar to adolescent acne.

Skin infections and infestations

Skin infections are common in childhood and can generally be divided into three main types: bacterial (e.g. staphylococcal and streptococcal), viral (e.g.

human papilloma virus, herpes simplex and varicella zoster) and fungal (e.g. yeasts). Skin swabs for microbiology and virology from clinically infected areas may be indicated to confirm bacterial and viral skin infections, whereas skin scrapes are helpful to confirm fungal skin infections. Treatment for skin infections should be tailored according to the causative organisms. Apart from skin infections, skin infestations are also common in children, particularly scabies and pediculosis capitis (head lice).

Scabies

Scabies is a skin infestation of *Sarcoptes scabiei* var. *hominis* in the skin. The mite is host-specific for humans and is transmitted by close contact. Infants and children are particularly prone to this infestation due to the close contact with other children at daycare centres and with their parents. Pruritus and skin rash usually start one month after the initial infestation with the mite. In infants, scabies burrows (a serpiginous tract) are most commonly found on the palms and soles. In children and adults, the burrows tend to be on the hands, feet, axillary folds, umbilicus and genitalia. Diagnosis is confirmed by a skin scrape of the contents of the burrow with the tip of a needle or a scalpel blade. Specimens are placed in a drop of mineral oil or potassium hydroxide (KOH) and examined microscopically. Burrows can also be visualized with a dermatoscope. Treatment consists of elimination of the mites with a topical insecticide (e.g. permethrin) or, in severe cases and in children older than 5 years of age, an oral anthelmintic agent (e.g. ivermectin). Close contacts should undergo the same treatment and all clothing and bedding should be hot washed. Pruritus and skin lesions usually resolve within 1–3 weeks with effective treatment unless re-infestation occurs. Scabies nodules may take months to clear and topical steroids are often helpful.

Pediculosis

Pediculosis capitis (head lice) is a common skin infestation in children. Transmission is primary via close head-to-head contact. Symptoms such as pruritus and stinging sensation are usually not apparent until a few weeks later due to the sensitization to the saliva and faecal material of the louse. The female louse cements its eggs to the proximal hair shaft for warmth, giving rise to the main clinical finding of nits on hair shafts. Diagnosis is made clinically and can be aided with dermoscopy to visualize the eggs of the lice. Topical pediculicides (e.g. lindane, malathion, pyrethrins and pyrethroids) are the standard treatment. All close contacts should also be examined carefully.

🧑‍⚕️ Case history

Fever and redness of the skin

John is a 3-year-old boy who presents to the accident and emergency department with fever and widespread redness of the skin. He is extremely irritable and his mother has noticed a few blisters and areas that look like a burn.

What is the differential diagnosis?

The most likely diagnosis is staphylococcal scalded skin syndrome. It is a bacterial skin infection characterized by red blistering skin that looks like a burn, or scald. It occurs mostly in children younger than 5 years. The blisters are superficial and typically occur around the flexures of the neck, axillae and groin. Affected children often have a fever and are irritable. Differential diagnosis should include burns, abuse and neglect, and blistering skin disorders.

What is the most likely causative organism?

Staphylococcal scalded skin syndrome often starts from a localized staphylococcal skin infection (i.e. *Staphylococcus aureus*). The bacteria release exotoxins that bind to the cell attachments (desmosomes) and cause the skin to blister easily.

What is the initial management plan?

The initial management plan should include hospitalization to start intravenous antibiotics to eradicate the staphylococcal infection. Other supportive treatment includes paracetamol for fever and pain, fluid management and skin care with emollients and non-adhesive dressings, if required. The blisters may persist for several days due to the toxin, despite treatment with antibiotics.

Disorders of pigmentation

The colour of human skin is highly variable, regulated by genetic, hormonal and environmental factors, which modulate the type, amount and distribution of melanin in the skin, hair and eyes. The synthesis of melanin occurs in melanosomes, which are contained in melanocytes that are situated within the basal epidermal layer. These melanosomes are then transferred to the surface keratinocytes. Within melanosomes, tyrosinase plays a critical role for melanogenesis, with P protein involved in regulation of the pH within melanosomes. Darker skin types have higher eumelanin-to-phaeomelanin ratio, larger melanosomes and slower melanosome degradation. In general, hyperpigmentation of the skin is due to an increased number, or activity, of melanocytes; whereas

hypopigmentation is often due to a reduction of melanocytes, or a reduction or inability of melanin production, or transport of melanosomes. Some of the common disorders of pigmentation are discussed below.

Post-inflammatory hyperpigmentation

Post-inflammatory hyperpigmentation is a common consequence of trauma or inflammation to the skin due to increased melanin production in the skin. Darker-skinned individuals tend to develop post-inflammatory hyperpigmentation and the skin changes can be long-lasting.

Café-au-lait macules

Café-au-lait macules are tan or brown macules, which are present at birth or in infancy. They are due to an increase in melanin in melanocytes and basal keratinocytes. About 10–30% of individuals have an isolated café-au-lait macule. However, the presence of more than six café-au-lait macules should raise suspicion for an underlying systemic disorder, such as tuberous sclerosis, neurofibromatosis, McCune–Albright syndrome or Fanconi anaemia.

Albinism

Albinism consists of a group of genetic disorders characterized by partial or total absence of melanin pigment within the normal number of melanocytes in the skin, hair follicles and eyes. There are two main types of albinism: oculocutaneous (OCA) and ocular albinism. OCA albinism is the most common inherited disorder. OCA subtypes 1 and 2 are the most common subtypes, and both are inherited in an autosomal recessive pattern. OCA1(A) presents characteristically with white hair, blue-grey eyes, and milky white skin. Due to an absence of tyrosinase activity, which leads to no synthesis of melanin, these patients are extremely photosensitive and have a strong predisposition to skin cancer. They may also have significantly impaired vision. OCA1(B) patients have a reduction in their tyrosinase activity and typically present with little or no pigment at birth, but they develop some pigmentation of the hair and skin gradually with age. The tyrosinase enzyme is temperature-sensitive, which loses its activity above 35°C, and as a result, melanin synthesis does not occur in warmer areas of the body, i.e. axillary region and scalp. The OCA2 patients have normal tyrosinase activity. However, due to a lack of functional P proteins, these patients have variable pigmentary dilution of the hair, skin and iris. They are able to develop pigmented melanocytic naevi in sun-exposed areas over time.

Fig. 25.9 White patches around the mouth.

Vitiligo

Vitiligo is an acquired skin disorder due to destruction of melanocytes resulting in white patches on the skin. About 50% develop before the age of 20 years. It is thought to be an autoimmune disorder and is associated with other autoimmune conditions, such as diabetes mellitus, thyroiditis, pernicious anaemia, alopecia areata (patchy areas of non-scarring hair loss), primary biliary cirrhosis and Addison's disease. Common sites include peri-orificial areas (around the mouth (Fig. 25.9), eyes, nipples, umbilicus), nappy area, body folds, sites of injury, and around pigmented moles. The patches are liable to sunburn. Spontaneous repigmentation occurs in a minority.

Case history

White facial patches
A 2-year-old boy presented with a 3-month history of symmetrical white patches on his face. He has a previous history of patchy hair loss. There is a family history of hypothyroidism.

What is the differential diagnosis?
The most likely diagnosis is vitiligo, which presents with depigmented white patches, which are often symmetrical. This is in keeping with his previous history of alopecia areata, which has an autoimmune association with vitiligo. Differential diagnoses include post-inflammatory hypopigmentation (pale rather than white patches and often with a previous history of skin disease/skin inflammation), pityriasis alba (pale patches limited to the face, thought to be post-inflammatory, preceded by eczema), and pityriasis

versicolor (yeast infection causing pale or brown scaly patches).

What are the potential treatment options for his skin?

As the main mechanism of vitiligo is thought to be an autoimmune lymphocytic attack on the melanocytes, the treatment options for vitiligo consist of various immunosuppressive and/or immune-modulating agents such as topical steroids, topical calcineurin inhibitors and phototherapy. Most patients are partially responsive to topical steroids. However, the risks of skin atrophy and telangiectasia preclude the prolonged use of topical steroids. In recent years, topical calcineurin inhibitors (e.g. tacrolimus 0.1% ointment) have been found to be effective for vitiligo, but with fewer side effects as compared to topical steroids. Sun protection, with sunscreens and protective clothing, and cosmetic camouflage can help to reduce the contrast between normal and the depigmented skin.

What are the potential side effects of topical steroids?

The potential long-term side effects of topical steroid use include skin infections, skin atrophy (telangiectasia, bruising and striae due to thinning of the skin), glaucoma and cataracts (prolonged use around the eyes), and allergic reactions (due to preservatives and additives in creams). The parents should be re-assured that most side effects are avoidable if appropriate strength and quantity of steroids is prescribed.

Manifestations of systemic disease

Skin signs of systemic disease can be a marker for systemic disease. In some cases, they can be an early or the only presentation of an otherwise asymptomatic systemic disease.

Erythema multiforme

Erythema multiforme (EM) is a self-limited hypersensitivity reaction usually triggered by infections, most commonly herpes simplex virus. The herpes simplex infection usually precedes the skin rash by a few days. Less than 10% of the cases are due to drugs such as penicillins, non-steroidal anti-inflammatory agents, and anti-convulsants.

EM is characterized by red papules which evolve into target lesions, with the tendency to recur. There is usually no prodromal illness prior to the onset of the skin lesions. The skin lesion has a sharp margin and three concentric rings – a dusky centre, a middle zone of pale oedema and an outer zone of erythema. Mucosal involvement can be involved in EM major. EM is considered to be a distinct condition from Stevens–Johnson syndrome and toxic epidermal necrolysis. It does not progress into either of these conditions. Treatment is directed to the underlying cause and symptomatic/supportive treatment for the skin may be needed. Patients with recurrent EM may have to be considered for long-term antivirals for 6–12 months.

Stevens–Johnson syndrome and toxic epidermal necrolysis

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, severe adverse cutaneous reactions usually due to drugs and less commonly associated with infections and vaccinations. Infections are generally associated with less severe disease than when drugs are the cause.

The most common drugs that cause SJS and TEN are antibiotics (sulphonamide, penicillins, cephalosporins), antivirals (nevirapine), antifungals (imidazole), allopurinol, non-steroidal anti-inflammatory agents (ibuprofen), and anti-convulsants (phenytoin, sodium valproate, carbamazepine, phenobarbitone). The onset is usually within the first month. Clinically, SJS is characterized by tender macules, target lesions, blisters with mucosal involvement with less than 10% skin detachment. SJS is characterized by the same skin lesions with epidermal detachment of between 10% and 30%, whilst TEN has greater than 30% skin detachment. There is usually a prodromal illness and the patient is often very ill with fever, malaise, cough, headache and rhinorrhoea. The Nikolsky sign (blistered skin on rubbing) is usually positive. Skin biopsy is usually required to diagnose the condition and typically shows keratinocyte necrosis in the epidermal layer with minimal inflammatory infiltrate in the dermis. Reported mortality of SJS is around 5%, whereas it is 30–50% with TEN. Management usually requires admission to the intensive care or burns unit, prompt withdrawal of the culprit drug, and installation of supportive treatment. The use of systemic corticosteroids, ciclosporin and intravenous immunoglobulin remains controversial.

Erythema nodosum

Erythema nodosum is the most common form of panniculitis presenting in both children and adults. It is thought to be a delayed hypersensitivity reaction to various stimuli. Clinically, it is characterized by symmetrical, tender erythematous nodules and plaques on the anterior lower legs, which heal without

scarring. Although the majority of cases are idiopathic, several potential causes have been reported in childhood, including infections (streptococcal and non-streptococcal respiratory infections, pneumonia, cat-scratch disease, tuberculosis, parvovirus, Epstein–Barr virus, dermatophytes), inflammatory diseases (e.g. inflammatory bowel disease, sarcoidosis, Behçet's disease, ankylosing spondylitis), drugs (e.g. oral contraceptive pills, antibiotics) and malignancy (leukaemia, Hodgkin's lymphoma, Langerhans cell histiocytosis). Treatment should be directed at the underlying cause. Supportive measures, such as bed rest and pain relief, may be all that is needed.

Morphoea

Morphoea (localized scleroderma) is a connective tissue disease characterized by initial oedema and hyperaemia of the skin, followed by fibrosis, sclerosis and, finally, atrophy of the skin. There is occasionally deeper involvement of the skin extending into the muscles or bone. It needs to be distinguished from systemic sclerosis (systemic scleroderma), which is a multisystem disease causing fibrosis and vascular abnormalities. Morphoea has an incidence of 1–2.7 per 100,000 individuals and predominantly affects females. The aetiology is still unknown. Several triggers have been described, including localized skin trauma, tick bites (Lyme disease due to *Borrelia burgdorferi*), pregnancy, viral infections, medications and autoimmune diseases. Linear morphoea is the most common subtype and usually a limb is affected. The lesions often start with an inflammatory patch, which progresses to become indurated and indented. Deeper involvement of the muscle or bone can result in shortening of the limb and joint contracture. *En coup de sabre* is a term used to describe linear morphoea of the head. It is often associated with scarring alopecia on the scalp and partial loss of eyebrows or eyelashes. A small proportion of patients (8–13%) with *en coup de sabre* experience neurological symptoms such as seizures, headaches and focal weakness. In addition, the eyes may be involved (e.g. uveitis, fixed pupils, globe retraction, and ocular changes), and there may be problems affecting the jaw and tongue.

Auto-antibodies (ANA, anti-Ro/SSA and rheumatoid factor) are often positive in these children; however, the relevance of this is uncertain. Anti-topoisomerase I antibodies (anti-Scl-70), on the other hand, a marker for systemic sclerosis, are rarely detected in these children. Clinical examination is most important to assess for progression of the disease. Other useful tools include ultrasound and/or magnetic resonance imaging (MRI, especially for neurological involvement).

Mild disease (confined to skin only) can be treated with topical steroids, vitamin D analogues, topical calcineurin inhibitors, and phototherapy (ultraviolet A1 (UVA1) or psoralen plus ultraviolet A (PUVA)). Severe disease can be treated with the combination of systemic steroids and methotrexate.

Henoch–Schönlein purpura

Henoch–Schönlein purpura represents the most common childhood vasculitis predominantly affecting small vessels. It often affects children between the ages of 4 and 7 years. It is often preceded by infections (upper respiratory tract infections) and manifests with palpable purpuric skin lesions on both legs and/or buttocks, arthritis, abdominal pain and nephritis. Spontaneous resolution occurs in up to 94% within 4 weeks. Due to this, the vast majority of patients only need supportive measures, such as hydration, bed rest, elevation of affected limbs and symptomatic pain relief. Of note, renal manifestations can present up to 6 months following the onset of skin lesions, and persistent proteinuria and severe renal symptoms (nephritis/nephrotic syndrome) are indicators of a worse prognosis.

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John W Gregory

Diabetes and endocrinology

The endocrine axis and hormonal regulation

Hormones are secreted by endocrine organs and, following circulation in the blood, bind to specific receptors which are broadly subdivided into two groups. Cell surface receptors on the plasma membranes bind to hydrophilic hormones such as insulin, catecholamines and those produced by the pituitary. Steroids and thyroid hormones, which are lipid soluble, enter cells to bind with cytosolic and nuclear receptors. Cell receptor sensitivity can be increased by increasing the number of binding sites through increased receptor synthesis or decreased degradation. Desensitization occurs when receptors are reduced in number, internalized from surface locations or molecules are recruited which deactivate intracellular signalling pathways.

Cell surface receptors are subdivided into two groups. In one group, the signalling is initiated by tyrosine kinase. They are known as growth factor (insulin, insulin-like growth factor-1, epidermal growth factor, fibroblast and platelet-derived growth factor) receptors. The other group are G-protein coupled receptors (GPCR). Defects in GPCRs can lead to both hormone resistance (mutations of the thyroid stimulating hormone (TSH) receptor can cause resistance to TSH) and also to upregulated activity (mutations of the luteinizing hormone (LH) receptor lead to testotoxicosis, while mutations of the TSH receptor can lead to neonatal hyperthyroidism). Mutations adversely affecting $G\alpha_s$ function cause pseudohypoparathyroidism and when maternally inherited lead to the downregulation of a range of GPCRs. By contrast, upregulation of $G\alpha_s$ function is associated with McCune–Albright syndrome, which is associated with upregulation of several GPCRs leading to the clinical features which include gonadotropin-independent precocious puberty (LH receptor), thyrotoxicosis (TSH receptor), Cushing's syndrome (ACTH receptor), hyperpigmented skin lesions and fibrous dysplasia.

Sex steroids, glucocorticoids, aldosterone and thyroxine are hydrophobic hormones which diffuse across the target cell membrane and bind to intracellular

receptors located in the cytoplasm (glucocorticoids) or nucleus (androgens and thyroxine). The response to these hormone receptors therefore takes longer than those associated with cell surface receptors. Some hormones, such as testosterone and T4, may be converted once intracellular to more potent forms such as dihydrotestosterone and T3 by 5α-reducatase and 5′-deiodinase, respectively. By contrast, 11β-hydroxysteroid dehydrogenase converts cortisol to a weaker metabolite, cortisone, in aldosterone-responsive cells in the kidney to avoid overstimulation of the mineralocorticoid receptor. Defects in the genes that encode these intracellular receptors lead to hormone resistance such as androgen insensitivity syndrome, glucocorticoid resistance and resistance to thyroid hormone.

Blood glucose regulation

Embryology

The pancreas plays a major role in the regulation of blood glucose concentrations. The pancreas is endodermal in origin, arising from the embryonic foregut. Islet cell clusters differentiate from pancreatic bud endoderm, on the edge of which pancreatic islets form. Under the influence of Pax-6 β- and δ-cells, insulin and somatostatin are produced, respectively, whereas Pax-0 facilitates development of α- and γ-cells responsible for glucagon and pancreatic polypeptide production, respectively. Endocrine function is evident from 10–15 weeks' gestation, though what contribution this makes to fetal development is unknown.

Normal anatomy

Pancreatic endocrine function is regulated in the human by approximately one million clusters of cells known as the islets of Langerhans. Insulin-secreting β-cells occupy the central part of the islets of Langerhans and are surrounded by a 'rind' of glucagon-secreting α- and somatostatin-secreting δ-cells (Fig. 26.1). Islets are well vascularized to facilitate rapid hormone release and are also innervated by sympathetic and parasympathetic neurons, implying that there is a neurological contribution to pancreatic endocrine regulation.

Physiology

When blood glucose concentrations rise after feeding, insulin is secreted to convert glucose into glycogen (Fig. 26.2) and facilitate cellular uptake, where the glucose is converted to glucose-6-phosphate. By contrast, when glucose levels fall during fasting, concentrations are maintained through secretion of glucagon, which facilitates glucose production from glycogenolysis. Other counter-regulatory hormones such as cortisol, growth hormone and epinephrine also contribute to gluconeogenesis through protein degradation and lipolysis. The latter is particularly facilitated by the switching off of insulin release as blood glucose concentrations fall.

Triglycerides are transported in blood by very-low-density lipoproteins to target tissues where lipases promote hydrolysis of triglycerides into glycerol and free fatty acids. Glycerol is then metabolized to rejoin the glycogenolysis and gluconeogenesis pathways. Free fatty acids are transported across the mitochondrial membrane to undergo a process of beta oxidation, which generates two-carbon molecules of acetyl co-A, which can enter the citric acid cycle to ultimately generate ATP.

Important differences exist between young children and adults with respect to blood glucose regulation.
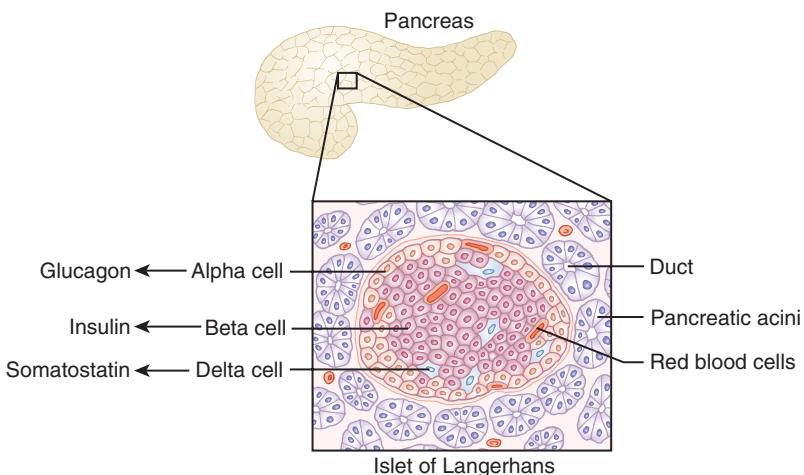
Fig. 26.1 Islet of Langerhans.
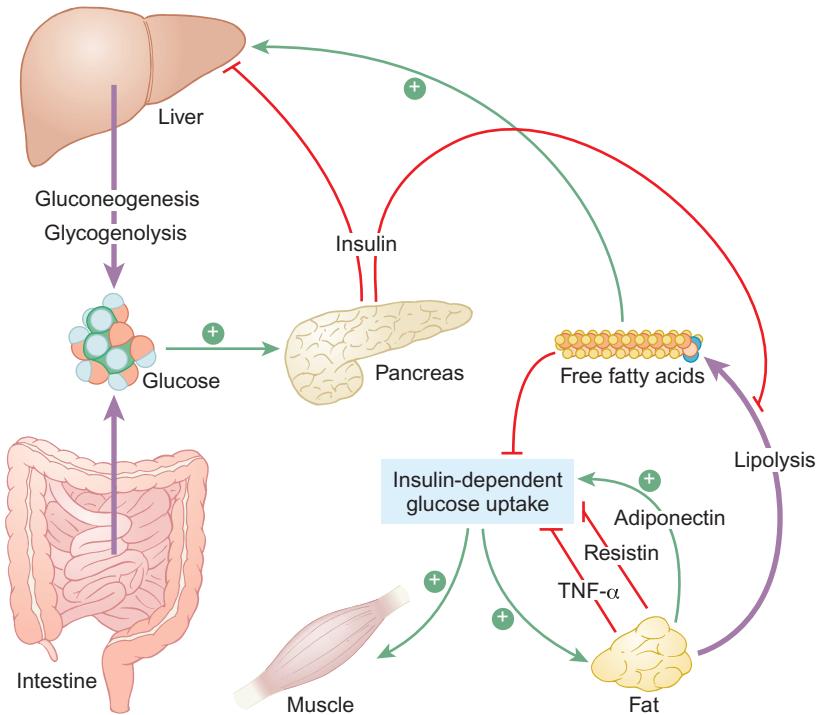
Fig. 26.2 Physiological response to feeding.

The young child is at particular risk from hypoglycaemia due to the relatively large brain size and limited glycogen stores. To compensate, infants in particular are able to generate ketones as an alternative cerebral fuel source more easily than adults.

Hyperglycaemia

History

In a child presenting with hyperglycaemia, the following history is important:

- Duration of symptoms such as polyuria, polydipsia, weight loss, lethargy, constipation or blurred vision
- Infection, particularly candidiasis
- Vomiting or abdominal pain might suggest ketoacidosis
- Family history of diabetes of any type or other autoimmune disease.

Examination

Many children with newly diagnosed diabetes will have no abnormal findings on clinical examination. In children with hyperglycaemia and presumed diabetes, the critical need is to distinguish between type 1 diabetes (T1D) and type 2 diabetes (T2D), as the approach to treatment will be very different for each form:

- Weight loss, dehydration, signs of acidosis such as Kussmaul breathing (deep and tachypnoeic, reflecting the respiratory effort to correct the metabolic acidosis) with sweet (acetone-smelling) breath, depressed consciousness and signs of cerebral oedema suggest type 1 diabetes
- Overweight, hypertension and acanthosis nigricans suggest developing insulin resistance and type 2 diabetes.

Investigations

In hyperglycaemic children, the following investigations need to be considered:

- If there is uncertainty about a diagnosis of diabetes, a random or two hour glucose tolerance test blood glucose of >11.1 mmol/L or fasting blood glucose >7 mmol/L indicates the presence of diabetes; however, in most children with type 1 diabetes, the diagnosis can be determined by clinical features and random blood glucose and no further investigations are required
- The degree of elevation in HbA1c levels, which may indicate the length of prodrome

- The presence of glutamic acid decarboxylase (GAD) antibodies indicates probable autoimmune-mediated T1D
- If a diagnosis of T1D seems likely, screening for other autoimmune disease (hypothyroidism, hyperthyroidism and coeliac disease) is indicated
- There can be uncertainty whether the child has T1D or T2D and a formal oral glucose tolerance test with measurement of high concentrations of insulin and c-peptide on baseline and two hour blood samples along with suppressed sex hormone binding globulin concentrations would indicate the presence of T2D.

Diseases of blood glucose regulation

Type 1 diabetes (T1D)

This is much the most common childhood form of diabetes, caused by T cell-mediated autoimmune damage to pancreatic β-cells evidenced by raised titres of GAD (glutamate decarboxylase) antibodies. There are strong HLA associations with linkage to the major histocompatibility class II genes DQA, DQB and DRB. It presents in genetically susceptible individuals with a more rapid onset evident in pre-school aged children than adolescents. The rapidly increasing incidence of type 1 diabetes, particularly in pre-school aged children implies in addition a change in some unknown environmental precipitant such as diet, viruses, hygiene or toxins. Although a classical presentation of polyuria, polydipsia and weight loss remains common, an increasing proportion are overweight at diagnosis, reflecting population changes in weight gain. Symptoms occur when approximately 90% of β-cells have been destroyed. Individuals with T1D are at increased risk of other autoimmune-mediated diseases such as coeliac and thyroid disease.

Treatment of T1D requires insulin injections two to four or more times daily or delivered by pump in a continuous subcutaneous infusion. In recent years, bioengineered insulin analogues have become available. One group (insulin lispro and insulin aspart) is very rapidly acting due to a change in their molecular structure which prevents polymerization into inactive hexamers following subcutaneous injection. Other long-acting forms work through molecular changes, which either shift their isoelectric point to result in precipitation and slow dissolution to release bioactive molecules (insulin glargine) or alternatively promote potent binding to albumin (insulin detemir) to prolong duration of action. Current research is evaluating autoimmune modulation at diagnosis to prolong residual β-cell activity, 'closing the loop' between continuous glucose sensing and insulin pump and islet cell transplants.

Affected individuals require considerable support and a detailed educational programme to help learn how to self-manage their diabetes through:

- Appropriate changes in insulin dose guided by the results of self blood glucose testing
- Their estimation of the carbohydrate content of food ('carb counting')
- Their estimation of the known effects of exercise on their blood glucose measurements.

The aim of treatment is to produce optimal blood glucose control, which reduces the risks of microvascular complications to a minimum. This is judged by repeat measurement of glycosylated haemoglobin (HbA1c), a consequence of non-enzymatic glycation of haemoglobin when exposed to plasma glucose. This provides an integrated measure of circulating blood glucose concentrations over the previous 2–3 months but may be unreliable in conditions which affect circulating red cell half-life such as haemoglobinopathies, in which circumstances other measures such as continuous glucose monitoring or fructosamine may be required.

Patients and their carers need to be trained to recognize hypoglycaemia and how to treat these episodes and also to have an awareness of the longer term effects of suboptimally managed diabetes. Inadequate insulinization in the short term leads to hyperglycaemia which, when it exceeds the renal threshold for capacity to reabsorb glucose, results in glycosuria and polyuria through concomitant osmotic effects. Excessive urinary glucose losses result in a negative calorie balance and in time weight loss. A cachexic state leads in the long term to growth hormone resistance with impaired growth and suppressed gonadotropin secretion causing pubertal delay. Excessive insulin deficiency leads not only to hyperglycaemia but also to ketosis due to lipolysis. Accumulation of ketones causes a progressive acidosis with vomiting and impaired consciousness. In the longer term, persistent hyperglycaemia produces microvascular changes in which the basement membrane of epithelial cells becomes damaged through the presence of excess glycoproteins, leading to retinopathy, nephropathy and neuropathy. There is clear evidence from the Diabetes Control and Complications Trial (DCCT) study in the USA, in which teenagers and young adults were randomized to either 'normal care' or intensive management with multiple daily injections of insulin and blood testing, that improved blood glucose control leads to dramatic reductions in all diabetes-related complications evaluated within 10 years. Furthermore, these benefits have persisted even when blood glucose

levels increased after the end of the trial, suggesting a 'memory effect' from this period of tight glycaemic control. These observations have driven an increased use of multiple daily injections and insulin pumps in routine clinical practice, to try and replicate the DCCT findings in routine care.

Type 2 diabetes (T2D)

This remains a relatively unusual cause of diabetes in childhood. Symptoms at presentation are similar to those of T1D, though ketoacidosis is less common. There is a clear genetic predisposition to T2D through different genes to those responsible for T1D. The primary mechanism appears to be obesity-induced insulin resistance with a secondary relative degree of insulin insufficiency leading to excessive hepatic release of glucose.

Management requires lifestyle changes to increase physical activity and reduce calorie intake to promote weight loss and increase insulin sensitivity. Most children require additional medical therapy using metformin, which acts primarily by suppressing hepatic gluconeogenesis. Additional therapy may be necessary using sulphonylureas, which bind to the potassium channel on the pancreatic β-cell, precipitating membrane depolarization, calcium influx and insulin release. Some individuals will also require additional insulin injections when adequate blood glucose concentrations cannot be achieved. Young people with T2D require similar screening to those with T1D for the development of microvascular complications. In addition, teenage girls are at risk of polycystic ovary syndrome (PCOS), which may cause distressing hirsutism and impair the menstrual cycle and fertility. The symptoms of PCOS may respond to the treatment of associated insulin resistance with metformin.

Other forms of diabetes

Genetic defects of genes (mostly transcription factors) expressed in the β-cell known as maturity-onset diabetes of the young (MODY) produce variable defects in insulin secretion (but not action). MODY is characterized by mild asymptomatic hyperglycaemia in non-obese children, often with a strong autosomal dominant family history of 'diabetes' associated with low or non-existent risks of complications. Most cases do not require treatment.

Rare causes of diabetes include those associated with mutations in mitochondrial DNA (e.g. maternally inherited diabetes and deafness syndrome and Kearns–Sayre syndrome) and those where insulin sensitivity is impaired by genetic defects in insulin receptor signalling (e.g. leprechaunism).

With increasing length of survival, teenagers with cystic fibrosis are at increasing risk of developing diabetes due to the combination of pancreatic destruction and insulin resistance, particularly during pulmonary exacerbations. This requires insulin treatment to support an unrestricted diet, whilst taking care to avoid hypoglycaemia, given the increased risks associated with coexistent α-cell damage.

Recently, neonatal diabetes has been recognized to be due to defects of genes expressed in the pancreatic β-cell. A particularly exciting outcome from understanding its pathogenetic basis has been the subsequent prediction and observation that in those with mutations of certain genes (encoding the Kir6.2 subunit of the ATP-sensitive potassium channel, KCNJ11), treatment with sulphonylureas can be even more effective than insulin, allowing patients to be weaned off daily injections.

Questions 26.1 and 26.2

Type 1 diabetes

A 14-year-old girl who was diagnosed with type 1 diabetes aged 8 years is admitted with an episode of ketoacidosis. Following rehydration and stabilization with intravenous insulin, she is found to have lost 8 kg in weight since her previous clinic visit 6 months earlier, having missed two appointments subsequently. She reports problems with recurrent hypoglycaemia and having had to reduce her daily dose of insulin (four injections daily) to less than 0.5 units/kg/day. She does not report any other symptoms of ill health. Inspection of her blood glucose diary shows largely normal blood glucose values but repeat measurement of her HbA1c shows a markedly elevated value (104 mmol/mol).

Question 26.1
What are the likely explanations for her weight loss? Answer each with true (T) or false (F).

A. Addison's disease

B. Coeliac disease

C. Eating disorder

D. Hyperthyroidism

E. Inadequate insulin therapy

Question 26.2
What additional treatment(s) is/are required? Answer each with true (T) or false (F).

A. Carbimazole

B. Gluten-free diet

C. Hydrocortisone

D. Recommended increased insulin doses

E. Referral to a psychologist

Hypoglycaemia

Hypoglycaemia in the immediate neonatal period is common and usually transient. It is considered in Chapter 11, Neonatal medicine. This section considers neonates, infants and children with recurrent hypoglycaemia.

History

When evaluating a child for hypoglycaemia, attention should be paid to:

- Autonomic symptoms of hypoglycaemia, such as pallor, sweating, tachypnoea in a neonate or anxiety, palpitations and tremor in an older child
- Neuroglycopenic symptoms of jitteriness, apnoea, hypotonia, feeding problems, irritability, abnormal cry, convulsions or coma in a neonate or hunger, abdominal pain, nausea, vomiting, pins and needles, headache, weakness, dizziness, blurred vision, irritability, mental confusion, odd behaviour, fainting, convulsions or coma in an older child
- In a neonate, pregnancy details (e.g. maternal symptoms of diabetes), mode of delivery (breech said to be more common in hypopituitarism), birth weight (hypoglycaemia more common in intrauterine growth restriction or large for gestational age due to maternal diabetes) and the relationship of hypoglycaemia to feeding (i.e. is this a question of inadequate fuel supply or excess fuel requirements as in hyperinsulinism?)
- Access to oral hypoglycaemic medication, which may have been accidentally ingested
- Family history of sudden infant death or consanguinity might suggest an inborn error of metabolism
- Development of symptoms in response to foods containing lactose, fructose or sucrose might suggest galactosaemia or disorders of fructose metabolism.

Examination

Most children with a history of hypoglycaemia will not have any abnormal clinical signs on examination unless actually hypoglycaemic at the time. However, the presence of the following signs may indicate an associated diagnosis:

- Optic atrophy – septo-optic dysplasia
- Cranial midline defects, short stature, microgenitalia – hypopituitarism
- Increased skin or buccal pigmentation, hypotension – Addison's disease
- Underweight or signs of malnutrition – accelerated starvation
- Tall stature, excess weight – hyperinsulinism
- Abnormal ear-lobe creases, macroglossia, umbilical hernia, hemihypertrophy – Beckwith–Wiedemann syndrome
- Hepatosplenomegaly – glycogen storage disorder.

Investigations

The aim of investigations is to establish the severity of hypoglycaemia and to evaluate the counter-regulatory responses and intermediary metabolite pathways by obtaining a blood sample before instituting treatment of the hypoglycaemic episode for measurement of:

- Glucose to confirm severity of hypoglycaemia
- Urea and electrolytes for evidence of adrenal insufficiency
- Bicarbonate or pH, as acidosis might imply adrenal failure or an inborn error of metabolism

- Liver function tests, as may be abnormal in primary liver disease, sepsis, glycogen storage disease, galactosaemia, fatty acid oxidation defects and hereditary fructose intolerance
- Ammonia, may be elevated in a number of inborn errors of metabolism and some forms of hyperinsulinism
- Insulin and c-peptide, should normally be suppressed
- Cortisol, ACTH and growth hormone should normally be elevated, implying an appropriate stress response
- Free fatty acids and β-hydroxybutyrate, if elevated in proportion imply appropriate lipolysis
- Acylcarnitine will be abnormal in some fatty acid oxidation defects
- Lactate will be elevated in metabolic liver disease, glycogen storage disorder and sepsis
- Alanine, if low suggests 'accelerated starvation' (see below)
- After glucose has been administered to correct the hypoglycaemia, the next urine sample should be collected to measure the presence of ketones, reducing sugars, dicarboxylic acids, glycine conjugates, carnitine derivatives, and amino and organic acids to screen for inborn errors of metabolism and a toxicology screen.

Treatment

Treatment depends on aetiology. Hypoglycaemia may be broadly subdivided into two groups:

1. Causes associated with reduced glucose availability arise due to defects in the counter-regulatory response including limited supplies of glucose precursors. These include:
   - Being born with intrauterine growth restriction
   - Prematurity
   - Hypopituitarism
   - Adrenal insufficiency
   - Growth hormone deficiency
   - Hypothyroidism
   - Glucagon deficiency
   - Accelerated starvation (ketotic hypoglycaemia)
   - Inborn errors of metabolism
   - Drugs such as alcohol, aspirin and beta blockers
   - Liver dysfunction
   - Congenital heart disease.

   Investigation of hypoglycaemia frequently fails to demonstrate any underlying abnormality. Accelerated starvation is an example of this. It can only be diagnosed once other endocrine and metabolic causes are excluded, and is of unknown aetiology. It is characterized by demonstration of a normal endocrine counter-regulatory response with raised fatty acid and ketone responses. It is more common in boys than girls and in those who were born small for gestational age or who have a thin physique; it usually resolves by puberty. Treatment of this group of causes involves avoidance of prolonged fasting, particularly during intercurrent illness, administration of complex carbohydrates such as cornstarch at bedtime to provide a prolonged glucose response to feeding and intravenous dextrose as required to reverse acute hypoglycaemia.

2. Alternatively, hypoglycaemia may occur in the context of increased glucose consumption due to:
   - Congenital hyperinsulinism
   - Transient neonatal hyperinsulinism
   - Being an infant of a diabetic mother
   - Insulinoma
   - Beckwith–Wiedemann syndrome
   - Rhesus haemolytic disease
   - Perinatal asphyxia
   - Malaria.

   Markedly excessive glucose requirements (e.g. in excess of 12 mg/kg body weight/hour) to avoid hypoglycaemia suggest underlying hyperinsulinism. Congenital hyperinsulinism may occur in relation to several genetic defects affecting the regulation of insulin release. The most commonly identified are those of genes encoding the sulphonylurea receptor (ABCC8) and associated potassium inward rectifying channel (KCNJ11). Affected children are at increased risk of hypoglycaemia-induced brain damage as the hyperinsulinism suppresses not only glucose but also ketone body production, which is an alternative cerebral fuel source. Some respond to diazoxide and chlorothiazide treatment, diazoxide exerting its effect through actions on the potassium channel by inducing hyperpolarization, decreased calcium influx and reduced insulin secretion. If these fail, then a somatostatin analogue may be used to exert a direct receptor-mediated inhibition of insulin release. Scientific advances in our understanding of the genetics and new imaging techniques such as [18F]DOPA positron emission tomography scanning allow, in persistent cases, distinguishing focal from diffuse pancreatic disease, the former being curable by surgical excision with minimal morbidity.

Seizure at 4 days old

A 4-day-old baby boy presented with a seizure. His blood glucose was extremely low at 0.8 mmol/L. There was no relevant family history and the pregnancy and birth had been unremarkable. His birthweight was 3.94 kg and there were no abnormalities on examination. He experienced recurrent hypoglycaemia despite full volume feeds and an intravenous dextrose infusion providing an additional 14 mg glucose/kg/min.

Question 26.3

What is the most likely diagnosis? Select ONE answer only.

A. Accelerated starvation
B. Congenital adrenal hyperplasia (CAH)
C. Congenital hyperinsulinism
D. Hypopituitarism
E. Medium chain acyl coA dehydrogenase (MCAD) deficiency

Question 26.4

What additional treatment is required? Select ONE answer only.

A. Chlorothiazide and diazoxide
B. Increased feed volume
C. Growth hormone
D. Hydrocortisone
E. Low-fat milk

Answer 26.3

C. Congenital hyperinsulinism.

Answer 26.4

A. Chlorthiazide and diazoxide.
    When faced with a neonate with severe, recurrent hypoglycaemia, it is critical, in order to make a diagnosis, to establish whether the problem is associated with restricted calorie intake, implying a defect in counter-regulation (e.g. CAH, hypopituitarism, MCAD deficiency or accelerated starvation), or whether it is associated with excess glucose requirements. Such dramatically elevated glucose requirements to avoid hypoglycaemia are seen with hyperinsulinism, for which specific treatment with diazoxide, which decreases insulin secretion by direct action on potassium inward rectifying channel, is indicated. Chlorothiazide is also given as it has a synergistic effect on insulin secretion as well as assisting in the tendency for diazoxide to cause fluid retention. Increased feed

volume will not overcome such high glucose requirements. Although low cortisol levels may occur in congenital hyperinsulinism, there is no evidence of any benefit from hydrocortisone or growth hormone therapy. Finally, this child requires increased calories to prevent hypoglycaemia-induced brain damage, not a low-fat milk.

The thyroid gland

Embryology

The thyroid develops from four weeks' gestation from an outpouching of the floor of the pharynx (the precursor of T4-producing follicular cells) and bilateral protrusions of the fourth pharyngeal pouches (which give rise to calcitonin-secreting cells). The thyroid descends along the thyroglossal tract, which then regresses, though remnants may come to form thyroglossal cysts. Failure of descent results in an ectopic thyroid gland, a common form of congenital hypothyroidism. The process of thyroid development is regulated by a number of transcription factors (including PAX-8, FOXE-1 and NKX2.1).

Normal anatomy

The thyroid gland is butterfly shaped with two lobes connected by an isthmus. It is located below the larynx anterior to the second and fourth tracheal rings. It consists of spherical iodine-absorbing follicles, the lumen of which contain colloid, which includes substrates necessary for thyroid synthesis, particularly thyroglobulin. The follicles are surrounded by a single layer of epithelial cells, which secrete the thyroid hormones T3 and T4. Parafollicular cells between follicles secrete calcitonin.

Physiology

TSH release is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Thyroid hormone synthesis is stimulated by binding of pituitary-derived TSH to the TSH receptor, which is a GPCR. This leads to iodine uptake by a sodium–iodide transporter and transport to the colloid by a protein (pendrin) within the thyrocyte. Hydrogen peroxide regulated by thyroid peroxidase (TPO) is responsible for oxidation of iodine to iodide. Tyrosyl residues on thyroglobulin are iodinated to form monoiodotyrosine (MIT) and diiodotyrosine (DIT), which are coupled under TPO control to form iodothyronines. Following cleavage from thyroglobulin, molecules of monoiodotyrosine (MIT), diiodotyrosine (DIT), T3 and T4 are released. T3 is formed by deiodination of

T4 and accounts for 10–20% of thyroid hormone release.

Whereas the thyroid is the sole producer of T4, the majority of T3 results from deiodination of T4 by type II deiodinase in peripheral tissues. T3 is three to four times more potent in its physiological actions than T4. Type III deiodinase converts T4 into the inactive form rT3.

Thyroxine has widespread effects, stimulating neurologic growth, metabolic and cardiovascular functions through binding of T3 and T4 to α receptors in the heart and brain, β1 receptors in liver and brain and β2 receptors in pituitary, hypothalamus and liver. During fetal life, the fetus is largely dependent on transplacental passage of T3 and T4, though there is an increasing contribution from the second trimester onwards of fetally-derived thyroxine. It is the former which largely protects the fetus with congenital hypothyroidism. Similar to the fetus, premature infants experience low T4 and T3 but high rT3 levels and it is unclear whether there is a benefit to correcting these levels, currently the subject of ongoing clinical trials. Postnatally, there is an acute surge in TSH, T4 and T3 concentrations in the first day or two of life in term infants, falling to later childhood levels by two weeks of age.

History

Given the known physiological effects of thyroid hormones, history-taking in suspected cases of thyroid disease should enquire about:

- Growth (delayed in hypothyroidism and advanced in hyperthyroidism) and pubertal development/menstrual history (if appropriate)
- Weight (loss in hyperthyroidism)
- Bowel habit (constipation in hypothyroidism and diarrhoea in hyperthyroidism)
- Neurodevelopment (delayed in hypothyroidism)
- Sleep patterns (excess fatigue in hypothyroidism and reduced sleep requirements in hyperthyroidism)
- Behavioural functioning (deteriorating school progress in hypothyroidism and poor attention span in hyperthyroidism)
- Environmental temperature tolerance (cold intolerance in hypothyroidism and heat intolerance in hyperthyroidism).

Examination

When thyroid disease is suspected, the following clinical observations should be made:

- The presence of short stature, overweight and delayed puberty (rarely precocious due to cross-stimulation of FSH receptors by TSH) may indicate hypothyroidism, whereas tall stature and underweight is indicative of hyperthyroidism due to the effects of increased metabolic rate
- Dry skin, increased hair, pallor and vitiligo may indicate hypothyroidism, whereas facial flushing, tremor and sweatiness are indicative of hyperthyroidism
- The neck should be examined for a goiter, which is occasionally nodular in Hashimoto's disease but will be smooth, homogeneous and occasionally associated with a bruit in Graves' disease
- Pulse rate will be slow in hypothyroidism but raised and associated with flow murmurs in hyperthyroidism, reflecting the hyperdynamic state
- Proximal muscle weakness occurs in hypothyroidism, whereas tremor and choreiform movements suggest hyperthyroidism
- The relaxation phase of the ankle jerk is prolonged in hypothyroidism but reduced in hyperthyroidism
- Exophthalmos and occasionally ophthalmoplegia are pathognomonic for Graves' disease
- In congenital hypothyroidism, the presence of deafness may indicate Pendred syndrome and a lump at the back of the tongue an ectopic thyroid.

Investigations

Seventy per cent of circulating T4 and 50% of T3 is bound to thyroxine-binding globulin (TBG) and the remainder to other proteins such as albumin. Just 0.03% of T4 and 0.3% of T3 circulate unbound and therefore measurement of free hormones (T4 and T3 along with TSH) provides a more relevant assessment of thyroid function than total thyroxine, which better reflects TBG levels. TPO (thyroid peroxidase) antibodies are usually positive in both Hashimoto's and Graves' diseases, whereas excess titres of TSH receptor antibodies (TRAb) indicate Graves' disease.

In addition to formal thyroid function testing, infants with suspected congenital hypothyroidism (identified in much of the developed world by screening capillary blood spot TSH, and in some areas T4, shortly after birth) merit imaging with ultrasound and isotope scanning (^{99m}Tc-pertechnetate or ^{123}I-labelled sodium iodide) to clarify whether the gland is absent, hypoplastic or ectopic. If present, abnormalities of iodide take-up and trapping (a positive discharge after perchlorate is indicative of a failure of organification) within the gland are consistent with a dyshormonogenesis. Imaging is essential when a thyroid nodule or cancer is suspected and, in the latter case, a raised plasma calcitonin would indicate medullary thyroid cancer.

Diseases and disorders of the thyroid gland

Congenital hypothyroidism

This is a common disorder affecting about $1:3,500$ births and is the commonest treatable cause of learning difficulties worldwide, most often caused by maternal iodine deficiency. In developed countries, the commonest form is an ectopic gland, followed by aplasia and hypoplasia. Transcription factor mutations are responsible for less than 2% of dysgenesis cases. Defects in a range of genes encoding proteins involved in thyroid hormone biosynthesis cause dyshormonogenesis in the presence of an ultrasonically normal gland and account for 10–15% of cases in the UK.

Newborn screening programmes target identified cases to be started on thyroxine treatment before two weeks of age, aiming to normalize thyroid function within two weeks to optimize neurodevelopmental

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Questions 26.5 and 26.6

Goitre

A 14-year-old girl presented to clinic with concerns that she had failed to develop beyond early breast development since starting puberty two years earlier. Whereas she had previously been one of the tallest girls in her class, she was now one of the shorter ones. She has, however, continued to gain weight. She complained bitterly of cold weather and slept 11 hours every night, but was otherwise well and asymptomatic. On examination, her pulse rate was 45 beats/min, she had a small goitre and fundoscopy was normal.

Question 26.5

What is the most likely cause of this child's problems? Select ONE answer only.

A. Craniopharyngioma

B. Hyperthyroidism

C. Hypothyroidism

D. Prader–Willi syndrome

E. Simple obesity with polycystic ovarian disease

Question 26.6

What treatment is indicated? Select ONE answer only.

A. Carbimazole

B. Ethinyloestradiol

C. Hydrocortisone

D. Metformin

E. Thyroxine

Answer 26.5

C. Hypothyroidism.

Answer 26.6

E. Thyroxine.

This girl presents with classical features of hypothyroidism in her early teens, including goitre, delayed growth and pubertal development. Her cold intolerance and tendency to gain weight reflects the lack of stimulating effect on metabolism of thyroid hormone deficiency and she requires thyroxine treatment to stimulate growth and puberty. Treatment with oestrogens without first correcting her thyroid defect would stimulate pubertal development whilst ongoing growth was suboptimal, thus impairing final adult height. Children with simple obesity are usually tall for their age and it is unlikely she would have previously grown as well as she had if affected by Prader–Willi syndrome. The absence of symptoms and signs of raised intracranial pressure make a craniopharyngioma unlikely.

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outcomes. Changes in the dose of thyroxine are guided by recurrent elevations in TSH. If a dose increase has not occurred by the third birthday, consideration should be given to a temporary withdrawal of therapy to establish whether lifelong thyroxine treatment is actually required, as there is uncertainty about the appropriate screening TSH cut-off to define normality. Long-term follow-up requires monitoring of growth and neurodevelopment.

Acquired hypothyroidism

Hypothyroidism may be acquired due to: iodine deficiency, autoimmunity (Hashimoto's disease), surgery, irradiation, antithyroid drugs or goitrogens (e.g. iodide, cabbage or soya), or diseases affecting the pituitary or hypothalamus.

Management involves simple thyroxine replacement, leading to a good prognosis.

Hyperthyroidism

Hyperthyroidism may be caused by Graves' disease due to TRAb (thyroid-stimulating hormone receptor antibody), which can also cross the placenta and cause transient hyperthyroidism in the offspring of affected mothers. The early stages of Hashimoto's disease may be associated with transient hyperthyroidism and rare causes include autonomous nodules, TSH hypersecretion or an activating mutation of the TSH receptor.

Treatment of Graves' disease is usually initiated with carbimazole or methimazole or, where adverse reactions occur to these, propylthiouracil, all of which

act by blocking synthesis of thyroxine. In severely thyrotoxic individuals, emergency control of symptoms can be achieved with propranolol and Lugol's iodine solution. When relapse occurs following withdrawal of antithyroid medication after two to three years, more definitive treatment in the form of radioiodine or surgery may be considered. Neonatal thyrotoxicosis due to maternal Graves' disease is self-limiting and resolves once maternally derived TRAbs have disappeared within three months of birth, though antithyroid treatment may be required in the early weeks after birth.

Thyroid hormone resistance is an unusual inherited disorder due to a mutation in the β-thyroid hormone receptor gene. This results in reduced feedback inhibition leading to elevated T4 and T3 concentrations but inappropriately normal or raised TSH levels. Although the condition does not require therapy in most cases, variable tissue sensitivity to thyroid hormones may lead to some irritating symptoms of hyperthyroidism in certain individuals.

Thyroid cancer

Most thyroid nodules in childhood are cysts or benign adenomas. Malignant nodules are mostly papillary or follicular carcinomas. They may present with a painless, rapidly enlarging mass, sometimes with lymphadenopathy. These lesions should be examined with ultrasound and fine needle aspiration. Treatment

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Question 26.7

Another goitre

A five-year-old girl presented with a recent history of heat intolerance, weight loss and hyperactivity. She was tall for her genetic background, had a small, smooth soft goitre, tachycardia and brisk ankle jerks, but no abnormal eye signs. She had raised serum T4 (62 pmol/L) and T3 (15 pmol/L) and suppressed TSH (<0.02 mU/L) concentrations and a four-year advance in bone age compared to chronological age. Her mother had presented with the same clinical problem 10 years earlier and had undergone thyroidectomy. Thirteen other family members in a pattern suggestive of an autosomal dominant mode of transmission had been treated for similar thyroid problems.

What is the most likely explanation for this child's problems? Select ONE answer only.

A. Activating mutation of the TSH receptor gene

B. Graves' disease

C. Hashimoto's disease (hashitoxicosis)

D. Inactivating mutation of the TSH receptor gene

E. Thyroid hormone resistance

Answer 26.7

A. Activating mutation of the TSH receptor gene.

This child has clear evidence of thyrotoxicosis, as indicated by suppression of serum TSH in the context of elevated T3 and T4 concentrations. These biochemical findings are not consistent with thyroid hormone resistance, in which elevated thyroxine levels do not suppress TSH levels due to down-regulation of thyroid hormone activity. Inactivating mutations of the TSH receptor gene would be expected to cause hypothyroidism not hyperthyroidism. When considering which of the three causes of hyperthyroidism seems most likely, the family history is important. Although a family history of autoimmune disease is common in new cases of Graves' or Hashimoto's disease, they do not conform to an autosomal dominant pattern of inheritance. The latter is more suggestive of an activating mutation of the TSH receptor gene and the absence of eye signs would be consistent with this diagnosis. As this form of thyrotoxicosis is caused by a germ-line mutation, it would not be expected to be transient as may occur in Graves' disease and permanent ablation of thyroid activity by radioiodine or surgery is required.

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requires surgery and aggressive thyroxine replacement postoperatively to suppress TSH levels, which may be a risk factor for recurrence due to trophic effects on thyroid tissue growth. Radioiodine therapy is given postoperatively if metastatic disease has occurred and recurrence of functioning thyroid tissue monitored by thyroglobulin measurements. The prognosis is generally good.

The posterior pituitary

Embryology

The posterior pituitary, otherwise known as the neurohypophysis, is derived from the neural ectoderm.

Normal anatomy

The posterior pituitary is formed by neuronal projections (axons) of magnocellular neurosecretory cells, which extend from the supraoptic and paraventricular nuclei of the hypothalamus. The infundibular or pituitary stalk bridges the hypothalamic and hypophyseal systems.

Physiology

Arginine vasopressin (AVP), otherwise known as antidiuretic hormone, is synthesized in neurons which originate in the supraoptic and paraventricular nuclei. Some paraventricular neurons end at the median
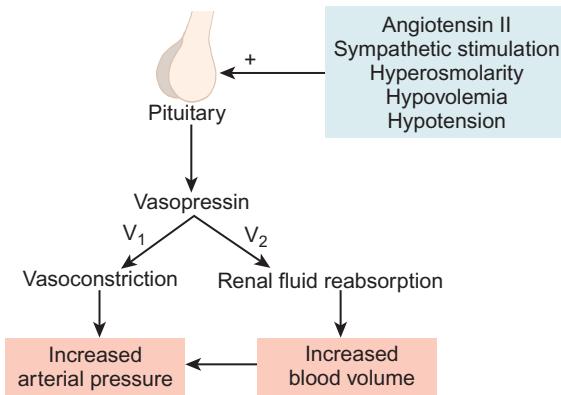
Fig. 26.3 Regulation of AVP release.

eminence where AVP is released into the hypophyseal circulation, whereas magnocellular neurons of the supraoptic and paraventricular nuclei end in the posterior pituitary from where AVP is released into the systemic circulation.

AVP is synthesized in a preprohormone format in the magnocellular neurons, following which a signal peptide is cleaved. The prohormone folds and places AVP into a binding pocket of neurophysin, which facilitates the production of high density neurosecretory granules, which are transported to the posterior pituitary. Vasopressin and neurophysin are released from these granules into the circulation after stimulation of vasopressinergic neurons. Vasopressin secretion is determined by plasma osmotic status, blood pressure and circulating volume (Fig. 26.3).

Vasopressin acts by binding to three GPCRs. Pressor effects are mediated by binding of vasopressin to V1 receptors in vascular smooth muscle. The main action of vasopressin is to regulate blood volume control by regulating clearance of free water through binding to V2 receptors in the kidney, stimulating expression of a water channel protein (known as aquaporin 2), which allows reabsorption of water from the collecting duct along an osmotic gradient. Vasopressin also facilitates ACTH release from corticotrophs by binding to V3 receptors in the anterior pituitary gland.

History

The most common disturbance of posterior pituitary function is diabetes insipidus, either due to insufficient vasopressin release (cranial diabetes insipidus) from congenital or acquired defects of posterior pituitary anatomy or due to renal resistance (nephrogenic diabetes insipidus) to vasopressin action. Rarely, the syndrome of inappropriate ADH secretion may result in pathological degrees of water retention.

When faced with a child who is referred with polyuria and a possible diagnosis of diabetes insipidus, one needs to establish from the history:

- Timing of onset of symptoms
- Details of mode of delivery
- Presence of a family history, particularly of diabetes mellitus
- An estimate of daily fluid intake with particular reference to whether this includes only flavoured fluids (suggesting a habitual preference rather than a defect in water homeostasis), water or unusual fluids such as shampoo and whether from unusual sources such as toilet bowls or flower pots (suggesting extreme thirst, as occurs in diabetes insipidus)
- Details of symptoms suggestive of wider pituitary defects, and whether there is a past history of head injury or other insults to the brain such as surgery
- The presence of headaches or disturbance to vision
- A history of renal disease
- The presence of other disorders, such as impaired vision or hearing defects or symptoms suggestive of hypercalcaemia (anorexia, abdominal pain or constipation)
- Medication.

Examination

Clinical examination should include assessment of:
- Hydration state
- Blood pressure
- Wider defects associated with abnormal pituitary function, including growth and pubertal staging, if relevant
- Craniofacial skeleton for midline defects
- Presence of enlarged kidneys.

Investigations

The commonest cause of referral for assessment of fluid balance abnormalities is habitual excess drinking. In older children, this can be excluded by asking the family to document a fluid intake and output diary whilst the child is allowed free access to water between meals with flavoured fluids only allowed at mealtimes. If excess fluid losses persist, then the following investigations are required:

- Fasting serum sample for measurement of sodium, potassium, creatinine, osmolality, glucose, calcium
- A paired fasting urine sample for glycosuria, proteinuria, sodium and osmolality.

If the above tests do not confirm the presence of diabetes insipidus by demonstrating an inappropriately dilute urine (<750 mOsm/kg) in the presence of a hyperosmolar state (serum osmolality >295 mOsm/kg), then further tests should be performed in

a specialist centre, as some of them are potentially dangerous. The child should be admitted to hospital for initial monitoring of fluid balance and then, if indicated, a water deprivation test, which requires withholding of fluids (usually for about 8 hours) until thirst cannot be tolerated any further, or weight loss exceeds 5% or serum osmolality exceeds 295 mOsm/kg. Once this state is achieved and a urine sample obtained, a test dose of desmopressin (DDAVP) is given to monitor serum and urinary osmolality responses over the next few hours. The presence of a urinary concentrating response will distinguish cranial from nephrogenic diabetes insipidus, in which no such response occurs.

An alternative to the water deprivation test is the hypertonic saline infusion test, in which 5% saline is given intravenously until the plasma osmolality exceeds 300 mOsm/kg, following which urinary osmolality and plasma AVP are measured. Low levels of AVP when hyperosmolar indicate cranial diabetes insipidus, whereas high levels of AVP suggest nephrogenic diabetes insipidus.

If the above results suggest cranial diabetes insipidus, then measurement of serum tumour markers β-human chorionic gonadotropin and α-fetoprotein and MRI scanning of the hypothalamo–pituitary axis are required to exclude infiltrative disorders. Consideration should also be given to the need for wider pituitary function testing.

Diseases and disorders of posterior pituitary function

Cranial diabetes insipidus

Cranial diabetes insipidus falls into three categories:

1. A triphasic pattern following neurosurgery, particularly for a craniopharyngioma, is not uncommon. Diabetes insipidus may occur for up to 24 hours followed by a period of vasopressin excess for 2–4 days, thought to be due to a necrotic posterior pituitary releasing vasopressin, and then the development of more permanent diabetes insipidus.
2. Cranial diabetes insipidus with intact thirst occurs in inherited forms of cranial diabetes insipidus or where the underlying pathology is confined to the posterior pituitary and does not affect hypothalamic functioning. Familial autosomal dominant neurohypophyseal diabetes insipidus is the most common inherited cause, usually due to mutations in the neurophysin coding region or signal peptide impairing processing, folding or dimerization, which is thought to cause accumulation of abnormal prohormone and degeneration of the magnocellular neurons. This

leads to a gradual but variable decline in vasopressin secretion in the first decade of life. By contrast, Wolfram (DIDMOAD) syndrome is an autosomally dominant inherited association of diabetes insipidus with insulin-dependent diabetes mellitus, optic atrophy and sensorineural deafness.
3. Anatomical defects of posterior pituitary function may be caused by congenital defects such as septo-optic dysplasia or in association with other intracranial or midline abnormalities. MRI scanning may show an absent posterior pituitary signal in addition to the other cranial abnormalities. Other acquired causes include tumours, infiltrations, infection, trauma, neurosurgery, autoimmune disease, hypoxia or idiopathic.

Treatment requires administration of desmopressin (DDAVP) given orally, nasally or parenterally. This should be introduced at low doses and slowly increased to avoid excess fluid retention. Free access to oral fluids should be allowed so the patient can correct inadequate therapy by increased fluid intake. Great care should be exercised when administering intravenous fluids to avoid overhydration, as patients following administration of desmopressin cannot excrete an excess water load.

Cranial diabetes insipidus with impaired thirst is an extremely challenging condition to manage. It occurs in some children with impaired osmoreceptor function associated with neurodisability and following tumours or surgery. This requires careful balancing of desmopressin dose and fluid intake as these individuals cannot correct abnormal fluid balance through perceived effects on thirst.

Nephrogenic diabetes insipidus

This form of diabetes insipidus is due to renal resistance to AVP action from congenital abnormalities or acquired causes including:

- Drug-induced (e.g. adverse effects of lithium on aquaporin 2)
- Metabolic (hyperglycaemia-induced osmotic diuresis or hypokalaemia or hypercalcaemia effects on aquaporin 2 function)
- Aquaporin-mediated effects of renal disease associated with acute or chronic renal failure.

This is a difficult condition to treat, as symptoms are often not completely abolished and patients require free access to extra fluids and attention to calorie intake. Some relief from symptoms may be gained from thiazide diuretics in combination with amiloride or indomethacin. Thiazides are thought to inhibit the NaCl cotransporter in the distal convoluted tubule, thereby increasing proximal tubular sodium and water reabsorption.

Syndrome of inappropriate ADH secretion

Syndrome of inappropriate ADH secretion (SIADH) is caused by:

- Central nervous system disorders, including meningitis, encephalitis, trauma, hypoxia
- Haemorrhage, ventriculo-peritoneal shunt obstruction, Guillain–Barré syndrome
- Respiratory conditions, such as pneumonia and tuberculosis
- Certain tumours, such as thymoma, lymphoma and Ewing's sarcoma
- Drugs that stimulate AVP release or potentiate its action.

SIADH results in impaired free water clearance, total body water excess and hyponatraemia.

Management of SIADH requires:

- Treatment of any underlying cause
- Fluid restriction when mild and asymptomatic
- When more severe, the use of democycline, which inhibits the antidiuretic action of vasopressin. Vaptans are a new class of drug which inhibits the action of vasopressin on its receptor, but have yet to be tested and licensed for use in children.

Question 26.8

Polydipsia in a six-year-old girl

An 18-month-old girl was referred for evaluation due to a family history of polydipsia and polyuria affecting nine other members in an autosomal dominant pattern of inheritance. She was thriving and an early morning urine sample showed a high osmolality of 756 mOsm/kg, so the family were reassured and she was discharged.

At six years of age, she was referred again, as she was drinking in excess of six litres of water on return home from school in the afternoons. She was growing normally and had no signs suggestive of pituitary dysfunction. On this occasion, a water deprivation test showed a maximal urine osmolality of 373 mOsm/kg with a coexistent serum osmolality of 292 mOsm/kg. After further diagnostic tests, she experienced an excellent symptomatic response to desmopressin treatment.

Which of the following is the correct interpretation of these test results? Select ONE answer only.

A. Factitious illness
B. Familial neurohypophyseal diabetes insipidus
C. Nephrogenic diabetes insipidus
D. Normal
E. Psychogenic polydipsia

Answer 26.8

B. Familial neurohypophyseal diabetes insipidus.

This child shows a relatively normal urine concentrating response at aged 18 months and further testing would have been hard to justify. The presence of so many affected family members consistent with an autosomal dominant pattern of inheritance is characteristic of familial neurohypophyseal diabetes insipidus due to a mutation of the AVP neurophysin II gene. Although this is a congenital disorder, it may take years to become apparent due to the progressive chemotoxic effect on the magnocellular neurons of abnormally folded AVP neurophysin II protein.

The water deprivation test result aged six years is surprising but in the context of a normal serum osmolality, the relatively dilute urine cannot be interpreted with confidence. When repeated water deprivation tests prove unclear, a hypertonic saline infusion test with measurement of the plasma AVP response is likely to clarify the situation, by confirming a clearly inadequate AVP response to a progressively hyperosmolar state. A good symptomatic response to desmopressin suggests underlying AVP deficiency and excludes nephrogenic causes of diabetes insipidus.

The parathyroid gland

This section focuses on the influence of the parathyroid on calcium and phosphate. Additional discussion on the influence of vitamin D on calcium balance can be found in Chapter 13, Nutrition.

Embryology

The parathyroid glands originate from the third (two inferior glands) and fourth (two superior glands) branchial arches. A number of transcription factors are involved (including Hoxa3, GATA3 and a number of others encoded by genes on the long arm of chromosome 22). Abnormalities of genes encoding these transcription factors interfere with parathyroid development, which may be associated with other abnormalities such as sensorineural deafness and renal dysplasia (GATA3) and the CATCH22 complex of which DiGeorge syndrome is a part.

Normal anatomy

Typically, four parathyroid glands are found posterior to the thyroid gland, two located superiorly and two inferiorly. The parathyroids, which are each the size of a rice grain, may be distinguished from the thyroid by their distinct encapsulated smooth surface. Histologically, they consist of parathyroid hormone (PTH)-containing chief cells and fat with a thin fibrous capsule dividing the gland into lobules.
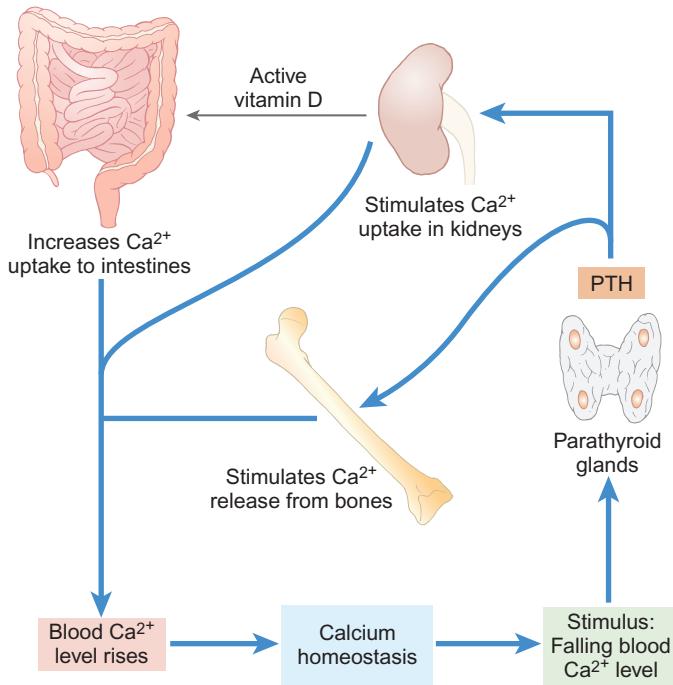
Fig. 26.4 Regulation of calcium balance.

Physiology

PTH secretion from the parathyroid is regulated by the calcium-sensing receptor, which is a GPCR. When calcium levels fall, these receptors become activated, stimulating the subsequent release of PTH. By contrast, high extracellular concentrations of calcium bind to the calcium-sensing receptor to inhibit PTH release. Magnesium can also influence PTH release through its binding to the calcium-sensing receptor and hypomagnesaemia inhibits PTH release.

PTH binds to a receptor on osteoblasts in bone and kidney to indirectly elevate plasma calcium concentrations (Fig. 26.4). Stimulated osteoblasts activate osteoclasts to resorb bone which contains 99% of total body calcium bound to phosphate and hydroxyl ions in the form of hydroxyapatite. PTH also stimulates a rise in plasma calcium by facilitating resorption of calcium and magnesium and loss of phosphate from the renal distal tubules and by activating the conversion of 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D which facilitates intestinal calcium absorption.

History and examination

Hypocalcaemia

Faced with a child with hypocalcaemia, the following details should be sought:

- The presence of symptoms of hypocalcaemia, such as paraesthesia, cramps, tetany, seizures or diarrhoea

- Risk factors for hypomagnesaemia, such as intestinal or renal disease
- Evidence of endocrine disease
- Symptoms of autoimmune disease
- Previous neck surgery
- Family history of hypocalcaemia.

  Clinical signs in an older child include:

- Latent tetany, which may be elicited by tapping the facial nerve in front of the ear and inducing facial twitching (Chvostek's sign)
- Carpal spasm within three minutes of inflating a blood pressure cuff above systolic pressure (Trousseau's sign)
- Stridor
- Chronic hypocalcaemia may be apparent from features of basal ganglia calcification, cataracts, papilloedema, dry skin, coarse hair, brittle nails, enamel hypoplasia and dental caries
- Signs in young children are often non-specific and include tremor, apnoea, cyanosis and lethargy
- Features of autoimmune hypoparathyroidism may include candidiasis, dental enamel and nail dystrophy, alopecia, vitiligo, Addison's disease and hypothyroidism
- Pseudohypoparathyroidism may be indicated in the presence of short stature, obesity, short fourth metacarpals and metatarsals and other skeletal anomalies, subcutaneous calcification and developmental delay
- Wider features suggestive of vitamin D deficiency.

Hypercalcaemia

In the presence of hypercalcaemia, the following features may arise:

- The presence of symptoms of hypercalcaemia, such as weakness, anorexia, nausea, vomiting, constipation, polyuria and polydipsia
- Symptoms suggestive of tuberculosis or sarcoidosis
- Vitamin D therapy
- A family history of hypercalcaemia or multiple endocrine neoplasia (MEN).

In the presence of hypercalcaemia, the presence of a broad, prominent forehead, short turned-up nose with flat nasal bridge, overhanging upper lip, late dental eruption, supravalvular aortic stenosis, peripheral pulmonary stenosis, learning difficulties and short stature may suggest underlying Williams syndrome.

Investigations

Investigation of abnormalities in calcium metabolism require a blood sample for measurement of serum calcium, phosphate, magnesium, PTH, alkaline phosphatase, 25-hydroxyvitamin D and a stored sample for possible 1,25-dihydroxyvitamin D, if subsequently indicated. Additional investigations may include bone X-rays and genetic tests (see below).

Diseases and disorders of the parathyroid gland

Hypoparathyroidism

Hypoparathyroidism has a number of causes, including:

- 22q11 microdeletion, as found in DiGeorge syndrome
- As part of autoimmune polyglandular endocrinopathies
- Following inadvertent removal during thyroid surgery
- In association with autosomal dominant activating mutations of the calcium-sensing gene in which calcium is 'sensed' to be normal at subphysiological levels
- In magnesium deficiency, given the key role of magnesium in regulating PTH secretion

The diagnosis is suggested by biochemical findings of inappropriately low serum PTH in the context of hypocalcaemia and raised serum phosphate concentrations.

When hypoparathyroidism is associated with clinically severe symptoms of hypocalcaemia, emergency treatment with intravenous calcium (e.g. as calcium gluconate) is indicated, preferably administered

through a central line to avoid phlebitis. Longer term treatment requires the use of oral vitamin D analogues and calcium, if needed. The aim is to increase calcium concentrations close to the normal range whilst avoiding hypercalciuria, which may predispose to nephrocalcinosis.

Pseudohypoparathyroidism

Pseudohypoparathyroidism causes hypocalcaemia and hyperphosphataemia, but is distinguished from hypoparathyroidism by the presence of raised PTH concentrations. It may be associated with characteristic dysmorphic features and TSH resistance.

Hyperparathyroidism

Hyperparathyroidism is rare in childhood and may be caused by a number of genetic defects.

Question 26.9

Hypocalcaemia

A fourteen-year-old prepubertal boy presents with concerns about weight gain, delayed puberty and a history of epilepsy which had been poorly responsive to anticonvulsants. He had delayed development and required additional teaching support in school. His weight was above the 99.6th centile and height on the 50th centile. Initial investigations showed hypocalcaemia (calcium 1.9 mmol/L), hyperphosphataemia (phosphate 2.0 mmol/L), elevated PTH (17 pmol/L), elevated TSH (7 mU/L), low normal free T4 (10.5 pmol/L) and normal renal function, alkaline phosphatase and 25-OH cholecalciferol concentrations.

What is the most likely diagnosis? Select ONE answer only.

A. Congenital hypothyroidism due to dyshormonogenesis
B. Hypoparathyroidism
C. McCune–Albright syndrome
D. Primary hyperparathyroidism
E. Pseudohypoparathyroidism

Answer 26.9

E. Pseudohypoparathyroidism.

The presence of hypocalcaemia with raised PTH levels implies a defect in PTH action and therefore excludes hypoparathyroidism, in which low PTH levels would be expected. It also excludes hyperparathyroidism, in which in the presence of normally active elevated PTH, hypercalcaemia would be expected. Pseudohypoparathyroidism is associated with a defect in G-protein signaling, which may affect other GPCRs such as the TSH

The adrenal gland

Embryology

By the 7th and 8th weeks of gestation, the fetal adrenal cortex is invaded by sympathetic neural cells, which will come to form the medulla. The fetal adrenal cortex contains an outer definitive zone (site of gluco-corticoid and mineralocorticoid synthesis) and a large fetal zone that synthesizes androgenic precursors for placental production of oestriol. At birth, the adrenal glands account for 0.5% of body weight compared to 0.0175% in the adult.

Normal anatomy

The adrenal glands are located on top of the upper pole of each kidney. The adrenal cortex has three zones: the outer zona glomerulosa (15%) immedi-ately below the capsule, a middle zona fasciculata (75%) and an inner zona reticularis (10%) lying next to the medulla. The large fetal zone disappears during the first year of life, whereas the definitive zone enlarges. The zonas glomerulosa and fasciculata are fully differentiated by three years of age, whereas the zona reticularis does not fully differentiate until 15 years of age, reflecting the ontogeny of adrenal steroid production.

Physiology

Three main groups of adrenal steroids are derived from a common precursor, cholesterol. Mineralocor-ticoids (principally aldosterone) are synthesized in the zona glomerulosa under control of the renin–angiotensin system, whereas glucocorticoids (princi-pally cortisol) in the zona fasciculata and androgens in the zona reticularis are synthesized under regula-tion by the hypothalamo–pituitary axis.

Corticotrophin-releasing hormone (CRH) from the hypothalamus stimulates anterior pituitary corti-cotroph cell production of proopiomelanocortin (POMC), a precursor of ACTH. ACTH binds to the melanocortin-2 receptor (a GPCR) in the adrenal cortex to enhance cholesterol transport by the ster-oidogenic acute regulatory (StAR) protein across the mitochondrial membrane, the first step towards corti-sol synthesis. Cortisol is responsible for maintenance of normal blood glucose concentrations and blood pressure, particularly in stressful circumstances. Secre-tion is maximal on waking and declines to a nadir at midnight, which has important implications for when to measure samples.

Renin secreted by the juxtaglomerular apparatus of the kidney stimulates conversion of angiotensinogen into angiotensin 1, which in turn is converted by angiotensin-converting enzyme into angiotensin 2. The latter stimulates aldosterone synthase to promote aldosterone release from the zona glomerulosa. Aldos-terone binds to an intracellular receptor in the distal renal tubule, which in turn enters the nucleus to stim-ulate protein synthesis, which regulates sodium reten-tion through enhancement of $Na^+K^+ATPase$ (sodium pump) activity and the amiloride-sensitive epithelial sodium channel.

Adrenal androgens (dehydroepiandrosterone (DHEA), DHEA sulphate (DHEAS) and androstenedi-one) are secreted by the zona reticularis and in par-ticularly large amounts during fetal life, though levels fall postnatally as the fetal zone involutes. Levels remain low until the age of 7–8 years when, approximately two years before puberty, they start to rise, regulated by unknown stimulatory mecha-nisms (so-called 'adrenarche'). Adrenal androgens have a very limited capacity to bind to androgen recep-tors but rather act as precursors for testosterone production.

History and examination

Adrenal insufficiency

When seeking possible evidence of adrenal insuffi-ciency, the following history should be sought:

- Timing of onset of symptoms or a positive family history may distinguish congenital from acquired causes
- Non-specific symptoms of weakness, muscle aches, nausea, vomiting or diarrhoea
- Neonatal hypoglycaemia may suggest congenital causes
- Excess early morning tiredness reflects the diurnal secretion of cortisol
- Craving for salty foods may reflect urinary sodium losses
- Drowsiness, especially at times of intercurrent illness, demonstrates the counter-regulatory role of cortisol and consequences of low levels on blood glucose concentrations or blood pressure

- Symptoms of other autoimmune illness, such as thyroid, parathyroid disease or type 1 diabetes, might imply polyglandular autoimmune endocrinopathy
- Symptoms of pathology affecting the hypothalamus or pituitary (headache, visual disturbance, symptoms of wider pituitary dysfunction, intracranial surgery, craniopharyngioma, radiotherapy, meningitis, previous exposure to glucocorticoids)
- Known pathology affecting adrenal function (abdominal surgery, tuberculosis, drugs such as cyproterone)
- Previous exposure to high-dose glucocorticoid therapy inducing suppression of ACTH secretion and iatrogenic adrenal insufficiency
- Neurological deterioration may suggest adrenoleukodystrophy.

The following findings might support a diagnosis of adrenal insufficiency:

- Increasing skin pigmentation due to increased ACTH synthesis from POMC resulting in increased melanocyte-stimulating hormone byproduct
- Weight loss or faltering growth shows the importance of normal salt homeostasis for normal growth
- Impaired consciousness may occur due to hypoglycaemia or dehydration
- Low blood pressure and orthostatic hypotension may reflect total body sodium depletion
- Genital ambiguity (a virilized female or undervirilized male infant might suggest CAH (see below))
- Goitre or vitiligo might suggest autoimmune polyglandular endocrinopathy.

Adrenal excess

Features in the history of a patient with possible adrenal excess include:

- Ongoing exposure to glucocorticoid medication, which might cause iatrogenic Cushing's syndrome
- Headaches or visual disturbance might suggest the presence of an ACTH-secreting pituitary adenoma
- Features of McCune–Albright syndrome (hyperpigmented skin lesions, skeletal fibrous dysplasia)

Findings in a patient with possible adrenal excess include:

- Growth failure or short stature demonstrating the effect of excess cortisol reducing growth hormone (GH) secretion and sensitivity

- Excess weight gain and fat especially around the back of the neck (buffalo hump), central abdomen and face or proximal muscle wasting reflect the effects of cortisol on fat and protein physiology
- Hypertension due to enhancement of epinephrine-induced vascular constriction and cortisol-induced mineralocorticoid effects increasing total body sodium
- Acne, hirsutism and striae caused by cortisol-induced haemorrhage of weakened and stretched skin.

Investigations

Most (80–90%) circulating cortisol is bound to cortisol-binding globulin and most assays measure total cortisol concentrations. Because of diurnal variation in cortisol secretion, timing of blood sampling is critical to the interpretation. To diagnose adrenal insufficiency, blood ACTH and cortisol samples should be obtained in the early morning:

- Low cortisol and ACTH levels imply secondary adrenal insufficiency due to disease in the hypothalamo–pituitary axis; intracranial imaging and wider pituitary function testing is then indicated
- By contrast, low cortisol and high ACTH levels due to failed feedback inhibition implies primary adrenal failure.

Further investigations to be considered for primary adrenal failure include:

- Adrenal or 21-hydroxylase antibody testing for 21-hydroxylase deficient CAH (see below) – diagnosed from measurement of elevated serum 17-hydroxyprogesterone and adrenal androgen concentrations
- Urinary steroid metabolite profiling to identify abnormal metabolite concentrations suggestive of a defect in adrenal biosynthesis (CAH)
- Very long chain fatty acid (VLCFA) measurement to exclude adrenoleukodystrophy
- Diagnostic tests for mineralocorticoid deficiency require measurement of plasma aldosterone and plasma renin activity, which will be elevated due to lack of aldosterone feedback inhibition.

Cushing's syndrome is rare and difficult to diagnose. The following tests are indicated:

- 24-hour urinary cortisol excretion rates measured over three days are a useful screening test. If values are elevated then:
  – Serum cortisol measurement at 0800 and 2400 hours to examine for loss of diurnal variation, which is indicative of Cushing's

syndrome, is useful (the midnight sample must be obtained from a sleeping child with free-flowing cannula for blood sampling to avoid the stimulatory effect of awakening and apprehension on adrenal function)

– Repeat ACTH and cortisol measurements following low- and high-dose dexamethasone (a potent glucocorticoid) suppression testing are indicated if there is loss of diurnal variation. Suppression of values in response to a low-dose test indicates normal function. Failure of suppression to either test suggests autonomous ACTH or cortisol secretion, whereas a response to high-dose suppression indicates pituitary ACTH release to be the cause of the Cushing's syndrome

– Depending on the presumed location of the underlying pathology, additional tests include pituitary MRI scanning or abdominal/thoracic CT scanning.

Diseases of the adrenal gland

Glucocorticoid insufficiency

Primary causes of glucocorticoid deficiency include:

- Congenital causes such as X-linked congenital adrenal hypoplasia (due to DAX-1 mutations), CAH (see below) and autosomal recessive familial glucocorticoid deficiency (due in some to mutations of the ACTH receptor gene)
- Acquired causes such as autoimmune adrenalitis (Addison's disease), either in isolation or in association with other autoimmune endocrine disease, adrenoleukodystrophy, tuberculosis, surgery or drugs such as cyproterone.

Secondary causes include:

- Congenital hypopituitarism
- Isolated ACTH deficiency
- Septo-optic dysplasia
- Other midline CNS disorders
- Acquired forms due to craniopharyngioma, cranial irradiation and surgery, steroid therapy and acquired pituitary dysfunction due to vascular causes, trauma or meningitis.

Adrenoleukodystrophy is an X-linked disorder (caused by mutations to the *ABCD1* gene) which leads to defective peroxisomal fatty acid β-oxidation and accumulation of high concentrations of VLCFAs, which can be used to diagnose both the carrier and affected states. Initial degenerative symptoms of behavioural changes and evolving dementia due to white matter disease predate the onset of adrenal insufficiency. Attempts at dietary therapy with Lorenzo's oil to prevent accumulation of endogenously synthesized

VLCFAs have not proved effective at preventing neurological deterioration despite normalization of VLCFAs. Stem cell transplant and gene therapy are the only beneficial interventions, if used early enough.

General treatment of cortisol deficiency requires administration of hydrocortisone, given two or three times a day, with the largest component given in the morning to replicate the natural diurnal cortisol profile. To mimic stress-induced increases in glucocorticoid secretion, it is recommended that this dose be increased two- to threefold or administered parenterally if the child is vomiting.

21-hydroxylase deficient congenital adrenal hyperplasia

CAH is a consequence of autosomal recessively inherited mutations of genes encoding enzymes involved in steroid hormone biosynthesis. Reduced enzyme function may result in impaired glucocorticoid and mineralocorticoid synthesis. This results in virilization due to failure of feedback inhibition of ACTH secretion from reduced cortisol levels and preservation of the androgen synthetic pathway and salt loss, which may be severe. The condition is described in Chapter 20, Genital disorders.

Cushing's syndrome

Cushing's syndrome may be iatrogenic from steroids given orally, by inhalation, cutaneously or intranasally. Rarely, it is a consequence of an ACTH-secreting pituitary or ectopic tumour or from bilateral micronodular adrenal dysplasia. Risk factors for endogenous Cushing's syndrome include MEN1 causing pituitary tumours and McCune–Albright syndrome, in which activating mutations of the GPCR for ACTH lead to excess cortisol.

Treatment of iatrogenic Cushing's syndrome requires careful withdrawal or minimization of steroid medication. Endogenous disease is best treated by surgical removal of the underlying cause, though mild variants of McCune–Albright syndrome may be managed with metyrapone, which blocks cortisol synthesis by inhibiting 11β-hydroxylase.

Mineralocorticoid abnormalities

Mineralocorticoid deficiency occurs in congenital adrenal hypoplasia (most commonly 21-hydroxylase deficiency, but also rarer variants) and Addison's disease. Pseudohypoaldosteronism presents with a clinically similar picture to mineralocorticoid deficiency, but is distinguished biochemically by elevated aldosterone levels. It occurs in a milder, self-limiting autosomal dominant form due to mutations of the *MLR* gene encoding the mineralocorticoid receptor and, in a more severe autosomal recessive form, due

to mutations of any of three genes which encode subunits of the epithelial sodium channel. The effects of these mutations are to impair sodium resorption in the mineralocorticoid sensitive cells of the distal renal tubule. In the autosomal recessive form, sodium reabsorption in the colon, sweat and salivary glands is also affected.

Treatment of hypoaldosteronism requires fludrocortisone and salt supplementation during the first year of life. By contrast, pseudohypoaldosteronism does not respond to fludrocortisone and requires administration of large amounts of salt and, in the severe autosomal recessive forms where hyperkalaemia may be life-threatening, the use of ion-binding

Answer 26.11

E. Oral sodium supplementation.
This baby has hyponatraemia with hyperkalaemia, a combination strongly suggestive of a defect in mineralocorticoid function. The differential diagnosis includes CAH, but the common 21-hydroxylase deficient form is unlikely in the absence of virilization. A good stress cortisol response (>550 nmol/L) excludes congenital adrenal hypoplasia and hypopituitarism. Diabetes insipidus would be associated with hypernatraemia. The markedly elevated renin and aldosterone levels are consistent with resistance to mineralocorticoid action. Although urinary tract infections in infancy are associated with resistance to mineralocorticoids through unclear mechanisms, resulting in a similar biochemical picture, there is no evidence of infection or underlying renal tract anomaly so antibiotics are not of value. This case demonstrates the fundamental role adequate sodium plays in normal growth. Given that aldosterone levels are already massively elevated, there would be no therapeutic value in administering fludrocortisone and additional oral sodium is required, often in large amounts for the first few years until resistance to mineralocorticoid action spontaneously decreases.

Questions 26.10 and 26.11

Abnormal electrolytes in a 12-week-old girl

A 12-week-old baby girl was referred with poor feeding, poor weight gain and a history of previous urinary tract infection and hyponatraemia. On examination there were no abnormal findings. Initial investigations showed a serum sodium of 125 mmol/L, potassium 6.2 mmol/L, bicarbonate 17 mmol/L, urea 7.0 mmol/L, osmolality 271 mOsm/kg. She has a normal urine microscopy and a normal abdominal and pelvic ultrasound. Additional investigations showed a serum cortisol of 794 nmol/L, a normal 17-OH progesterone (6 nmol/L) and a raised plasma renin (35 pmol/mL/hour; normal 2.8–4.5 pmol/mL/hour) and aldosterone (38,000 pmol/L; normal 100–450 pmol/L).

Question 26.10
What is the most likely diagnosis? Select ONE answer only.

A. 21-hydroxylase deficient CAH
B. Congenital adrenal hypoplasia
C. Diabetes insipidus
D. Hypopituitarism
E. Pseudohypoaldosteronism

Question 26.11
What is the most appropriate treatment? Select ONE answer only.

A. Antibiotics
B. Desmopressin
C. Fludrocortisone
D. Hydrocortisone
E. Oral sodium supplementation

resins. Monitoring growth during follow-up is important given the key importance of adequate sodium to facilitate normal growth.

Phaeochromocytoma

Phaeochromocytoma is a neuroendocrine chromaffin cell tumour which most commonly occurs in the adrenal medulla but may appear in any part of the embryologically related sympathetic chain. The condition may be isolated or in association with neurofibromatosis type 1 and a range of rare syndromes. Characteristically, it presents with catecholamine-induced episodes of headache, flushing, sweating and hypertension. Diagnosis is confirmed by the presence of excess levels of urinary catecholamine metabolites. Treatment requires surgical removal following pre-operative α-adrenoreceptor blockade to prevent adverse effects from catecholamine release when the tumour is manipulated during surgery.

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Mary Brennan, Helen Foster, Flora McErlane, Rajib Lodh, Sharmila Jandial

Musculoskeletal disorders

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Understand the embryology and anatomy of the musculoskeletal system
- Understand the histology and physiology of normal muscle and how structure relates to function
- Understand the pathophysiological changes which occur in muscle and joint disorders
- Know the commoner genetic and environmental factors in the aetiology of musculoskeletal disorders
- Know the investigations used in the diagnosis of musculoskeletal disorders
- Understand the pharmacology of agents, including monoclonal antibodies, used in the treatment of musculoskeletal disease
- Know the disease associations of rheumatological conditions with other conditions, including eye disease and metabolic disorders.

Embryology of the musculoskeletal system

The embryological development of the musculoskeletal (MSK) system is complex with many components (bones, skeletal muscles, connective tissues (cartilage, ligaments and tendons), blood vessels and nerves). Development requires differentiation into these specific cell types and coordination to produce an integrated and functional system. This complexity results in problems that can and do arise and MSK developmental abnormalities are one of the largest groups of congenital conditions.

The MSK system mainly develops from the mesodermal germ layer with some neural crest contribution. Mesoderm is subdivided by position into three parts: the paraxial, intermediate and lateral mesoderm. In the 3rd week of gestation, the paraxial mesoderm forms 'little balls' (somites), which are paired each side of the neural groove. These somites differentiate differently in different regions. The sclerotome eventually splits segmentally giving rise to the vertebral column, and the dermomyotome develops into dermal and muscle components. Lateral mesoderm and dermomyotome cells migrate to the limb field and proliferate to create the limb buds. Mesodermal cells give rise to mesenchyme, which is loosely organized connective tissue. Mesenchymal cells are pluripotent and differentiate into many different cell types, including those that give rise to bones and cartilage.

Endochondrial ossification

Whilst the cranial bones of the skull and clavicle form from direct ossification from mesenchyme, the bones of limb and girdle form from ossification of a cartilaginous precursor of the long bones of the skeleton (a process known as endochondrial ossification). Condensation of lateral plate mesenchyme occurs in a rod-like structure along the axis of the limb bud. Cartilage cells (chondrocytes) respond to growth factors and differentiate (chondrification). These cells secrete proteoglycans and collagen to form cartilage. Initially there is deposition of cartilage around the entire limb condensations but then further chondrification is limited to future bone sites, sparing the interzone regions, resulting in the site of future joints.

Joint formation

For the joints of the long bones, mesenchymal cells at the interzones of long bones differentiate into multiple fibroblastic connective tissue layers. These then differentiate further to provide the articular cartilage at either end of the joint, and connective tissue in the middle forms the internal structures of the joint – synovial tissue, menisci and ligaments. Vacuoles form within the connective tissue which then becomes the joint cavity. The mesenchymal sheath becomes the joint capsule (Fig. 27.1). Fibrous joints, or immobile joints which connect bones (e.g. in the skull, pelvis) are also developed from interzones, which differentiate into a single layer of fibrous connective tissue.

Primary ossification

Following chondrification, ossification occurs from the primary ossification centre. In response to growth factors, mesenchymal cells in this area differentiate into bone cells (osteoblasts). These cells secrete the calcium matrix of mineralized bone. Bone-resorbing osteoclasts also appear. These enable remodeling of growing bone, a process which continues throughout development into adult life.

Skeletal muscle

The limb musculature develops from two condensations of somitic mesoderm that in the 5th week invades the limb bud, one ventrally, the other dorsally. Ventral somatic mesoderm gives rise to mainly flexors, pronators and adductor muscles whilst dorsal somatic mesoderm dorsally gives rise to mainly extensors, supinators and abductor muscles. Cells in these condensations differentiate into myoblasts (muscle cell precursors). Myoblasts fuse together to form syncytia.

The innervation of the limb muscles develops from branches that develop from spinal nerve axons in a multistep process. Branches of the ventral spinal nerve innervate ventral muscles, and branches of the dorsal spinal nerve innervate dorsal muscles.

Congenital abnormalities

Question 27.1

Congenital musculoskeletal problems

Following is a list (A–I) of aetiologies of congenital MSK problems:

A. Amniotic band
B. Fetal/child myopathy
C. Idiopathic
D. Maternal nutrient deficiency
E. Mitochondrial disorder
F. Oligohydramnios
G. Polygenic inheritance
H. Single gene disorder
I. Teratogenic drug exposure

From the above list, select the MOST LIKELY aetiology for each of the following conditions:

1. Talipes equinovarus
2. Meromelia (partial absence of ring and middle finger of left hand)
3. Isolated postaxial polydactyly

Answer 27.1

1. C. Idiopathic.
2. A. Amniotic band.
3. H. Single gene disorder.
See below for discussion.
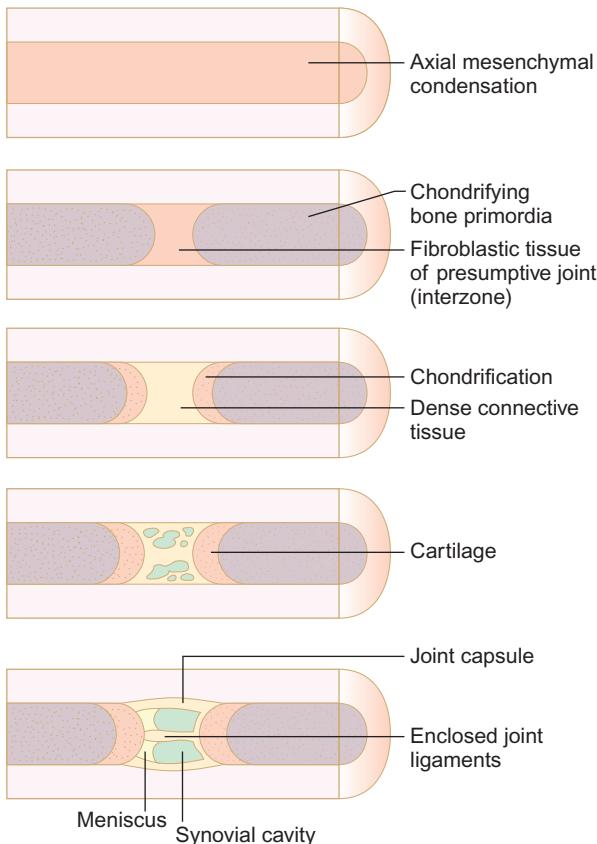
Fig. 27.1 Synovial joint formation. Mesenchymal condensation forms the limb long bones. The joint capsule, cartilage and ligaments arise from the interzone region. *(From: Stanley D, Trail IA. Operative elbow surgery. Churchill Livingstone, 2012.)*

Labels in figure:
- Axial mesenchymal condensation
- Chondrifying bone primordia
- Fibroblastic tissue of presumptive joint (interzone)
- Chondrification
- Dense connective tissue
- Cartilage
- Joint capsule
- Enclosed joint ligaments
- Meniscus
- Synovial cavity

Limb defects

Limb defects can be grouped into three categories:

1. *Reduction defects*, in which the entire limb (amelia) or part of the limb (meromelia) is missing.
2. *Duplication defects*, in which there are extra limb elements. The commonest defect being the extra presence of digits (polydactyly).
3. *Dysplasia* (malformation) of the whole of any part of the limb. This includes fusion of digits (syndactyly) or excessive growth of parts of the limb (gigantism).

Limb defects can be broadly attributed to the following processes:

- Development arrest (failure to form)
- Failure of differentiation
- Duplication
- Overgrowth (hyperplasia)
- Undergrowth (hypoplasia)
- Focal defects, e.g. amniotic fluid band syndrome
- General skeletal abnormalities, e.g. osteogenesis imperfecta (see below)

Most limb defects have multifactorial aetiologies, from a combination of environmental and genetic influences, but either may predominate. Examples of conditions where genetic (familial) aetiologies predominate include most causes of polydactyly or ectrodactyly (absence of fingers or toes). Polydactyly is a relatively common finding in newborns, affecting 1 in 500 newborns. Over 100 genes have been described but most cases result from abnormalities in a single gene. Postaxial hand polydactyly is a common isolated disorder in Black African children, especially males, and autosomal dominant transmission is suspected. In contrast, postaxial polydactyly seen in white children is usually syndromic and associated with an autosomal recessive transmission.

Developmental dysplasia of the hip

The cause of developmental dysplasia of the hip (DDH) is not clear but it is usually multifactorial. Known risk factors include female gender, family history, oligohydramnios, breech position, and the presence of other congenital abnormalities, e.g. neuromuscular disorders. In the normal development of the hip joint, the head of the femur is smooth and rounded, and the acetabulum is cup-shaped. However, in DDH there may be abnormalities of the shape of the head of the femur, the shape of the acetabulum or the surrounding structures. This means that the acetabulum and femur may not be in close contact.

Depending on the degree of abnormality, the hip may be subluxed or dislocated.

Talipes equinovarus

Talipes equinovarus is a complex abnormality affecting 1 in 1000 live births. The entire foot is inverted and supinated, the forefoot adducted and the heel is rotated inwards and in plantar flexion. The affected foot is shorter and the calf muscles thinner than normal. The position of the foot is fixed, cannot be corrected completely and is often bilateral. It is more common in males (2:1) and can be familial but is usually idiopathic. However, it may also be secondary to oligohydramnios during pregnancy, a feature of a malformation syndrome or of a neuromuscular disorder such as spina bifida. The Ponseti method for correction is a manipulative technique involving serial casting and usually avoids the need for invasive surgery. Talipes equinovarus needs to be differentiated from positional talipes, where the foot is of normal size, the deformity is mild and can be corrected to the neutral position with passive manipulation, and the rare congenital *vertical talus*, where the foot is stiff and rocker-bottom in shape. Many of these infants have other malformations.

Environmental causes of limb defects

Drug teratogens

Many drugs which might be taken during pregnancy, particularly if taken between 4–8 weeks' gestation, can result in limb defects:

- Thalidomide, which disrupts cell adhesion receptors and inhibits angiogenesis. Exposure is associated with limb defects, which include amelia and phocomelia, in addition to minor deformities, for example thumb hypoplasia and syndactyly between the index finger and the thumb.
- Any drug which influences general cell metabolism or cell proliferation, e.g. triethylene melamine, a chemotherapeutic alkylating agent.
- Other teratogens causing limb defects in humans include warfarin, phenytoin, valproic acid and acetazolamide.

Amniotic tissue/constricted uterus

In utero limb growth requires physical space. Constricted uterine environment or intrauterine compression, e.g. bicornate uterus or multiple pregnancy, can result in deformity of a limb. Occasionally, fibrous amniotic tissue detaches and wraps around the developing limb, forming an amniotic band. This physical

stricture can prevent growth or development of a limb or part of a limb. Amniotic band syndrome affects up to 1 in 1200 live births and is associated with increased risk of other abnormalities, including cleft lip and palate and talipes equinovarus.

Spine defects

Congenital structural defects of the spine may occur secondary to failure of vertebrae formation, separation or fusion, e.g. abnormal induction of the sclerotome and the neural tube. Depending on the position of the abnormality, the spine may develop to the left or right (scoliosis), or convex overcurvature (kyphosis) or sway backwards (lordosis). Growth potential depends on the involvement of the vertebra growth plate and gives rise to the differences in progression and deformity.

Congenital scoliosis is the most common developmental spine condition. Although the aetiology is not fully understood, failure of sclerotome segmentation results in vertebrae that are abnormally connected on one side, causing asymmetrical growth rates. There may also be disruption of the normal shape of the vertebra causing a wedge shape. Similarly, asymmetrical growth may occur. This is different to *idiopathic scoliosis,* which presents with either early onset (less than 5 years old) or late onset. The most common presentation is late-onset idiopathic scoliosis, mainly in girls 10–14 years of age during their pubertal growth spurt. Secondary scoliosis is common and related to other disorders that result in neuromuscular imbalance, e.g. cerebral palsy, muscular dystrophy, polio; disorders of bone or cartilage, such as neurofibromatosis, Marfan's syndrome; or leg length discrepancy. If a child has a congenital vertebral abnormality, other systems should be investigated to exclude syndrome characteristics, e.g. VACTERL association.

Joint defects

Arthrogryposis is the collective term for a number of conditions associated with joint contractures at birth. Factors that inhibit normal joint development or movement (extrinsic or intrinsic) can result in joint contractures. *Extrinsic* factors may include environmental problems, such as oligohydramnios or viral infections. *Intrinsic* factors include underlying genetic/molecular abnormalities leading to connective tissue, muscle or neurological abnormalities. Arthrogryposis is divided into three main categories:

- Amyoplasia: muscle weakness and multiple severe joint contractures
- Distal: contractures affecting the hands and feet
- Syndromic: associated with congenital neurological or muscle disease

Skeletal development and pathology

Bones

At birth, the diaphyses ('shafts') of the long bones are completely ossified, whereas the epiphyses ('ends') remain cartilaginous. Secondary ossification centres arise from the epiphyses, resulting in the ends gradually ossifying. Growth of the long bones relies on proliferation of chondrocytes in the epiphyseal cartilaginous plate (growth plate), which persists between the epiphysis and growing end of diaphysis (metaphysis). The epiphyses and diaphysis fuse around the age of 20 years. During childhood, if trauma occurs to the growth plate, the growth of that limb may be affected.

During the ossification process, bone is invaded by numerous blood vessels, which branch from the limb vasculature. A dominant nutrient artery develops, which nourishes the bone. During life, if this nutrient vessel becomes interrupted then cellular death of bone components occurs (avascular necrosis) and if this involves the bones around a joint, the articular surface may become damaged (osteochondritis dissecans). The blood supply in certain areas is vulnerable. Osteochondroses are a group of conditions in which the primary or secondary ossification centre undergoes avascular necrosis, and there is resorption of old dead bone, with replacement of new bone tissue. Examples include:

- Perthes disease – femoral head
- Osgood–Schlatter disease – tibial tubercle
- Freiberg disease – second metatarsal head
- Thiemann disease – phalangeal epiphyses
- Scheuermann disease – lumbar or midthoracic
- Köhler disease – navicular tarsal

Legg–Calvé–Perthes, or Perthes disease, is one of the most common of the osteochondroses, most often seen in young boys (age range: 4–8 years; male : female ratio: 4.5 : 1). Interruption of the blood supply causes avascular necrosis of the capital femoral epiphysis of the femoral head, and is followed by revascularization and reossification over 18–36 months. Slipped capital femoral epiphysis (SCFE) results in displacement of the epiphysis of the femoral head posteroinferiorly, requiring prompt treatment in order to prevent avascular necrosis. It is most common at 10–15 years of age during the adolescent growth spurt, particularly in obese boys, and is bilateral in 20%.

The cause of the osteochondroses is not clear, but they may be associated with trauma, especially at sites where vascular supply to the bone is vulnerable (e.g. femoral head) or follow a transient synovitis (e.g. Perthes disease after an irritable hip) or can be associated with metabolic endocrine abnormalities (e.g.

hypothyroidism and hypogonadism in slipped capital femoral epiphysis (SCFE)).

Bone remodeling

Bones consist of two cell types, osteoclasts (bone-resorbing cells) and osteoblasts (bone-forming cells). These act together to control bone growth and metabolism through the bone remodeling cycle. Each remodeling cycle takes several weeks to complete. In childhood, resorption and formation usually occur at the same rate, except when extra bone matrix is required for growth (for example, during skeletal development). In pathological situations, increases in bone resorption or decreases in bone formation may result in an overall net loss of bone (osteoporosis). Inadequate mineralization of the bone matrix (osteomalacia) can cause bone deformity if it occurs in a growing skeleton (rickets). Osteoporosis may be classified into primary or secondary causes.

Primary osteoporosis

There are two main types of primary osteoporosis. Idiopathic juvenile osteoporosis may present pre/early puberty with metaphyseal and vertebral crush fractures. Osteogenesis imperfecta presents at any age with varying degrees of severity. The principal features include bone fragility and low bone mass.

Case history

Osteogenesis imperfecta

A 6-month-old was taken to the emergency department by his parents due to inconsolable crying. He was found to not be moving his right leg and an X-ray confirmed a fractured femur. X-rays revealed several other fractures in various stages of healing. His parents could not explain what may have caused them. He was referred to the safeguarding team with suspected non-accidental injury. Subsequent investigations revealed a mutation in the *COL1A1* gene.

- This baby had osteogenesis imperfecta (type I).
- Osteogenesis imperfecta is a group of inherited (autosomal dominant and recessive, although may be sporadic) abnormal collagen conditions.
- Mutations in *COL1A1* and *COL1A2* result in abnormalities in the production of alpha chain of type 1 collagen, the major protein found in bones, ligaments and tendons.
- Abnormal collagen metabolism causes bone fragility, with bowing, frequent fractures and hypermobility.
- In the most common form (type I), which is autosomal dominant, there are fractures during childhood, a typical blue appearance to the sclerae, and some develop hearing loss. Treatment with bisphosphonates reduces

fracture rates. Fractures require careful management to minimize joint deformity. Prognosis is variable.
- There is a severe, lethal form (type II) with multiple fractures already present before birth. Many affected infants are stillborn. Inheritance is variable but mostly autosomal dominant or due to new mutations.
- In other types, scleral discoloration may be minimal.

Secondary osteoporosis

Secondary osteoporosis can result from inflammatory conditions (e.g. inflammatory bowel disease, juvenile idiopathic arthritis (JIA), cystic fibrosis, prolonged use of glucocorticoids or following disuse (e.g. cerebral palsy, muscular dystrophies, immobility) and in children and young people with endocrine disturbances (e.g. thyroid disease and hypogonadal states).

Osteomalacia/rickets

Most cases of osteomalacia are due to lack of vitamin D (see later in this chapter), resulting from poor sunlight exposure or dietary inadequacy. Osteomalacia is more common in darker-skinned individuals living in colder climates. Vitamin D deficiency results in myopathy and MSK aches and pains. Infants are usually miserable, and other features can include bowed limbs, metaphyseal swelling, bossed forehead and bone pain. Inherited forms of rickets include X-linked hypophosphataemic rickets, and children with McCune–Albright syndrome/polyostotic fibrous dysplasia.

Osteopetrosis (marble bone disease)

In this rare disorder, there is increased bone mass due to failure to resorb bone – the bones are dense but brittle. The severe autosomal recessive disorder presents with faltering growth, recurrent infection, hypocalcaemia, anaemia and thrombocytopenia (due to bone marrow failure). Prognosis is poor, but bone marrow transplantation can be curative. A less severe autosomal dominant form may present during childhood with fractures.

Skeletal dysplasias

Skeletal dysplasias are a group of clinically and genetically heterogeneous disorders causing generalized abnormalities of bone growth and/or bone modeling. Most are rare and usually present with one or more of:

- Short stature (usually disproportionate). If the limbs are short, it is important to note which segment(s) are affected:
  - Proximal segment (shoulder to elbow, or hip to knee) – rhizomelic
  - Middle segment (elbow to wrist, knee to ankle) – mesomelic

– Distal segment (hands, feet) – acromelic, or all segments micromelic
- Bone deformity/joint malalignment, including skull shape and circumference, face with dysmorphic features, spine (including scoliosis and kyphosis), limb and digit abnormalities
- Recurrent fractures usually after minimal trauma
- Associated features, including abnormalities of vision, hearing, teeth, palate, heart, abdominal organomegaly, development, neurological function.

Joint problems

Joints may be classified by their movements and tissues. Synovial joints (diarthroses) move freely, have a fibrous joint capsule and distinct joint cavity. There are several distinct subtypes including:

- Ball and socket – hip, shoulder
- Hinge – elbow, knee
- Saddle – thumb
- Gliding – intercarpal
- Condyloid – wrist

Synovial joints are lined with a highly vascular synovial membrane. Synovial fluid is produced naturally to lubricate the joint but can be produced in excess if the synovial membrane becomes inflamed (synovitis – see juvenile idiopathic arthritis, JIA). The blood supply of the bone is an important factor in the presence of infection such as septic arthritis, as it can lead to bone destruction and usually results from haematogenous spread, especially in neonates and young children, where spread from adjacent osteomyelitis into joints can occur where the capsule inserts below the epiphyseal growth plate. Other problems may arise in joints due to disruption of supportive cartilage (e.g. meniscal problems at the knee) or ligaments.

Histology and physiology of muscles

An appreciation of muscle histopathology and physiology allows the clinician to better appreciate and understand the spectrum of skeletal muscle diseases. Muscle biopsy samples may be helpful.

The structure of skeletal muscles and a simplified description of how muscles contract are summarized in Figure 27.2. Muscle cells respond to electrical

Muscle fibre
Each is a single cell with multiple nuclei. It is striated with light and dark banding

Skeletal muscle

Sarcomere

Thick and thin filaments (myofilaments)

Microfibrils
Muscle fibres consist of myofibrils which are made up of thick and thin protein filaments.
Thick filaments are made up of myosin, thin filaments of actin.
A unit of alternating thick and thin filaments is a sarcomere.
Sarcomeres are separated by dense Z lines.

Muscle bundle
A bundle comprises numerous muscle fibres

Sarcomere

Sarcomere

Z line

Thin filament (actin)

Thick filament (myosin)

Contracted muscle
The actin (thin filament) and myosin (thick filament) slide over each other, reducing the distance between the Z lines.

Relaxed muscle
The actin and myosin slide apart, increasing the distance between the Z lines.

Fig. 27.2 Summary of the structure of skeletal muscle and its contraction.

impulses by contracting in size and developing tension. Motor neurons stimulated by electrical impulses release acetylcholine into the neuromuscular synapse. When acetylcholine binds to the motor end-plate of the muscle fibre, it results in the initiation of an action potential throughout the cell membrane of the muscle fibre (or the sarcolemma). The method by which muscle excitation (the presence of an action potential in the muscle) results in contraction of muscle fibres depends on excitation–contraction coupling. This process can be thought of as consisting of three elements:

1. Release of calcium stores from the sarcoplasmic reticulum
2. Calcium-dependent activity of mitochondria in order to produce adenosine triphosphate (ATP)
3. ATP and calcium leading to myofibrils contracting.

At the start of exercise, when there is insufficient oxygen available for the Krebs cycle to occur effectively, ATP is generated from creatine phosphate stores in muscle fibres by the action of the enzyme creatine kinase. This store of creatine phosphate is soon depleted. During brief, vigorous exercise, pyruvate is converted to acetyl-coenzyme A (acetyl-CoA) which then enters the mitochondrial Krebs cycle. This process leads to generation of ATP (adenosine triphosphate). During prolonged exercise, free fatty acids are oxidatively converted by mitochondria to acetyl-CoA in order to enter the Krebs cycle.

During anaerobic exercise, the small amount of ATP generated from the breakdown of glycogen to pyruvate is the primary source of ATP. The build-up of pyruvate leads to lactic acid formation, as there is insufficient oxygen available for the pyruvate to enter the Krebs cycle.

There is a wide range of pathological processes which cause skeletal muscle disorders. Pathologies either affect the nerves (neuropathies) or the muscles directly (myopathies). Diseases that cause degeneration and destruction of muscle fibres are known collectively as muscular dystrophies. Muscle fibre development and maturation may be delayed (for example in congenital inherited myopathies) or may be affected by abnormalities in the metabolic or signaling pathways. These conditions are described in Chapter 5, Developmental problems and the child with special needs. A number of infections (e.g. influenza, Coxsackie B) can result in a muscle inflammatory response (myositis). In addition, myositis may be part of a number of systemic inflammatory conditions (e.g. juvenile dermatomyositis, systemic lupus erythematosus and systemic sclerosis/mixed connective tissue disease).

Case history

Juvenile dermatomyositis

A 9-year-old girl was referred with a 7-month history of gradual tiredness and weakness. She had become unable to climb the stairs and frequently complained of pains in her legs. Her mother described a persistent 'sunburn' rash across her face. Blood tests revealed raised creatine kinase (CK) of 600 IU/L. Muscle biopsy of her quadriceps revealed an inflammatory infiltrate, in a perivascular distribution with variation in muscle fibre size.

- This girl has juvenile dermatomyositis (JDM), a rare small vessel vasculopathy of childhood, which affects the muscles and skin, but also may involve the joints, gastrointestinal system and heart.
- Typical features include a heliotrope rash over the face, periorbital oedema, Gottron papules over the extensor surfaces and proximal muscle weakness.
- Presentation may also include systemic symptoms such as malaise, fever, weight loss or anorexia. Arthritis, joint contractures and myalgia, dysphagia, dysphonia, dyspnoea, calcinosis and skin ulceration, and oedema may also be present.
- Muscle enzymes (creatinine kinase) are often raised.
- Muscle MRI in early JDM may show increased tissue density from muscle oedema, and subcutaneous tissue. Active myositis may be demonstrated. MRI is now regarded as diagnostic.
- Muscle biopsy may show inflammation, fibre necrosis and small vessel vasculitis, but is not required for diagnosis. Electromyogram (now rarely performed) shows myopathy/denervation.

Additionally, any condition which leads to derangement of cellular potassium, calcium or magnesium can lead to a global muscle dysfunction. This is discussed in the case history below and in Chapter 6, Paediatric emergencies and critical care, and Chapter 19, Nephrology, in more detail.

Case history

Hyperkalaemic periodic paralysis

A two-year-old girl presents with intermittent symptoms of profound weakness. In between these events, she is well. Each event typically lasts for 2 hours, but may last up to 12 hours and she may have several attacks in one day. The paralysis usually involves her shoulders and hips. Her facial, respiratory and bulbar muscle movements are preserved. Her parents report that these events usually occur when she is resting following a period of activity. Her father had similar episodes,

although milder, and these became less prevalent after he reached the age of 30. Her serum potassium is raised during one such event.

- This young girl has hyperkalaemic periodic paralysis. This is a rare, autosomal dominant condition affecting the *SCN4A* gene.
- There is a resultant alteration to the voltage-gated sodium channel, which leads to a failure of inactivation of this channel.
- These abnormal channels are sensitive to raised potassium levels (e.g. after eating excessive amounts of potassium-rich foods).
- During these episodes, the voltage-gated sodium channels on the sarcolemma remain activated and the muscle fibre remains in a depolarized state.
- Calcium remains bound to troponin C and the intracellular stores of ATP and calcium become depleted.
- Muscle paralysis ensues until repolarization occurs.
- This is a poorly understood condition, like many other channelopathies. However, affected individuals appear to have improvement of their symptoms after the 3rd or 4th decade.
- Individuals may have normal or high serum potassium levels during episodes.

Genetics

Abnormalities of the MSK system are seen in a number of genetic conditions (chromosomal, single gene and mitochondrial disorders). Commoner examples of these are summarized in Tables 27.1 and 27.2. Some features may be present at birth (e.g. hypotonia), but often become apparent as the MSK develops during childhood (e.g. hypermobility).

Case history

Marfan's syndrome

A 10-year-old boy, who was the tallest in his class, was referred to ophthalmology by an optician as he had been having problems seeing clearly. He was found to have upward subluxation of the lens. Two months later, he presented to the local emergency department with acute onset of shortness of breath. His father was also tall and attended regular cardiology follow-up.

- This boy has Marfan's syndrome, an autosomal dominant disorder of connective tissue associated with tall stature, long thin digits (arachnodactyly), hyperextensible joints, a high arched palate, dislocation (usually upwards) of the lenses of the eyes and severe myopia.
- The body proportions are altered, with long, thin limbs resulting in a greater distance between

Table 27.1 Common chromosomal conditions with musculoskeletal features

Condition	Chromosome abnormality	Musculoskeletal features
Down's syndrome	Trisomy 21	General hypotonia Hypermobility Patella dislocation Scoliosis Inflammatory arthritis Cervical spine instability Hip dislocation/subluxation Metatarsus primus varus Short stature Brachydactyly (short fingers)
Patau's syndrome	Trisomy 13	Polydactyly
Edward's syndrome	Trisomy 18	Rocker-bottom feet Clinodactyly
DiGeorge syndrome	22q11 deletion	Inflammatory arthritis Scoliosis Short stature Micrognathia Retrognathia
Turner's syndrome	XO	Inflammatory arthritis Cubitus valgus Clinodactyly (curved fingers) Brachydactyly Micrognathia Short stature
Klinefelter's syndrome	XXY	Tall stature

the pubis and soles (lower segment) than from the crown to the pubis (upper segment). The arm span, measured from the extended fingers, is greater than the height. There may be chest deformity and scoliosis.
- Pneumothorax is common, secondary to apical bullae.
- Life expectancy is reduced due to cardiovascular complications. Degeneration of the media of vessel walls results in a dilated, incompetent aortic root with valvular incompetence, mitral valve prolapse and regurgitation, and aneurysms of the aorta may dissect or rupture.

Case history

Achondroplasia

A four-month-old boy was referred with short arms and progressive enlargement of the head since birth. He was mildly hypotonic with frontal bossing and a wide open anterior fontanelle. He had rhizomelic pattern shortening of his upper and lower limbs. His parents are both of normal height (25th–50th percentile).

- This boy has achondroplasia. Inheritance is autosomal dominant, but about 50% are new

mutations. Skeletal abnormalities include marked short stature from shortening of the limbs, a large head, frontal bossing and depression of the nasal bridge. The hands are short and broad. A marked lumbar lordosis develops.

- Hypotonia and delayed motor milestones are common. Other clinical features include hydrocephalus (1–2%), obstructive sleep apnoea and serous otitis media.

Table 27.2 Examples of single gene disorders with musculoskeletal features

Pattern of inheritance	Musculoskeletal features
Autosomal dominant	
Neurofibromatosis type 1	Scoliosis Short stature
Neurofibromatosis type 2	Spinal tumour
Achondroplasia	Shortened limbs
Facioscapulohumeral dystrophy	Muscle weakness
Marfan's syndrome (see Case history, below)	Tall stature, disproportionately long limbs, arachnodactyly, pectus excavatum/carinatum, pes planus
Noonan's syndrome	Short stature, scoliosis, pectus, excavatum/carinatum, hypotonia
Stickler syndrome (may also be autosomal recessive)	Marfanoid habitus, scoliosis, joint hyperextensibility, spondyloepiphyseal dysplasia, premature osteoarthritis
Cleidocranial dysostosis	Absence of part or all of the clavicles, short stature
Autosomal recessive	
Cystic fibrosis	Arthralgia Inflammatory arthritis Hypertrophic pulmonary osteoarthropathy
Mucopolysaccharidoses (except Hunter's syndrome)	Joint contractures, scoliosis, wide range of skeletal deformities
Sickle cell anaemia	Dactylitis, bone pain, avascular necrosis
Homocystinuria	Tall stature, arachnodactyly, pectus excavatum/carinatum, scoliosis
X-linked	
Hypophosphataemic or vitamin D-resistant rickets	Genu varum (bow legs)
Duchenne muscular dystrophy	Abnormal gait, muscle weakness, scoliosis, calf and deltoid muscle pseudohypertrophy
Becker muscular dystrophy	Abnormal gait, muscle weakness, toe walking, scoliosis
Haemophilias A and B	Haemophilia arthropathy
Hunter's syndrome (mucopolysaccharidoses)	Stiffness, joint contractures, skeletal deformities (e.g. claw hand)
Fabry's disease	Pain and burning sensation in hands and feet

Mucopolysaccharidoses

The mucopolysaccharidoses are a group of heritable lysosomal enzyme disorders (often autosomal recessive) that lead to accumulation of glycosaminoglycans (GAGs) (see also Chapter 29, Metabolic medicine). The clinical presentations are variable, with a spectrum of multisystem features including MSK (joint/finger contractures, trigger fingers, carpal tunnel syndrome, kyphoscoliosis), upper airways obstruction (snoring, sleep apnoea from large tongue, tonsils and adenoids, recurrent infections and glue ear/deafness), learning difficulties, recurrent hernias, characteristic appearance and cardiac valve problems and cardiomyopathy. The diagnosis is made by demonstration of raised urinary GAGs, with confirmation by either genetic or white cell enzyme testing.

Mitochondrial disorders

Mitochondrial disorders arise from mutations in either the mitochondrial DNA (maternal inheritance pattern) or the genes within the nucleus that are involved in transportation of proteins into the mitochondria. Mitochondrial disorders result in abnormalities in the adenosine triphosphate (ATP) energy production pathways. In addition to neurological and cardiovascular problems, mitochondrial disorders affect the MSK system, predominately causing hypotonia (see Chapter 9, Genetics, and Chapter 29, Metabolic medicine, for further details).

Genetic susceptibility in autoimmune conditions

There are also a number of genetic susceptibility genes, which play a role in the development of autoimmune conditions, many of which have abnormalities affecting the MSK system (such as inflammatory arthritis). There is an increased incidence of most autoimmune conditions when another family member is affected and there is a higher concordance in monozygotic compared to dizygotic twins. The human leukocyte antigen (HLA) system is linked with a number of autoimmune conditions. The HLA system allows our immune system to distinguish the self-made proteins from proteins made by foreign invaders (such as viruses and bacteria). There are many different normal variations within each HLA gene facilitating each person's immune system ability to react to a wide range of foreign proteins. For example, a range of normal variations of HLA genes exists which affect the risk of developing JIA; HLA-B27 is strongly associated with enthesitis-related arthritis.

Musculoskeletal normal development

Gait development

There is considerable variation in the way normal gait patterns develop – these may be familial (e.g. 'bottom-shufflers' often walk later) and subject to racial variation (e.g. Black African children tend to walk sooner and Asian children later than Caucasian children). The normal toddler has a broad base gait for support, and appears to be high-stepped and flat-footed with arms outstretched for balance. The legs are externally rotated with a degree of bowing. Heel strike develops around 15–18 months with reciprocal arm swing. Running and change of direction occur after the age of 2 years, although this is often accompanied by frequent falls until the child acquires balance and coordination. In the school-aged child, the step length increases and step frequency slows. Adult gait and posture occur around the age of 8 years. Normal gait follows 'swing', 'stance', and 'toe-off' phases; a painful or antalgic gait leads to shortening of the stance phase on the affected limb, and therefore lengthening of the swing phase.

Leg alignment and feet position

As children develop, there are a range of 'normal' abnormalities of leg alignment and feet position that generally are self-limiting and correct themselves over time (Table 27.3). In many children, leg alignment 'evolves' with initially a degree of leg bowing (in toddlers) followed by a degree of knock-knee (valgus) appearance. These changes usually resolve, with normal adult leg alignment being the case from around 8 years of age. The following are normal variants and most resolve without any treatment, but if painful, severe, progressive, or asymmetrical, should be referred for specialist opinion.

Table 27.3 Normal variants of gait and posture seen in children

Normal variants	Normal age range	Differential diagnoses to consider
Bow legs	1–3 years	Rickets, osteogenesis imperfecta, Blount's disease
Knock knees	2–7 years	Juvenile idiopathic arthritis (JIA)
Flat feet	1–2 years	Hypermobility, congenital tarsal fusion
In-toeing	1–2 years	Tibial torsion, femoral anteversion
Out-toeing	6–12 months	Hypermobility, Ehlers–Danlos and Marfan's syndromes
Toe walking	1–3 years	Spastic diplegia, muscular dystrophy, JIA

Toddlers learning to walk usually have flat feet due to flatness of the medial longitudinal arch and the presence of a fat pad, which disappears as the child gets older. An arch can usually be demonstrated on standing on tiptoe or by passively extending the big toe. Marked flat feet is common in children with hypermobility. However, in older children and young people, a rigid flat foot is pathological and is suggested by absence of a normal arch on tiptoeing; it may be due to an associated tendo Achilles contracture (ankle), or tarsal coalition (see below) or inflammatory arthropathy (JIA). *Tarsal coalition* results from lack of segmentation between one or more bones of the foot, and coalitions that were fibrous or cartilaginous become symptomatic as they begin to ossify. They become progressively more rigid and limit normal foot motion and often become symptomatic during the pre-adolescent years.

In-toeing and out-toeing

There are three main causes of in-toeing:

- Metatarsus varus – an adduction deformity of a highly mobile forefoot. This occurs mainly in infants and is passively correctable. The heel is held in the normal position and no treatment is required unless it persists beyond 5 years of age.
- Medial tibial torsion – at the lower leg, when the tibia is laterally rotated less than normal in relation to the femur. This occurs mostly in toddlers and may be associated with bowing of the tibia. It typically corrects by 5 years.
- Persistent anteversion of the femoral neck – at the hip, when the femoral neck is twisted forward more than normal. This usually presents in early childhood and usually self-corrects by 8 years of age. It may be associated with hypermobility of the joints. Often children will sit between their feet with the hips fully internally rotated ('W' sitting).

Out-toeing is uncommon but may occur in infants between 6 and 12 months of age. When bilateral, it is due to lateral rotation of the hips and resolves spontaneously.

Toe walking is common in young children and may become persistent, usually from habit; they can walk normally on request. Alternatively, it may be due to mild cerebral palsy or tightness of the Achilles tendons and inflammatory arthritis in the foot and ankle (as in JIA). In older boys, Duchenne muscular dystrophy should be excluded.

Pes cavus

In pes cavus there is a high arched foot. When presenting in older children, it is often associated with neuromuscular disorders, e.g. Friedreich's ataxia and type

I hereditary motor sensory neuropathy (peroneal muscular atrophy). High fixed arches, pes cavus, and persistent toe walking may suggest neurological disease, but the latter has been reported as a feature of JIA.

Clinical assessment of a child with musculoskeletal problems

Young children may have difficulty in localizing or describing pain and the history is often given by the parent or carer or based on observations from others (e.g. teacher) and may be rather vague, with non-specific complaints such as 'my child is limping'. Symptoms such as pain, stiffness, decreasing ability (e.g. hand skills, handwriting, or sport), and reduced or altered interest in play activities may be observed and caregivers may have concerns about deterioration in behaviour (e.g. irritability, poor sleeping). Assessment of pain is important and may be conveyed through non-verbal signs such as withdrawal, crying, or distress. A *delay* in major motor development may indicate MSK problems as well as neurological disease. However, *regression* of achieved motor milestones is more likely in acquired MSK disease, such as muscle or joint disease; for example, the child who was happy to walk unaided but has recently refused to walk or resorted to crawling again.

It is important to ask open questions and to enquire about mode of onset, site, distribution and nature of the symptoms and observations, features suggestive of multisystem involvement (e.g. rash, abdominal pain, headaches, Raynaud's, fatigue), and red flags that warrant concern.

It is often necessary to probe for symptoms of inflammatory joint or muscle disease (e.g. asking about the child's mood, 'gelling' after periods of rest such as long car journeys, regression of achieved motor milestones, intermittent limping); a child will often adapt their activities to compensate for joint stiffness, pain, or weakness, and a change in the child's play or reluctance to participate in activities may signify inflammatory joint or muscle disease. The features of inflammatory arthritis include joint swelling, warmth, loss of movement and tenderness on examination – an isolated hot red joint warrants mandatory investigation to exclude sepsis. However, in a well child with a monoarthritis, in the absence of trauma and sepsis, JIA is the most likely diagnosis; nonetheless mycobacterial infection must always be considered, especially in the immunocompromised or in endemic areas.

The history alone may not identify sites of joint involvement and in all cases where MSK disease is suspected, physical examination is performed including an MSK examination (pGALS – paediatric Gait Arms Legs Spine; and pREMS – paediatric Regional Examination of the MSK System; see Further reading). Non-specific MSK pain in children is common and often labelled as 'growing pains'; a confident diagnosis can be made when applying the 'rules' of growing pains (Table 27.4).

Many children with non-specific aches and pains, including growing pains, are found to have joint hypermobility, although not all hypermobile children are symptomatic. In the child with hypermobility, rare but important syndromes need to be excluded (e.g. Marfan's, Stickler's, and Ehlers–Danlos syndromes), as these children are at risk of retinal and cardiac complications.

Understanding applied science in musculoskeletal conditions

The limping child

The limping child is a common diagnostic problem. The differential diagnosis varies by age and is

Table 27.4 Features of growing pains and indications of concern

'Rules' of growing pains	Pains never present at the start of the day after waking Child does not limp Physical activities not limited by symptoms Pains symmetrical in lower limbs and not limited to joints Physical examination normal (joint hypermobility may or may not be detected) Systemically well and major motor milestones normal Age range 3–12 years
Indications for concern	Systemic upset (red flags to suggest sepsis or malignancy) Abnormal growth (height and weight) Abnormal developmental milestones: *Delay* (especially major motor skills) suggestive of neurological disease or metabolic bone disease, OR *Regression* of achieved motor milestones (consider inflammatory joint or muscle disease) Impaired functional ability (ask about play, sport, schoolwork, 'clumsiness') Limping (intermittent or persistent) Morning symptoms (other than tiredness after disturbed sleep) or mood changes may suggest inflammatory arthritis Widespread pain (such as upper limbs and back) School absenteeism

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Question 27.2

Non-weight-bearing child with acute illness

A 5-year-old boy presents with a 12-hour history of right leg pain and refusal to weight bear. He had been awake overnight complaining of severe, unremitting leg pain. On examination, he was flushed, tachycardic and had a temperature of 38.5°C.

Which of the following is the most likely diagnosis? Select ONE answer only.

A. Acute lymphoblastic leukaemia
B. Developmental dysplasia of the hip
C. Juvenile idiopathic arthritis
D. Osteomyelitis
E. Septic arthritis

Answer 27.2

E. Septic arthritis.
See below for explanation.

summarized in Table 27.5 and the accompanying clinical histories.

Septic arthritis

Septic arthritis is a bacterial infection of the joint, most common in the first two years of life. Osteomyelitis is an infection of bone, again most common under two years of age, and may be acute, sub-acute or chronic. Most bone infections are spread via the haematogenous route and organisms are not always isolated. Septic arthritis and osteomyelitis may occur separately or together.

The synovial membrane of the hip, ankle, shoulder and radial head inserts distally to the epiphysis in young children, allowing bacterial infection to spread directly from the bony metaphysis to the joint space. Around half of neonates with septic arthritis have concomitant osteomyelitis. This figure decreases to around one fifth in infancy and continues to decrease throughout early childhood. Sepsis from adjacent osteomyelitis is particularly common in the hip.

Septic arthritis is most common in lower limb joints (knee>hip>ankle). Common causative organisms vary with age but include *Staph. aureus,* Group A streptococci and Gram-negative bacilli. Mycobacterial infection should be considered in the immunocompromised and in endemic areas.

Septic arthritis usually presents with one or more of the following features:

- Fever and associated constitutional symptoms
- Joint pain, swelling, warmth and/or redness
- Guarding of the affected area (e.g. refusal to weight bear)

Signs and symptoms may be subtle and non-specific.

Septic arthritis is a medical emergency, as bone and joint infections can be rapidly destructive. Delay in diagnosis or treatment can result in irreversible damage to the joint with associated long-term pain and functional impairment. Blood tests are not diagnostic of septic arthritis; they can only be used in the context of clinical findings.

Table 27.5 Significant causes of limp, by age

	0–3 years	4–10 years	11–16 years
Most common	Trauma (including toddler's fracture)	Trauma Transient synovitis Perthes disease	Trauma Osgood–Schlatter disease
Conditions requiring urgent intervention	Osteomyelitis Septic arthritis Non-accidental injury Malignancy (e.g. neuroblastoma) Testicular torsion Inguinal hernia	Osteomyelitis Septic arthritis Non-accidental injury Malignant disease (e.g. acute lymphocytic leukaemia) Testicular torsion Appendicitis Inguinal hernia	Osteomyelitis Septic arthritis Slipped upper femoral epiphysis Malignancy (e.g. bone tumours) Testicular torsion Appendicitis Inguinal hernia
Other important conditions to consider	Developmental dysplasia of the hip JIA Metabolic (e.g. rickets) Haematological disease (e.g. sickle cell anaemia) Reactive arthritis Lyme arthritis	JIA	JIA

(Reproduced from Foster and Brogan (eds). Oxford Handbook of Paediatric Rheumatology. 2012.)

Kocher proposed four factors to predict septic arthritis:

- Fever >38.5°C
- Non-weight bearing or pain with passive motion of the joint
- ESR >40 mm/hour (a raised CRP may be used as an alternative)
- White blood cell count >12×10^9

Therefore, helpful investigations include:

- Full blood count (FBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP): Children may have markedly elevated neutrophil and platelet counts. CRP is a better predictor than ESR for acute infection (see 'Inflammatory markers', below).
- Blood cultures: Not always positive in septic arthritis and frequently negative in osteomyelitis.
- Joint aspiration with Gram stain microscopy and culture of synovial fluid.
- X-ray: May be normal in the early stages of infection. Bony changes can take up to 21 days to evolve.
- Ultrasound: Can be useful in septic arthritis to demonstrate joint effusion and guide aspiration.
- Magnetic resonance imaging (MRI): Useful if diagnosis unclear. Radionuclide bone scanning is an alternative if MRI is unavailable.

Management requires appropriate antibiotics and should be in conjunction with the local microbiology team. Cefuroxime, a broad spectrum second-generation cephalosporin with good bone penetration, is frequently the first-line antibiotic of choice. Total duration of treatment is controversial, but children are commonly given 10–14 days of IV antibiotics before switching to oral preparation if response is adequate.

Transient synovitis

Transient synovitis is the most common cause of hip pain in children between three and ten years of age and is more common in boys. It is a diagnosis of exclusion. Little is known about the aetiology of this condition, although viral, autoimmune and allergic associations have been suggested.

Around half of children with transient synovitis report a viral infection during the preceding week. A painless limp in a relatively well child is the most common presentation; high fever, markedly elevated inflammatory markers, severe pain or functional impairment suggest an alternative diagnosis. Hip X-ray should be normal but ultrasound scan (USS) of the hips may reveal a small effusion.

Most cases of transient synovitis settle quickly. Review is necessary if the limp persists to exclude Perthes disease (or SCFE in older children) or evolving JIA.

Case history

Limp and normal blood tests

A four-year-old girl presented to her local walk-in centre with a four-day history of left leg pain and reluctance to walk. She had been off nursery with a viral infection five days earlier but was now relatively well in herself, playing happily if allowed to remain seated. She was afebrile and systems examination was unremarkable. Left hip had a reduced range of active and passive movement compared to the right. Blood tests (FBC, CRP and ESR) and hip X-ray were normal. In the absence of 'red flag' features suggestive of serious underlying illness, she was diagnosed with transient synovitis of the left hip and allowed home with instructions to return if symptoms did not settle completely within the next few days.

Case history

Chronic history of leg pains and poor growth

A four-year-old girl presented to rheumatology clinic with a several month history of bilateral leg pain, worse towards the end of the day, associated with an increased frequency of falls. She was a previously healthy child of South Asian origin with no family history of note. She was the youngest of three children, all of whom had been exclusively breastfed to six months. The child appeared generally healthy, although clingy, and was noted to be on the 0.4th centile for weight and height. There was no suggestion of synovitis and muscle strength was normal throughout. Genu varum ('bowing' of the legs) was noted.

Bloods tests revealed normal inflammatory markers and a mild hypochromic anaemia. The serum alkaline phosphatase was markedly elevated with low/normal serum calcium and phosphate. 25-hydroxyvitamin D was 18 nmol/L (normal >50 nmol/L, insufficient 25–50 nmol/L and low <25 nmol/L). X-ray of the legs demonstrated widened growth plates and metaphyseal fraying of the long bones with marked genu varum. Wrist X-ray revealed cupping and fraying of the metaphyseal region. Chest X-ray was normal.

Rickets

A 3-year-old girl presents to the emergency department with a short history of abdominal pain and muscle weakness. On examination she is small (<2nd centile for weight and height) with frontal bossing and bowing of the legs. You suspect she may have rickets secondary to vitamin D deficiency.

Are the following statements about vitamin D deficiency true (T) or false (F)?

A. 25-hydroxylation of vitamin D occurs in the skin

B. Breast milk contains more vitamin D than formula milk

C. Calcidiol is the biologically active form of vitamin D

D. It is more common in infants born to mothers with higher vitamin D levels

E. Typically less than 10% of vitamin D comes from dietary sources

Answer 27.3

A. False; B. False; C. False; D. False; E. True. See below for discussion.

Vitamin D deficiency rickets

Rickets is a defective ossification of the bony matrix and can be due to deficiency of the active form of vitamin D (1, 25-dihydroxyvitamin D or 1, 25-vitamin D), deficiency of phosphate or, rarely, deficiency of calcium. Signs and symptoms include bone tenderness, joint pain, proximal muscle weakness, delayed dentition, increased frequency of fractures, growth delay and skeletal deformities. Skeletal deformities include bowing of the long bones and persistent genu varum, splaying of the rib cage and costochondral swelling (the so-called 'rachitic rosary'). X-rays reveal impaired mineralization of the growth plates with cupping and fraying of the margins of the metaphyses.

Vitamin D deficiency is the commonest cause of rickets in the UK and worldwide. The normal source of 1,25-vitamin D is the skin (which is responsible for production of 90% of bioavailable vitamin D in temperate regions). In the skin, ultraviolet light rays convert 7-dehydroxycholesterol into the vitamin D prohormone. The prohormone is converted to 25-hydroxyvitamin D (calcidiol) in the liver and then to 1,25-dihydroxyvitamin D in the kidneys. Cutaneous vitamin D production is higher in pale-skinned individuals. Deficiency of 1,25-dihydroxyvitamin D

may result from low exposure to ultraviolet light rays, nutritional deficiency, liver or kidney disease.

Breastfed infants whose mothers are not exposed to sunlight or who themselves are not exposed to sunlight are at higher risk. The incidence of vitamin D deficiency in the UK has increased in the last few years with cases reported in children of all ethnic origins. One putative association is the widespread use of sunblock, preventing ultraviolet light from reaching the surface of the skin.

The definition, prevention and treatment of vitamin D deficiency in the UK remains controversial (see Chapter 13, Nutrition). The Royal College of Paediatrics and Child Health suggests treatment doses of between 3000 and 10,000 U daily, depending on the age of the child, for 4–8 weeks.

Case history

Joint swelling and intermittent limp

A previously healthy seven-year-old girl presented to her general practitioner with a seven-week history of right knee swelling and intermittent limp. She was stiff and grumpy in the mornings but otherwise well in herself. Her teacher had reported that she was finding it difficult to sit cross-legged in assembly.

She was systemically well with no 'red flags' in the history. If a limp persists for >3 weeks, the likelihood of JIA is high. It is advisable to refer to paediatric rheumatology prior to invasive procedures (arthroscopy or MRI) as such investigations are usually not necessary to confirm the diagnosis. Although there is no diagnostic test for JIA, further investigation must exclude alternative diagnoses such as Perthes disease, chronic infection or malignancy. JIA is a clinical diagnosis and blood tests (FBC, ESR, CRP) can be normal and rheumatoid factor is invariably negative. Eye screening is essential if JIA is suspected as chronic anterior uveitis, if present, is usually asymptomatic. This child was referred to her local paediatric rheumatology team and diagnosed with JIA.

Arthritis in children and young people is invariably a result of inflammatory pathways and likely triggered by a combination of genetic and environmental factors. JIA is the commonest cause of chronic arthritis in children (incidence 1 in 10,000 per year, prevalence 1 in 1000) and encompasses a heterogeneous group of diseases of unknown aetiology. Without treatment, inflammatory arthritis can result in joint damage and disability along with impact on growth, both localized (such as leg length discrepancy or micrognathia) through to generalized growth retardation from chronic disease and compounded by use of corticosteroids.

Investigations

Many MSK diseases do not have 'gold standard' diagnostic tests or simple, reliable measures of disease activity and instead require a high index of suspicion in the context of the history and examination. Patients may require multiple laboratory and radiological examinations, the results of which have to be pieced together like a jigsaw puzzle.

Laboratory investigations

The roles of the most commonly requested laboratory examinations are discussed in more detail below.

Full blood count and serum ferritin

The haematological indices can suggest an infective or inflammatory process. However, in JIA many children have normal blood counts despite obvious inflammation on clinical examination. In extensive polyarticular disease, systemic-onset juvenile idiopathic arthritis (SOJIA) or connective tissue disease (such as SLE), marked thrombocytosis and leukocytosis (predominantly polymorphs) can be seen. The serum ferritin is an acute phase reactant and can be markedly elevated in systemic onset JIA and SLE. A sudden dramatic rise in the serum ferritin in association with low or falling haematological indices can herald the onset of macrophage activation syndrome (MAS), a severe and potentially life-threatening complication of SOJIA and other chronic rheumatic diseases of childhood. Unexpectedly low/normal platelet or white cell counts in children with marked systemic inflammation suggest the possibility of occult malignancy (for example, leukaemia or lymphoma). A normocytic normochromic anaemia of chronic illness can develop in chronic inflammatory disease and iron deficiency is common in children with long-standing or severe disease. Autoimmune haemolytic anaemia can complicate systemic inflammatory illnesses such as SLE.

Inflammatory markers

Inflammatory markers can be useful measures of disease activity. The C-reactive protein (CRP) is an acute phase protein, synthesized by the liver in response to activated macrophages. Its physiological role is to bind to phosphocholine, expressed on the surface of dead or dying cells, thereby activating the complement system. The CRP rises very rapidly in response to acute inflammation such as infection, rising to above normal by six hours and peaking by around 48 hours. The level is determined by the rate of production or the severity of the inflammatory process.

The erythrocyte sedimentation rate (ESR) is a measure of the rate of fall of erythrocytes in anticoagulated blood during a one-hour period (mm/hour). During inflammation, relatively high levels of fibrinogen cause erythrocytes to form rouleaux (chains or stacks of erythrocytes), which settle more quickly. The ESR is therefore a reliable measure of systemic inflammation.

ESR and CRP appear to be equally reliable as an initial screening test but there are important differences in rates of increase and subsequent reduction. The CRP is rapidly responsive to resolution of inflammation (particularly relevant in the case of acute infection) but the ESR will rise more slowly and remain elevated for a longer period of time following inflammation.

In the absence of a definitive gold standard assay of disease activity, the ESR is frequently used to assess disease activity at presentation and during follow-up of

children with rheumatic illnesses. The ESR is central to the majority of composite indices of disease activity developed for paediatric rheumatic illnesses, for example the Juvenile Arthritis Disease Activity Score (JADAS). A sudden drop in the ESR can herald the onset of MAS in children with SOJIA or SLE. As the CRP increases more rapidly than the ESR in response to systemic inflammation it is more readily confounded by the presence of infection.

Immunosuppressed children, particularly children using interleukin-6 blockade, may not mount a normal immune response to infection. Acute phase reactants such as the CRP must be interpreted with caution in this situation. Serum immunoglobulins and the C4 complement factor reflect the acute phase reactants and can be markedly elevated in children with very active inflammatory disease. Low C3 or C4 complement factors suggest active SLE.

Rheumatoid factors and anti-cyclic citrullinated protein (anti-CCP) antibodies

Classic rheumatoid factors (RF) are IgM antibodies directed against human IgG. The significance of RFs of other immunoglobulin isotypes is uncertain. RF is not a diagnostic test for JIA. In contrast to adults, less than 10% of children with JIA are RF positive. RF can be elevated as an acute phase reactant (for example in bacterial endocarditis), so a result can only be considered positive if the RF is present in high titre on at least two occasions. RF can be associated with other rheumatological illnesses of childhood, in particular SLE and the overlap conditions such as mixed connective tissue disease.

Anti-cyclic citrullinated protein (anti-CCP) antibodies are less prevalent in children with JIA than in adults with rheumatoid arthritis, but occur in children with RF-positive polyarticular JIA. Anti-CCP antibodies are thought to be associated with an increased risk of erosive (and therefore potentially disabling) joint disease.

Antinuclear antibodies

Autoantibodies are immunoglobulins produced in response to self-antigens. Antinuclear antibodies (ANAs) are directed against the nuclear contents of the cell. Titres are usually reported as positive between 1 : 40 and 1 : 80. ANAs are not a useful screening tool for autoimmune disease and results must be interpreted in the context of clinical findings. A positive ANA can be found in up to 15% of healthy children and can occur as a consequence of viral infection, malignancy or IgA deficiency. A persistently positive ANA can be associated with a number of rheumatological conditions, including SLE, drug-induced lupus, undifferentiated

connective tissue disease, Sjögren's syndrome, juvenile dermatomyositis, scleroderma and systemic sclerosis. A positive ANA can occur in some children with JIA, most frequently girls with younger age at onset and an oligoarticular disease course. Children with oligoarticular JIA who are ANA positive are at highest risk for chronic anterior uveitis, a potentially devastating complication of this illness.

Anti-double stranded DNA antibodies (dsDNA)

dsDNA autoantibodies are highly specific for SLE and are seen in the majority of children with lupus nephritis. Titres correlate with disease activity in some children with SLE. Other extractable nuclear antigens (including anti-RNP antibodies, anti-Sm antibodies, anti-Ro and anti-La antibodies) occur with variable frequencies in children with SLE and related connective tissue disorders.

Anti-phospholipid antibodies

This is a heterogeneous group of autoantibodies which bind to phospholipids in the cell membrane. Examples include anticardiolipin antibodies and β_2-glycoprotein 1 antibodies. Antiphospholipid antibodies may occur in primary antiphospholipid syndrome, SLE and some vasculitides. They can be found in association with viral infections and may be drug induced. Not all antiphospholipid antibodies are pathogenic and are known to occur in up to 8% of the normal adult population. In view of this, antiphospholipid antibodies should only be considered positive if present on at least two occasions at least three months apart. Children with persistently positive antiphospholipid antibodies should be commenced on prophylactic low-dose aspirin to modify the risk of thromboembolic phenomena.

Anti-neutrophil cytoplasmic antibodies

This group of antibodies target lysosomal enzymes (myeloperoxidase and proteinase 3) in neutrophils and monocytes. There are two main patterns of immunofluorescent staining: perinuclear (pANCA) and cytoplasmic (cANCA). About 90% of cANCA is directed against proteinase 3 (PR3) and around 70% of pANCA against myeloperoxidase. PR3-ANCA is commonly found in granulomatosis with polyangiitis (previously known as Wegener's granulomatosis) and can be found in microscopic polyangiitis. MPO-ANCA is typically associated with microscopic polyangiitis or occasionally with Churg–Strauss syndrome.

ANCAs are not absolutely specific for the ANCA-associated vasculitides. They can be detected in chronic infection (including tuberculosis, the viral hepatides and HIV), malignancy, inflammatory bowel disease, sclerosing cholangitis and can be drug-induced.

Autoantibodies in systemic sclerosis

The autoantibody profile can predict the disease pattern in some children with complex multi-system connective tissue disease. Systemic sclerosis is a multi-system autoimmune disease characterized by increased fibroblastic activity. Autoantibodies can predict the extent of skin and other organ involvement. Anti-topoisomerase 1 (Scl 70) antibody occurs in systemic sclerosis and is associated with lung fibrosis and renal disease. Anti-PM-Scl antibody is associated with a combination of myositis and scleroderma. Anti-U1RNP antibody is associated with arthritis and overlap syndromes. Anti-centromere antibody is found in limited cutaneous systemic sclerosis and is associated with an increased risk of pulmonary hypertension. Anti-RNA antibody is associated with diffuse cutaneous systemic sclerosis.

Radiological examination

Plain X-ray can be used in the initial investigation of children with bone pain. Classical appearances can be seen, e.g. Perthes disease (irregularity of the femoral head) and SCFE (displaced femoral head). The presence of periosteal reaction suggests the possibility of bony infection or malignancy. An AP view of the hand and wrist can be a useful screening tool in the investigation of metabolic bone disease (for example, rickets). If a skeletal dysplasia is suspected, specific skeletal radiographic survey may be performed.

X-rays may be normal in early JIA. Although plain X-rays may reveal soft tissue swelling around joints or demonstrate bony erosions, they are insensitive for the diagnosis of acute synovitis.

Ultrasound

Musculoskeletal ultrasound can help to identify which structures are involved in a clinically swollen joint. Ultrasound can, with specialist interpretation, differentiate between joint effusions, synovial hypertrophy, synovitis, enthesitis, tendonitis and tenosynovitis. It is cheap, more readily available and is well tolerated by most children.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) allows the localization and differentiation of bony and soft tissue lesions. It provides an anatomical overview and can detect inflammation, damage and pathology such as tumour. MRI is sensitive to early changes in JIA. However, MRI is not always available and requires sedation or general anaesthesia in younger children. Gadolinium contrast may be indicated to identify if inflammatory disease is present. MRI scanning of the thigh muscles can be diagnostic in children with suspected juvenile dermatomyositis and has supplanted muscle biopsy in diagnosis and disease monitoring.

Other investigations

Synovial fluid examination to exclude sepsis is mandatory in the assessment of a child with a single hot, swollen joint. Mycobacterial infection can be indolent and easily missed and diagnosis may require further examination of the synovial fluid or tissue culture, although polymerase chain reaction (PCR), if available, can give quicker results.

Muscle enzymes, bone chemistry and other indicators of systemic disease may be required, as well as genetic investigations for conditions with known mutations.

Investigations in clinical practice

These are outlined in the case histories below.

Case history

Investigation of suspected JIA

A two-year-old girl is referred to your clinic with an eight-week history of swollen right knee. Her parents have noticed that she is asking to be carried more often but she remains generally well. What would be the appropriate initial investigations?

This little girl is likely to have oligoarticular JIA, but initial investigations must exclude other possible diagnoses, including septic arthritis and malignancy.

Investigations should include:

FBC: This should be normal in a child with one swollen joint. Low indices should raise the possibility of haematological malignancy, such as acute lymphoblastic leukaemia and further investigations including blood film and bone marrow aspirate may be required. Significantly elevated neutrophil or platelet count may indicate underlying infection and further investigations including blood cultures and synovial fluid aspiration may be required.

Acute phase reactants: Significantly elevated acute phase reactants are unusual in oligoarticular JIA and should trigger further investigations to exclude infection and/or malignancy.

Anti-nuclear antibody: A positive ANA can occur in JIA and is associated with an increased risk of uveitis. Although all children with JIA are at risk from uveitis, young children, particularly girls, with persistently positive ANA are at higher risk.

Rheumatoid factor: RF is unlikely to be positive in children with oligoarticular JIA.

HLA B27: There are HLA associations for each JIA subtype, particularly important in oligoarticular disease. HLA B27 plays an important role in the classification of JIA and is associated with both enthesitis-related arthritis and psoriatic arthritis. HLA B27 positivity predicts more aggressive disease.

Plain XR: May be indicated in children with long-standing disease to delineate the presence of erosive damage.

US: Can be very useful in determining the presence of sub-clinical synovitis and/or tenosynovitis.

MRI: May be useful in children with unusual presentations or long-standing disease in which it can be difficult to differentiate between damage and active synovitis.

Slit-lamp examination: Chronic anterior uveitis affects one third of children with JIA, is invariably asymptomatic in early stages, and can result in blindness if not diagnosed and treated. Slit-lamp examination is essential for diagnosis.

Case history

Investigation of suspected connective tissue disease

A 14-year-old girl is referred urgently to clinic with a six-month history of worsening fatigue and arthralgia, complicated by recent-onset dry cough and epistaxis. What would be the appropriate initial investigations?

This girl is systemically unwell and the differential diagnosis has to include chronic infection (for example, tuberculosis), connective tissue disease, vasculitis and malignancy. Investigation of complex multisystem illness is initially non-specific and early results will determine further, disease-specific investigations:

FBC: A normochromic, normocytic anaemia is typical of chronic illness, although a hypochromic picture can also occur. Neutrophils and platelets may be normal or elevated in connective tissue disease, reflecting the underlying inflammatory process. Low white cells or platelets should raise the suspicion of malignancy.

Acute phase reactants: Acute phase reactants are often elevated in connective tissue disease (CTD), although can be normal in vasculitis.

Renal function and urinalysis: Renal involvement is common in connective tissue disease (particularly in SLE) and vasculitis (particularly Henoch–Schönlein purpura, granulomatosis with polyangiitis, microscopic polyarteritis and Churg–Strauss syndrome). Renal function is usually preserved until late in the illness, but microscopic haematuria and proteinuria are common early manifestations of nephritis. Urine dipstick is therefore integral to the initial investigation of a child with suspected CTD/vasculitis and any abnormalities should trigger a request for renal biopsy.

Liver function: Liver enzymes are commonly elevated in the early phases of connective tissue disease/vasculitis. The differential diagnosis must include chronic viral infection and malignancy.

Complement and immunoglobulins: Immunoglobulins can be elevated in any chronic inflammatory process. Low C4 is a consistent and reliable indicator of lupus nephritis.

Autoantibodies: Autoantibodies can be very helpful in the investigation of suspected connective tissue disease/vasculitis, but must be interpreted in the context of the clinical picture. The ANA is very non-specific, but is frequently positive in children with CTD/vasculitis. Antibodies to dsDNA are virtually pathognomonic of SLE and may occur in combination with anti-Ro and anti-La antibodies (associated with neonatal lupus erythematosus and Sjögren's syndrome) and anti-Sm antibodies. Anti-RNP antibodies are found in high titres in children with mixed connective tissue disease.

Echocardiogram: Pericardial effusions, reduced left ventricular function and myocardial involvement can all complicate multisystem CTD/vasculitis.

USS abdomen and pelvis: Important to exclude intra-abdominal infection or masses. May demonstrate organomegaly or serositis.

High-resolution CT chest: Pulmonary involvement is a potentially devastating consequence of a number of CTD/vasculitides, including granulomatosis with polyangiitis, Churg–Strauss syndrome and systemic sclerosis.

Angiography: Angiography is central to the diagnosis of vasculitis. CT/MR angiography are very useful and relatively safe procedures and can be used in place of conventional angiography.

Treatment of inflammatory musculoskeletal conditions

Immunopharmacology treatment

Case history

A ten-year-old girl came home from school complaining of some discomfort in both her knees. Bilateral knee swelling was noted by her GP and regular ibuprofen advised. While this eased her pain, morning stiffness became problematic and she was referred to her local paediatric rheumatology

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) act by inhibiting enzymes (cyclo-oxygenase-1 (COX-1) and COX-2) involved in prostaglandin synthesis (Fig. 27.3), resulting in analgesic, anti-inflammatory and antipyretic effects. There are two broad groups of NSAIDs – the older, traditional, non-selective NSAIDs (e.g. ibuprofen, piroxicam, diclofenac, aspirin) that inhibit both COX-1 and COX-2 and the newer, selective COX-2 inhibitors that predominantly inhibit COX-2 (e.g. celecoxib). The clinical effects of NSAIDs depend largely on their selectivity for these enzymes. The non-selective group act widely, resulting in varying degrees of analgesic, anti-inflammatory, antipyretic and antiplatelet effects, whereas the selective group has fewer gastrointestinal tract side effects.

NSAIDS may provide some symptom relief initially from their anti-inflammatory effect, although they are not disease-modifying and do not prevent joint damage in JIA. The last decade has seen a marked change in treatment with the emergence of potent immunosuppressive agents used early in the disease course to optimize long-term outcomes.

Corticosteroids

These are potent immunosuppressants but their use is limited by troublesome side-effects and the risk of iatrogenic adrenal suppression. Common routes of administration include oral, intra-articular, intravenous, intramuscular and topical (e.g. for skin and eyes). If a child is taking oral corticosteroids, dietary intake of calcium and vitamin D should be optimized; however, the role of calcium and vitamin supplements to reduce the risk of osteoporosis is unclear.

Disease-modifying anti-rheumatic drugs

Methotrexate (MTX) is the most widely used disease-modifying anti-rheumatic drug (DMARD) in the treatment of JIA and is often used in other inflammatory diseases. It is a structural analogue of folic acid, which competitively inhibits dihydrofolic acid, binding to the enzyme dihydrofolate reductase. The amount of intracellular folinic acid (the active metabolite of dihydrofolic acid) is decreased, and affects the intracellular folinic acid-dependent metabolic pathways. Purine and pyrimidine metabolism are two such pathways. Whilst these pathways are considered important, the exact mechanism of action of MTX in these conditions remains unclear. Other DMARDs, including sulphasalazine, azathioprine and ciclosporin, may be useful. In the child with severe disease resistant to or intolerant of MTX, biological therapies are often used (see below), although in many parts of the world, access to these is very limited due to their high cost.

Biologic and novel therapies

A major advance in the management of many inflammatory conditions has been the advent of 'cytokine modulators' or 'biologics', to block selectively the effects of pro-inflammatory cytokines. Anti-TNF treatment has been a major advance in the management of JIA. Table 27.6 summarizes the cytokine modulators which have been used in severe JIA, although not all are licensed for use in children, and Box 27.1
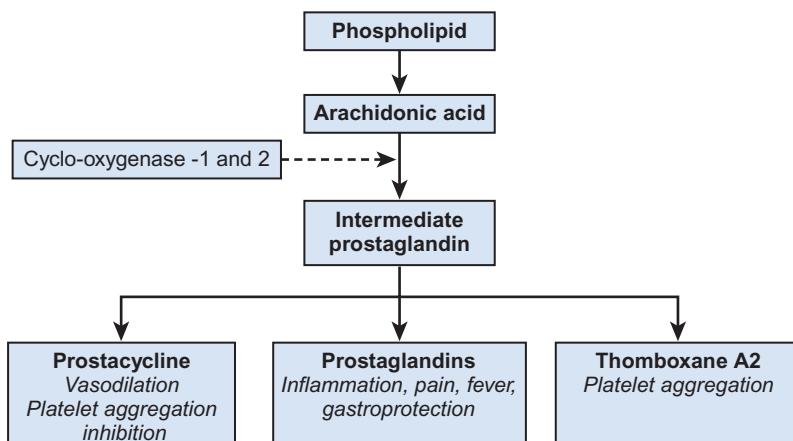
Fig. 27.3 Enzymes cyclo-oxygenase-1 (COX-1) and COX-2 are involved in prostaglandin synthesis. NSAIDs act by inhibiting the enzymes.

Table 27.6 Cytokine modulators currently used in rheumatic disease

Generic name	Mechanism of action	Route of administration
Etanercept	TNF-α soluble receptor that binds to circulating TNF and competes with membrane receptor	Subcutaneous injection
Infliximab	Human–murine chimeric antibody that neutralizes TNF-α	Intravenous infusion.
Adalimumab	Fully human monoclonal antibody that neutralizes TNF-α	Subcutaneous injection
Anakinra Rilonacept Canakinumab	IL-1 receptor antagonists	Subcutaneous injection
Rituximab	Human–murine chimeric antibody against CD20 (depletes B cells)	Intravenous infusions
Tocilizumab	IL-6 receptor antagonist	Intravenous infusion
Abatacept	CTLA4-antagonist to block T cell and B cell interaction and initiation of the pro-inflammatory pathway	Intravenous infusion

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Box 27.1 Important issues for the child taking cytokine modulators*

- Avoid live viral vaccines
- Promote annual flu vaccine
- Promote pneumococcal immunization (current advice: 5-yearly)
- Be vigilant regarding infections (e.g. varicella and shingles, opportunistic infections such as listeriosis). Vaccinations against varicella advised if there is a window of time; specialist advice needed.
- Advice regarding travel abroad, with medicines and travel insurance

*These apply to all cytokine modulators.

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summarizes the important issues for children taking cytokine modulators. Emerging evidence demonstrates dramatic and sustained improvement with reduced joint damage in children with JIA who had failed MTX due to ongoing disease or intolerance (nausea and vomiting most common). Long-term safety and efficacy data will be obtained through registries and international collaboration is necessary to collect data to address the potential theoretical concerns about infection risk, impact on fertility and malignancy risk. The use of biological therapies in JIA-related uveitis is increasing and clinical trials are in progress. For those few children with severe refractory disease failing to respond to cytokine modulators, a further option is T-cell depletion coupled with autologous haematopoietic stem-cell rescue; this procedure is limited to specialist centres and needs careful selection of patients.

Periodic fever syndromes and autoinflammatory disease

Hereditary periodic fever syndromes have onset usually in early childhood and are associated with genetic mutations. Many of the syndromes (Table 27.7) have mutations described and diagnostic tests and specific highly effective biological treatments now available. Others, such as PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis), Behçet's disease and chronic recurrent multifocal osteomyelitis (CRMO), have less clear aetiologies but have clinical features that suggest they are likely to be autoinflammatory.

These disorders of innate immunity are characterized by recurring episodes of fever and constitutional upset, but the child is often well between attacks. Other systemic inflammatory symptoms are variable and often include joints, skin, eyes, serosa and central nervous system with high morbidity. High acute phase reactants are typical along with leukocytosis. Long term, if not treated, they can result in AA amyloidosis with high mortality.

Case history

Use of biologics in periodic fever syndrome
A 2-year-old boy was referred with history of fatigue, frequent fever episodes and muscle pain. He developed an urticarial rash during the first few months of his life and had been admitted with two episodes of presumed meningitis (cultures were negative). He subsequently developed swellings of both knees. He was investigated by paediatric rheumatology and clinical genetics and found to have a mutation in *NLRP3*. He was treated initially with anakinra but struggled with daily subcutaneous injections. He subsequently received monthly canakinumab with marked improvement in his well-being and reduction in his episodes of fever and rash.

Cryopyrin-associated periodic syndrome (CAPS) is subdivided into familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) and chronic infantile, neurological, cutaneous and

Table 27.7 Periodic fever syndromes

Periodic fever syndrome	Gene	Mode of inheritance	Typical duration of attacks	Typical frequency of attacks	Characteristic laboratory abnormalities	Treatment
Familial Mediterranean fever	*MEFV* Chromosome 16	Autosomal recessive (dominant in rare families)	1–3 days	Variable	Marked acute phase response during attacks	Colchicine
TRAPS (tumour necrosis factor alpha receptor-1 associated syndrome)	*TNFRSF1A* Chromosome 12	Autosomal dominant, can be *de novo*	More than a week, may be very prolonged	Variable, may be continuous	Marked acute phase response during attacks. Low levels of soluble TNFR1 when well	Etanercept High-dose corticosteroids with attacks Anti-IL-1 therapies
HIDS (hyperimmunoglobulin D syndrome)	*MVK* Chromosome 12	Autosomal recessive	3–7 days	1–2 monthly	Elevated IgD and IgA, acute phase response, and mevalonate aciduria during attacks	Anti-TNF and anti-IL-1 therapies Anti-IL-1 therapies
CAPS (cryopyrin-associated periodic syndrome)	*NLRP3* Chromosome 1	Autosomal dominant or sporadic	Continuous, often worse in the evenings	Often daily	Varying but marked acute phase response most of the time	Anti-IL-1 therapies
PAPA – Pyogenic arthritis, pyoderma gangrenosum and acne	*PSTPIP1* (CD2BP1) Chromosome 15	Autosomal dominant	Intermittent attacks with migratory arthritis	Variable, and may be continuous	Acute phase response during attacks	Anti-TNF therapy or Anti-IL-1 therapies
DIRA (deficiency of IL-1-receptor antagonist)	*IL1RN* Chromosome 2	Autosomal recessive	Continuous	Continuous	Marked acute phase response	IL-1Ra
Blau syndrome	*NOD2 (CARD15)* Chromosome 16	Autosomal dominant	Continuous	Continuous	Sustained modest acute phase response	Immunosuppressive therapies

TNFR1, tumour necrosis factor alpha receptor-1 gene.
(Modified from Foster and Brogan (eds). Oxford Handbook of Paediatric Rheumatology. 2012.)

articular syndrome/neonatal onset multisystem inflammatory disease (CINCA/NOMID). CAPS is associated with mutations in *NLRP3/CIAS1* on chromosome 1q44, and such mutations result in IL-1 activation. Disease onset is in early infancy and features may be present from birth. Inheritance is autosomal dominant (75% of FCAS and MWS patients). CINCA however often results from new mutations.

FCAS typically presents with bouts of urticarial rash, fever, arthralgia and conjunctivitis and is often triggered by damp or cold conditions. MWS typically presents with fever, usually daily (afternoon/evening), along with arthralgia, myalgia, urticarial rash (which may be persistent), conjunctivitis and malaise. Deafness develops later. CINCA/NOMID – clinical features result from chronic widespread inflammation – headaches, raised intracranial pressure, optic atrophy, uveitis, deafness, developmental delay, joint damage. IL-1 blockade is an effective treatment for CAPS.

Summary

We have described the spectrum of MSK diseases and disorders, with their link to basic science as appropriate. Many MSK conditions do not have diagnostic tests and the case histories highlight the importance of MSK assessment as an integral part of general paediatrics, with a need to interpret clinical examination and investigations within their clinical context.

Further reading

Foster HE, Brogan PA. Oxford handbook of paediatric rheumatology. Oxford: Oxford University Press; 2012.

Newcastle University and Northumbria University. Paediatric musculoskeletal matters (PMM), <http://www.pmmonline.org>; 2015 [accessed 31.08.15]. A free online resource with a wealth of information about musculoskeletal medicine, including video demonstrations of joint examination (pGALS, pREMS), and cases.

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Gary McCullagh, Dipak Ram, Nadya James

Neurology

Development of the central nervous system

During the third week of gestation, the three germ layers of the embryo are formed (ectoderm, mesoderm and endoderm; Fig. 28.1). The central nervous system appears at the beginning of the third week, being derived from the primitive streak. The cephalic end of this streak is known as the primitive node and surrounds the primitive pit. This process is called gastrulation.

From the 3rd to 8th weeks, each of the three germ layers give rise to specific tissues and organs. This is the embryonic phase, following which the shape of the embryo changes markedly; the major external features are recognizable by the end of the second month.

Inside-out development

Primitive neural tissue arises from the ectoderm. Maturation of the primitive pit leads to the neural plate and neural folds. This is the basis of the nervous system. The neural folds become elevated and grow towards the midline to fuse and thus form the neural tube. The process of fusion begins in the cervical region and progresses both in the cephalic and caudal directions, with full closure being achieved at 25–27 days. The caudal end of the neural tube is composed of neuroepithelial cells, which give rise to primitive nerve cells known as neuroblasts, which following maturation form the grey and white matter of the future spinal cord. The cephalic end progresses through a process of folding to form the primitive hindbrain, midbrain, and forebrain.

The hindbrain, midbrain, and forebrain have distinct but interlinked functions, ranging from the hindbrain, which controls basic processes necessary to sustain life, to the intricacies of cerebral cortex activity in higher functions, such as completing a jigsaw puzzle or playing a musical instrument. Development in general begins with the 'primitive' brain and works upwards to the cortex. Therefore, it progresses first in
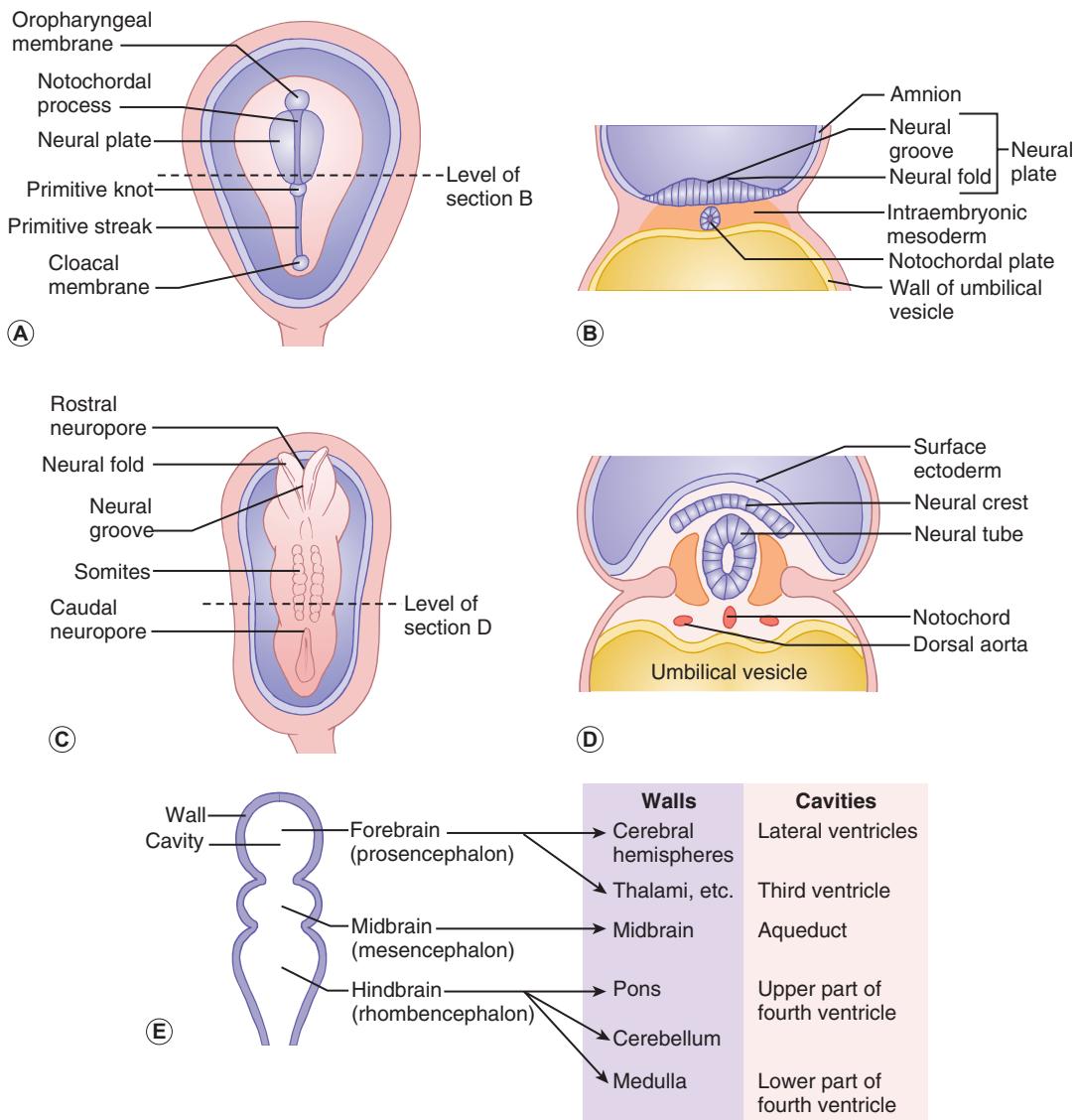
Fig. 28.1 Embryology of central nervous system. A. The nervous system develops from the neural plate, and the area of ectoderm. Dorsal view at 18 days. B. Transverse section showing the neural plate and early development of the neural groove and neural folds. C. Neural folds are open at both ends. Dorsal view at 22 days. D. Transverse section showing formation of the neural tube. The neural tube differentiates into the CNS, i.e. the brain and spinal cord. The neural crest forms most of the peripheral and autonomic nervous system. E. The three primary vesicles, the forebrain, midbrain and hindbrain and the walls and cavities formed from them. *(Adapted from Fig. 16.1 in Moore KL, Persaud TVN, Torchia MG. Before we are born, 8th edition, Saunders 2013, with permission.)*

the hindbrain, then midbrain, then forebrain. This is logical given that the need to eat and breathe is more important for survival than the ability to read and understand a newspaper.

Neural tube defects

Failure of the neural tube to form correctly leads to a variety of congenital defects:

- Cranial defects – anencephaly, where there is failure of development of most of the cranium and cerebral hemispheres
- Midline defects – failure of fusion, e.g. of skull in encephaloceles, most often occipital, with herniation of meninges and may include neural tissue
- Spina bifida – by definition involves splitting of the vertebral arch, and may involve the spinal cord.

Question 28.1

Spinal swelling

A baby boy is born after a concealed pregnancy, and is estimated to be at term. A 6 cm thin-walled, fluid-filled swelling is noted at the base of the spine. He appears healthy but has weakness in his lower limbs. What is the approximate risk of recurrence in mother's next pregnancy?

A. 0.5%

B. 3%

C. 7%

D. 10%

E. 15%

Answer 28.1

B. 3%.
   See below for discussion.

Spina bifida

A combination of genetic and environmental factors contribute to spina bifida. After having an affected infant, the risk of a second is 3–5%, and after two affected children have been born to a mother, the risk to the third is approximately 5–10%.

Drugs are known to have an effect. There is a 10–20 times increased risk in mothers taking valproate. The biological availability of folate to the fetus appears pivotal to the observed risk. The prevalence is reduced by maternal folic acid supplementation before and during early pregnancy, although in most people, the maximum effect is probably reached at small daily doses.

Cereal grain products are fortified with folic acid in the United States but not in the UK or most countries in Europe. There has been a marked decline in the prevalence of neural tube defects in the UK, due to improved maternal nutrition, folic acid supplementation and antenatal screening, mainly with ultrasound, and the option of termination of pregnancy. In the UK, 1.2 per 1000 pregnancies are affected; the birth prevalence is 0.2 per 1000 live births.

Genetic polymorphisms in genes that are involved in folate metabolism such as methylenetetrahydrofolate reductase (*MHTFR*) show strong associations with the risk of spina bifida and anencephaly. Polymorphisms (variations) in this gene are common in the general population, though, and most do not lead to abnormalities in the fetus. The exact mechanism of risk is not known but is likely to be related to the folate–homocysteine–methionine pathway.

Spina bifida comprises a spectrum of disorders:

- *Spina bifida occulta* – a defect in development of the vertebral arch, which is covered by intact skin and does not involve the spinal cord. The lumbar spine is the most frequent location and occurs in up to 10% of healthy people. In asymptomatic people, it is usually identified on incidental X-rays. If there is an overlying patch of hair or naevus or other skin abnormality, tethering of the spinal cord may occur during childhood. An ultrasound or MRI scan of the spine should be performed and a neurosurgical opinion obtained.
- *Spina bifida cystica* – more severe neural tube defect in which spinal cord tissue and/or meninges protrude through the skin. Most cases involve the lumbar spine. Includes meningocele and myelomeningocele:
   - Meningocele – the fluid filled meninges, but not the spinal cord, protrude through the defect
   - Myelomeningocele – neural tissue is involved and protrudes.

These lesions are often associated with downward displacement of the cerebellar tonsils through the foramen magnum, called the Chiari malformation (also known as Arnold–Chiari malformation), which may cause non-communicating hydrocephalus.

Cell differentiation

Once the basic three-region structure of the brain is completed, it must be populated with active brain cells. Precursors of brain cells are the pluripotent neural stem cells. These differentiate into neurons, astrocytes, and oligodendrocyte lineages:

- Neurons:
   - comprise a cell body (soma), dendrites and a single axon that terminates in one or more synapses
   - are electrically excitable
   - rely on metabolically active ion channel pumps to maintain voltage gradients
   - action potentials arise via voltage-gated ion channels
- Astrocytes:
   - dominant cell line in the brain and spinal cord
   - star shape
   - support blood–brain barrier
   - neurotransmitter recycling
   - modulate synaptic signaling
   - maintain extracellular ion balance
   - provide nutrients to neural cells
   - brain repair and scarring
   - can transform into neurons

- Oligodendrocytes:
  - support and insulate the axon
  - permit saltatory conduction of nerve impulses (propagation of action potentials along myelinated axons from one node of Ranvier to the next)
  - increase conduction velocity along neurons
  - decrease metabolic workload of neurons

Answer 28.2
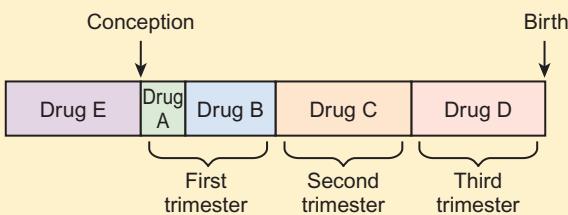
1. Drug B (taken between 2 and 3 months).
2. Drug A (although Drug E might also be implicated here, Drug A is still more likely).
3. Drug C.
   See Table 28.1 for rationale.

Question 28.2

The timing of CNS development

A baby is born at term following a concealed pregnancy to a 17-year-old mother with depression. During pregnancy, she was treated with Drug A for the first 4 weeks before changing to Drug B for the next 8 weeks, Drug C (alone) for months 3–6 and Drug D (alone) during the final trimester. She took Drug E in the year prior to conception but coincidentally stopped it in the week before she fell pregnant.

Conception				Birth
Drug E	Drug A	Drug B	Drug C	Drug D
	First trimester		Second trimester	Third trimester

For the following defects, select the MOST likely drug (Drugs A–E) with the observed abnormality:

1. Agenesis of the corpus callosum
2. Anencephaly
3. Lissencephaly

Cell migration

Neural cells migrate to their correct locations along specially created 'highways' of glial cells, known as radial glia. Each layer of brain cells is laid down, and then forms a scaffold upon which the next layer can be built on top – in other words, the brain develops 'inside out'. When this process is complete, the cortex has six distinct layers of organization. This amazingly complex system can, and does, go wrong (Table 28.1). Neuronal migration disorders can be visible on MRI scan (for example, lissencephaly – lack of development of brain folds) and are associated with a wide spectrum of clinical difficulties, including some forms of epilepsy.

Synaptogenesis

Synaptogenesis is the creation of functional signalling mechanisms between neurons. It 'explodes' at around 20 weeks' gestation, and continues for the first couple of years after birth. In the central nervous system, a projection from a dendrite (a filopodium) makes contact with an axon. This contact triggers the axon to recruit synaptic vesicles and active proteins to the area, which now forms the presynaptic membrane. Neurotransmitter receptors gather in the membrane of the dendrite, i.e. the postsynaptic membrane. Both cells

Table 28.1 Summary of embryology of the central nervous system and associated disorders

Gestation	CNS development	Associated disorders
Weeks 3–4	Primary neurulation	Spina bifida Anencephaly
Months 2–3	Prosencephalic development	Holoprosencephaly Agenesis of the corpus callosum Septo-optic dysplasia
Months 3–4	Neuronal proliferation	Microencephaly Macroencephaly/cerebral gigantism
Months 3–5	Neuronal migration	Schizencephaly (grey matter lined clefts extending inwards to the ventricles) Lissencephaly (absence of normal sulci and gyri) Polymicrogyria Heterotopias Focal cortical dysplasia
Month 5 onwards	Neuronal organization	Learning disability Link to epilepsy and autism
Birth through childhood	Myelination	Range of disorders including adrenoleukodystrophy

now express a protein called N-cadherin, which stabilizes the synapse. This now matures into the familiar arrangement, with a presynaptic (axonal) and postsynaptic (dendritic) membrane, separated by the synaptic cleft. A myelin sheath forms around the-structures, and the synapse is complete.

Myelination

Neuronal cells consist of the cell body, branching dendrites that receive information from surrounding cells, and long axons to carry information in the form of electrical impulses. Many axons are covered in myelin, produced by glial cells. Myelin can be thought of as being like insulation on an electrical wire; it increases the speed and accuracy of the transmission of information in the form of action potentials that propagate along neurons. The process of myelination begins *in utero*, and between 36 weeks and term myelin increases from 1% to 5% of total brain volume.

Normal myelination progresses in a set sequence, beginning around birth and infancy with the basic senses of sight, smell, taste, touch and sound. From then onwards into adulthood, myelination continues in areas of the brain linked to thought, emotion, executive planning, and conceptualization. Just like other aspects of neuronal maturation, a child's experiences and learning influence the rate and growth of myelination.

Ion channels and the action potential

As nerve cells rely on voltage gradients to produce an action potential, the nerve cell must maintain a membrane potential by modulating the concentration of intracellular ions. In a resting state, a nerve cell has high intracellular potassium and low intracellular sodium. The voltage gradient is maintained by two mechanisms:

1. The cell membrane has many potassium channels, which allow passive movement of potassium out of the cell along the concentration gradient, but few sodium channels to allow sodium to diffuse into the cell.
2. An adenosine triphosphate-dependent (ATP) pump actively transports three positively charged sodium ions (Na^+) out of the cell in exchange for two positively charged potassium ions (K^+). This energy-dependent process leads to a voltage differential across the cell membrane of around $-70\,mV$, and a high potassium concentration inside the cell relative to outside.

In order to depolarize, ion channels in the cell membrane must activate and trigger ion redistribution. When neurotransmitter molecules bind to receptors located on a neuron's dendrites, voltage-gated ion channels open. Positive ions enter the target neuron and depolarize the membrane, decreasing the difference in voltage between the inside and outside of the neuron. When this reaches the threshold potential ($-55\,mV$), Na^+ channels open. Na^+ rapidly enters the cell and the neuron completely depolarizes to a positive membrane potential of about $+40\,mV$. The action potential travels down the neuron as more Na^+ channels open.

Once an action potential has been generated, the Na^+ ion channels close, and the cell is refractory to any further stimulus. Voltage-gated K^+ channels open, and K^+ ions leave the cell. This takes the membrane potential down below the original $-70\,mV$ (hyperpolarization), resetting the Na^+ channels ready for the next signal. The cell then 'resets' itself by once again pumping out Na^+ in exchange for K^+ and returns to a voltage differential of around $-70\,mV$.

Ion channels are of clinical relevance in certain diseases and also as targets for therapeutic drugs. As well as the voltage-gated ion channels mentioned above, channels may be ligand-gated (activated by ligand binding), mechanosensitive (activated by stretch and mechanical forces), cyclic-nucleotide-gated (activated by substances such as cAMP), light-gated (in the eye), and temperature-gated.

Conditions known to be caused by ion channel malfunction include: many of the epilepsies, including generalized epilepsy with febrile seizures plus (GEFS+), Dravet syndrome (SCN1A mutation), familial hemiplegic migraine, and some of the ataxias. Drugs affecting ion channels include lidocaine (a local anaesthetic, blocks sodium channels), phenytoin and carbamazepine (antiepileptics, block sodium channels), ondansetron (an antiemetic, ligand binding to 5-HT$_3$ receptors), lamotrigine (an antiepileptic, ligand-gated channels) and gabapentin (an antiepileptic, ligand binding to inhibit calcium channels).

Cell growth and apoptosis

Neuronal cell growth depends on many things, including the hormone nerve growth factor (NGF). This protein, and other cell-signalling protein known collectively as 'neurotrophins', are responsible for the growth, maintenance, and survival of neurons. NGF has a role in myelin formation and also inhibits cell apoptosis. The precursor of NGF (pro-NGF) is also important in its own right. Although not biologically active in itself, in combination with tumour necrosis factor type receptors it can either promote cell growth or conversely promote apoptosis.

Cell apoptosis or 'programmed cell death' is an essential part of the reorganization of the brain that occurs during growth and development of the child

(see Neuronal plasticity, below). NGF is thought to have a role in many neurological conditions, including psychiatric and neurodevelopmental disorders, and to be a potential therapeutic agent for neuro-degenerative conditions and multiple sclerosis.

Craniocaudal and centrifugal development

Once the basic structure of the nervous system is formed, the development of skills and abilities follows a craniocaudal (head to tail) and centrifugal (central to peripheral) sequence. This can be clearly seen in the way infants gain motor skills. First to emerge are essential skills, such as coordinated suck and swallow, then head control, then shoulder and upper trunk stability to reach for toys, followed by hip stability and sitting, then lower limb control for standing and walking. Peripheral skills, such as fine motor coordination to use a tripod grasp and draw pictures, come later than the central skills, such as stabilizing the shoulders to allow the arm to push their dinner plate off the high chair.

Neuronal plasticity

When first developing, the human brain divides into two distinct hemispheres, linked via a large bundle of fibres called the corpus callosum. Initially, the two halves are mirror images of each other, and share functions. Over time, functions begin to lateralize to one side or the other, and 'handedness' develops. The ability to change and strengthen neuronal pathways is known as 'plasticity'. Put simply, pathways that are used grow stronger, and those that are not used will diminish and may disappear altogether.

Figure 28.2 illustrates lateralization relating to hand function. Initially, the right hand is supplied by motor fibres from both hemispheres. Around the time of birth and shortly afterwards, contralateral fibres from the left cerebral hemisphere begin to dominate, and the ipsilateral pathway from the right hemisphere diminishes. This explains why brain damage at different stages of development produces different clinical outcomes. If, for example, an infant suffers a left hemi-spheric stroke early *in utero*, the right hand is still
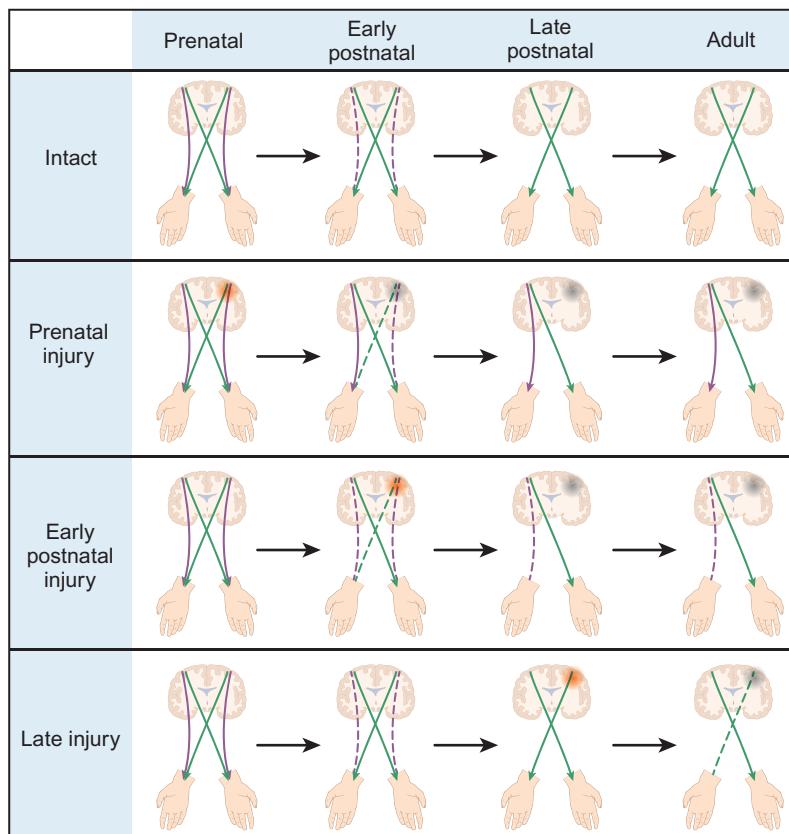
Fig. 28.2 Schematic representation of the differing effects of injury (orange circle) to primary motor cortex at different ages. The final, adult architecture (far right in each row) differs in each case because of interaction between the injury and developmental milestones; shown here is the physiological regression and loss of ipsilateral corticospinal projections (blue) that occurs in normal early postnatal life due to competitive inhibition from the contralateral corticospinal tract (green). *(From Forsyth R. Back to the future: rehabilitation of children after brain injury. Arch Dis Child 2010;95:554–9, with permission.© BMJ.)*

supplied by both sides of the brain at that time. The left side simply takes over control of both hands, and the infant retains bimanual function. If the same injury occurs in the postnatal period, there may still be some capacity for ipsilateral pathways to develop. The right hand will be weak, but may have some function. In a young adult, the same stroke will eliminate the contralateral innervation of the right hand, and with no remaining ipsilateral fibres to utilize, function is lost. Fortunately, even adults may still have some residual ipsilateral fibres; people who have less hand preference or who have bilateral innervation show greater scope for recovery of function.

When developing, neurons have a wealth of synaptic connections. By age 3, the brain has around 1000 trillion synapses. Synaptic connectivity is maximal in early childhood and it is at this time that the brain is most receptive to the accumulation of new skills and knowledge, and maximum learning is possible.

Neuroplasticity is of utmost importance in visual development. As demonstrated by the experiments of Hubel and Wiesel (who famously studied visual cortex firing in cats): without binocular visual stimulation, anatomical abnormalities develop in the ocular dominance columns of the lateral geniculate nucleus and visual cortex. Visual deprivation in the first 3 months of life in infants (the *critical period of visual neuroplasticity*) may result in permanent visual impairment (amblyopia). The neonatal (performed within 72 hours after birth) and GP (at 6–8 weeks) eye screening checks should detect and enable the management of ocular abnormalities, such as cataract, within this period. The higher visual pathway continues to develop and differentiate over the first eight years of life (the *sensitive period of visual neuroplasticity*); visual deprivation, strabismus (squint) or uncorrected refractive error during this period will result in amblyopia.

Young children have more capacity for plasticity than adults, and can make remarkable recovery from significant brain injuries. However, the true extent of the damage may not become known for many years, when ongoing maturation 'unmasks' a neurological deficit. An example is traumatic brain injury, when the child may seem to make a full recovery in terms of returning to previous level of function, only to show significant cognitive difficulties when reaching adolescence. Similarly, it is easier to regain a function lost as a teenager than develop it from scratch as a toddler; for example, a concert pianist who has had a stroke will find it easier to learn to play again than a similar stroke sufferer who has never touched a piano.

Although synaptic pruning means that connections are lost throughout puberty and is complete soon after the end of puberty, learning and therefore a degree of plasticity is possible throughout life and into old age.

Furthermore, an older person has the benefit of experience and has pre-established pathways that can augment both learning and speed of cognition.

Question 28.3

Neurological development

Which of the following statements are true (T) and which are false (F)?

A. Anencephaly results from failure of closure of the anterior neuropore

B. Myelin develops from birth

C. Neurones migrate along myelinated bundles to their eventual position in the brain

D. The maximum number of synaptic connections are present at term

E. The retina originates from the forebrain (prosencephalon)

Answer 28.3

A. True; B. False; C. False; D. False; E. False.

Whilst brain development is complex, it is well studied and much is known. Anencephaly results from failure of closure of the anterior neuropore but all our other answers are false. Neural cells migrate to their correct location along specially created 'highways' of glial cells, known as radial glia. The retina originates from the diencephalon, along with the thalamus and hypothalamus. The forebrain (prosencephalon) gives rise to the cerebral hemispheres and basal nuclei.

Myelination begins *in utero*, and between 36 weeks and term increases from 1% to 5% of total brain volume. Synaptic connectivity is maximal in early childhood rather than at birth. It is at this stage that the brain is most receptive to the accumulation of new skills and knowledge. As the brain matures, unused synaptic connections are lost via the process of 'synaptic pruning'.

Question 28.4

The blood–brain barrier

Which of the following substances is least able to cross the blood–brain barrier? Select ONE answer only.

A. Ammonia

B. Amoxicillin

C. Carbon dioxide

D. Glutamine

E. Unconjugated bilirubin

The blood–brain barrier

The brain and spinal cord are uniquely protected by a physical barrier that isolates them from biochemical changes in the rest of the body. This shield is known as the blood–brain barrier (BBB). Not to be confused with the interface between cerebrospinal fluid (CSF) and the brain, the BBB lies along the individual capillaries that feed deep into the brain tissue itself. It is formed by closely sealed endothelial cells in cooperation with brain astrocytes, and regulates and adjusts transfer of nutrients, ions, proteins, and components of the immune system. It achieves this by highly selective permeability and use of specialized transporters. Glutamine differs from other amino acids in that it passes across the BBB through such a mechanism. Facilitative carriers for glutamine and glutamate at the luminal membrane may provide a mechanism for removing nitrogen and nitrogen-rich amino acids from brain.

Some molecules are able to freely cross the BBB: water, gases, and also some lipid-soluble substances. Increased BBB permeability for ammonia is considered to be an integral part of the pathophysiology of hepatic encephalopathy. This permeability to lipid-soluble agents is clinically important. In the jaundiced neonate, unconjugated bilirubin is highly lipid-soluble. As such, it passes readily across the BBB and into the brain, leading to neurological damage and kernicterus. Exposure to light of a specific range of wavelengths converts the bilirubin to a water-soluble state, by converting insoluble bilirubin into water-soluble structural isomers. It also generates bilirubin molecules in an excited state, and these react with oxygen to produce colourless oxidation products. Once the molecules are water-soluble they can no longer cross the BBB, and thus no longer damage the brain. Lipid solubility is also clinically relevant when prescribing. Agents that are lipid soluble are more likely to cross the BBB and alter CNS function. This may be desirable, for example when giving a general anaesthetic, but may lead to unwanted effects of sedation or brain disturbance with other drugs.

The BBB is susceptible to damage, in particular from inflammation in conditions such as meningitis. This is mediated by pro-inflammatory cytokines, and leads to opening up of spaces between endothelial cells and loss of the tight regulation of transport across the BBB. This can be advantageous (for example, allowing white blood cells and immune components to enter the brain), but can also lead to chemical imbalances and cell damage. In meningitis, however, we capitalize on the fact that the BBB is no longer preventing entry of chemicals into the brain, as it permits a far greater penetration of prescribed antibiotics (including the water-soluble amoxicillin) than would ordinarily be possible.

Anatomy and physiology of the nervous system

Knowledge of the structure and physiology of the nervous system allows understanding of how damage to different areas may present. The general structure of the brain is shown in the sagittal view in Figure 28.3.

At the spinal level, 31 pairs of mixed motor and sensory nerve bundles emerge (Fig. 28.4):

- Cervical (C): 8 pairs
- Thoracic (T): 12 pairs
- Lumbar (L): 5 pairs
- Sacral (S): 5 pairs
- Coccygeal: 1 pair

These nerves further combine to produce nervous plexi:

- Cervical plexus (C1–C4): muscles of the neck, shoulder and skin, phrenic nerve (diaphragm)
- Brachial plexus (C5–C8 + T1): muscles from the base of the neck to the fingertips and skin
- Lumbar plexus (L1–L3 + part of L4): skin and muscles of the lower abdomen, thighs and groin
- Sacral plexus (L4–L5 + S1–S4): muscles and skin of the pelvic area and legs
- Coccygeal plexus: muscles and skin of pelvic area and sphincters

Cerebrospinal fluid

Distinct from the BBB, the CSF–brain barrier relates to the extracerebral fluid that is found within the ventricles and around the brain. It has two main categories of function: physical and biochemical. From a physical standpoint, it acts to cushion and protect the brain from shear forces and impact, and plays a role in regulating intracerebral blood pressure and thus prevents ischaemia. Biochemically it serves to remove waste and toxins from the CNS, and helps regulate levels of hormones and neurologically active substances.

CSF is produced by a type of glial cell called an ependymal cell. It is chiefly produced in the choroid plexi in the lateral ventricles of the brain, and exits through the intraventricular foramen of Munro, into the third ventricle, through the aqueduct of Sylvius into the fourth ventricle, then down the spinal cord and over the cerebral hemispheres. It is reabsorbed
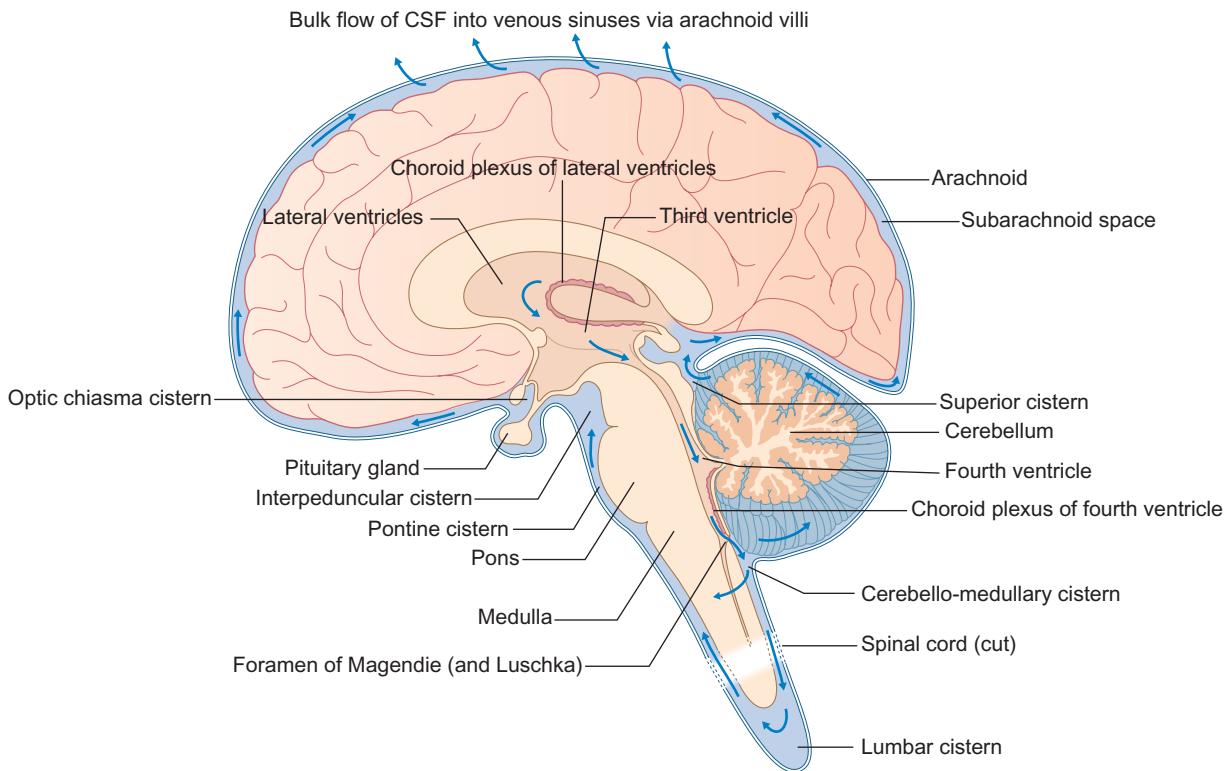
Fig. 28.3 **General anatomy of the brain in the sagittal view.** *(From Naish J, et al. Medical sciences, 2e. Saunders 2014, with permission.)*

into the circulation via arachnoid villi. CSF is produced at a rate of around 30 mL/hour. The volume after the age of 2 years is around 150 mL, with about 35 mL in the ventricular system. Abnormalities of the CSF circulation may result in hydrocephalus:

- *Communicating hydrocephalus* – no obstruction between ventricles and subarachnoid space. Caused by:
  - Excessive CSF production (rare, e.g. choroid plexus tumour)
  - Impaired CSF resorption (e.g. blockage of arachnoid granulations by debris after meningitis or haemorrhage)
- *Non-communicating hydrocephalus* – physical obstruction between ventricles and subarachnoid space. Caused by:
  - Congenital malformation (e.g. aqueduct stenosis, Arnold–Chiari malformation)
  - Acquired obstruction (e.g. brain tumour)

Idiopathic intracranial hypertension is a special case where the CSF is elevated in the absence of hydrocephalus or intracranial mass lesion, and is described later in this chapter.

Treatment of hydrocephalus depends on the cause. It may be via resection of an intracranial obstruction, placing of a stent in a stenosed aqueduct, or by removal of excess CSF. In many children this requires insertion of a one-way valved ventriculoperitoneal shunt, which forms a direct drainage route for CSF from the cranial vault to the low pressure of the peritoneal cavity.

Clinical features of hydrocephalus depend on the site of the obstruction and also on the capacity of the cranial vault to expand if the sutures are not yet fused. Symptoms of hydrocephalus may be acute (vomiting, irritability, headache, change in consciousness) or chronic (visual disturbance, 'sunsetting eyes', early morning vomiting, pressure headache, deterioration in school performance). Untreated, acute hydrocephalus (for example, in a child with a blocked ventriculoperitoneal shunt) can lead to brainstem herniation and death. It is a neurosurgical emergency.

CSF analysis is of value in many disorders, the most common of which is meningitis (Table 28.2). It is also of value in diagnosis and management of metabolic disorders, leukaemias, neurodegenerative conditions and autoimmune disorders.

Meningitis

CSF microscopy (see Table 28.2) may initially be normal in meningitis, so clinical impression is of prime importance. It is unusual to find neutrophils in CSF beyond the neonatal period, so this should raise the possibility of bacterial infection. CSF white cell

Table 28.2 CSF analysis values in diagnosis of meningitis*

	White cell count		Biochemistry	
	Neutrophils (× 10⁶/L)	Lymphocytes (× 10⁶/L)	Protein (g/L)	Glucose (CSF:blood ratio)
Normal (>1 month of age)	0	≤5	<0.4	≥0.6 (or ≥2.5 mmol/L)
Normal term neonate	<5	<20	<1.0	≥0.6 (or ≥2.5 mmol/L)
Bacterial meningitis	100–10,000 (but may be normal)	Usually <100	>1.0 (but may be normal)	<0.4 (but may be normal)
Viral meningitis	Usually <100	10–1000 (but may be normal)	0.4–1 (but may be normal)	Usually normal
TB meningitis	Usually <100	50–1000 (but may be normal)	1–5 (but may be normal)	<0.3 (but may be normal)

*Although helpful, treatment should not be delayed if it is not possible or safe to perform a lumbar puncture.
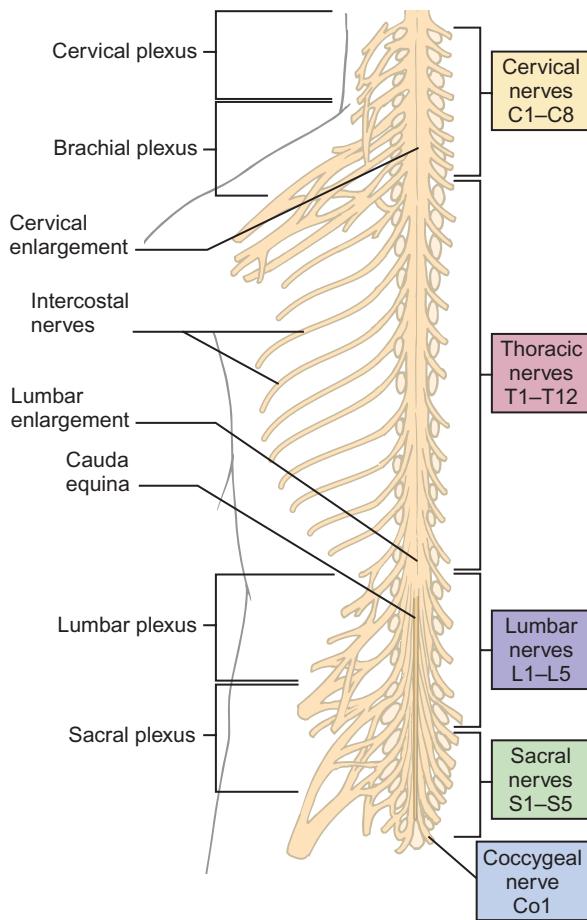
Fig. 28.4 Spinal nerves. *(From Naish J, et al. Medical sciences, 2e. Saunders 2014, with permission.)*

difficult to distinguish between viral and bacterial meningitis. Antibiotics do not significantly change the CSF cell count or biochemistry in samples taken within 24 hours of the initial dose. Meningococcal PCR testing on CSF samples is particularly useful in patients with a clinical picture consistent with meningococcal meningitis but who have received prior antibiotics.

CNS inflammatory diseases

CSF IgG may be raised in patients with central nervous inflammatory diseases (e.g. multiple sclerosis, subacute sclerosing panencephalitis). The most commonly used diagnostic tests for multiple sclerosis are a raised CSF index (the ratio of CSF IgG to CSF albumin compared to the serum IgG to serum albumin ratio) and oligoclonal band detection.

CSF neurotransmitter disorders

The monoamine neurotransmitter disorders are caused by defects in the synthesis, degradation, or transport of dopamine, noradrenaline (norepinephrine), adrenaline (epinephrine), and serotonin. They are implicated in a varied group of conditions including mitochondrial disorders, Rett's syndrome and leukodystrophies. They usually present with abnormal neurological features (encephalopathy, epilepsy, and pyramidal and extrapyramidal motor disorders). Their diagnosis may include analysis of neurotransmitters in the CSF, which involves a precise protocol for collection and rapid freezing of samples. Specialized laboratory analysis is required.

History and examination

History

History is the cornerstone of neurological diagnosis. Particular attention should be paid to the age at

count and protein level are higher at birth than in later infancy. In the first week, 90% of well babies have a white cell count less than 20, and a protein level <1.0 g/L. Although lymphocytes are more characteristic, neutrophils may predominate in viral meningitis even after the first 24 hours, which may make it

onset, developmental history including age of milestones, any loss of skills or deterioration of school performance, detailed family history, and the impact of the problem on family life and functioning. Typically, presentation falls into one of the following categories:

- Developmental delay – single domain or multi-domain
- Developmental regression – e.g. Rett's syndrome
- Weakness – e.g. muscular dystrophy
- Abnormal movements – e.g. ataxia
- Change in level of consciousness – e.g. encephalopathy
- Paroxysmal events – e.g. epilepsy
- Headache – e.g. migraine
- Traumatic injury – e.g. head injury

Examination

A full neurological examination is a skilled and lengthy procedure, and is not required unless a neurological disorder is suspected. In those who do have a neurological symptom, your history will allow you to focus your attention on a specific part of the neurological system, with a more generalized exam of the rest of the child. Detailed neurological examination can be tricky in children, as you need a cooperative patient! However, it is usually possible to gain a good assessment of ability through a combination of observation of play and use of 'games' to encourage the child to do what you need. For example: a child may not cooperate with a 'finger–nose pointing' test, but is likely to join in with a 'sweetie–mouth' test if you hold out a pretend sweet for them to grasp. A child may not want to show you their gait or to demonstrate shoulder abduction for you, but is likely to join in a 'race' or to 'flap your elbows like a chicken'.

Examining the neonate and infant
(Box 28.1)

With very young babies, starting with the baby lying supine on their back, you move them through sitting, to prone, and then to lying on their back again. At all stages, assess the symmetry of their limb movements and reactions. Always take any concerns from parents seriously.

Examining the older child

In older children, it is helpful to consider examination of each area of the nervous system individually: the cranial nerves (Fig. 28.5), cerebellum, upper limb, lower limb, and gait (Boxes 28.2–28.6).

Box 28.1 Examining the infant

Supine:
- Assess general movements, posture, and alertness
- Check for birthmarks (neurocutaneous markers)
- Measure and plot head circumference
- Assess fontanelles (hydrocephalus) and head shape (craniosynostosis)
- Lift head, and if you wish to elicit the Moro reflex (usually unnecessary and unpopular with parents), allow head to fall back quickly supported in your hand by a short distance, assess reaction of arms
- Individually assess tone, power, movement and reflexes in each limb (remember Babinski will be positive)
- Observe response to sound
- Assess pupil responses, reaction to light, object fixation and red reflexes/fundoscopy
- Take both hands (grasp reflex)
- Pull baby by hands to sitting (head lag)

Sitting:
- Degree of back rounding (tone)
- Ability to self-support (tone and posture)
- Grasp gently around the chest below each axilla and lift

Standing:
- 'Slipping through hands'? (hypotonia)
- Rigid legs (hypertonia)
- Stepping and walking reflexes (neonatal reflexes)
- Lay infant prone across your hand/forearm

Prone suspension:
- Degree of drape/ability to lift head and legs (tone)
- Examine spine for abnormalities or defects
- Stroke side of spine to see infant curl towards stimulus (Galant reflex)
- Lay infant back down on the bed, prone (head raise, rolling, attempt to crawl)
- Turn infant onto their back again, redress infant

Spinal n. fibres
Efferent (motor) fibres
Afferent (sensory) fibres

I
Olfactory

II
Optic

III
Oculomotor
Ciliary m., sphincter of
pupil, and all external
eye mm. except
those below

IV
Trochlear
Superior oblique m.

V
Trigeminal
Sensory–face
sinuses, teeth

Ophthalmic

Maxillary

Mandibular

VI
Abducens
Lateral
rectus m.

Motor–mm. of
mastication

VII
Facial
Mm. of face

Intermediate n.
Motor–submandibular,
sublingual, lacrimal
glands; Taste–anterior
2/3 of tongue, sensory
soft palate

VIII
Vestibulocochlear
Cochlear   Vestibular

IX
Glossopharyngeal
Taste–posterior 1/3 of tongue
Sensory–tonsil, pharynx, middle ear
Motor–stylopharyngeus, upper
pharyngeal mm., parotid gland

X
Vagus
Motor–heart, lungs, palate, pharynx,
larynx, trachea, bronchi, GI tract
Sensory–heart, lungs, trachea,
bronchi, larynx, pharynx,
GI tract, external ear

XI
Accessory
Sternocleidomastoid,
trapezius mm.

XII
Hypoglossal
Tongue mm.

Fig. 28.5 The cranial nerves. *(© 2016 Elsevier Inc. All rights reserved. www.netterimages.com)*

Box 28.2 Cranial nerve examination

1. Olfactory nerve (smell)
   a. Often not tested and, if required, is assessed by asking the patient if they have noted any change in their sense of smell if test done on each nostril in turn
2. Optic nerve
   a. Visual acuity (by observation or with Snellen chart)
   b. Visual fields (see Chapter 30, Ophthalmology, for more detail)
   c. Pupillary reflexes – assess for direct and consensual responses to light, subsequently testing for accommodation.
   d. Fundoscopy
3. Oculomotor nerve – examine as below
4. Trochlear nerve – examine as below
5. Trigeminal nerve
   a. Motor component – supplies the muscles of mastication
      i. Ask the child to open their mouth, whilst you try to close it. It will deviate to the side of weakness
      ii. Clench teeth together and feel muscle mass of the masseters
   b. Sensory component – ophthalmic, maxillary and mandibular divisions
      i. Examine by testing each division comparing both sides
      ii. Do not assess the corneal reflex
6. Abducens
   a. Examine cranial nerves 3, 4 and 6 by asking the child to fix and follow on an object (lots of people use their finger although the light of a pen torch is often more successful)
7. Facial
   a. Motor component supplies the muscles of facial expression
      i. Ask the child to close their eyes tightly, open their eyes really wide, blow out their cheeks and show their teeth
   b. Sensory component supplies the anterior two thirds of the tongue
8. Vestibulocochlear
   a. You should be aware of how to perform a Rinne's/Weber's test.
9. Glossopharyngeal – examine as below
   a. Motor component – supplies stylopharyngeal muscle
   b. Sensory component supplies:
      i. Posterior third of tongue for taste
      ii. Tonsillar fossa and pharynx
10. Vagus nerve – examine 9 and 10 together by asking the child to open their mouth and say 'ahh' whilst looking at the palatal movement. Gag reflex should be considered but not performed.
    a. Motor component supplies pharynx and larynx
    b. Sensory component supplies larynx alone
11. Accessory nerve – ask the child to shrug their shoulders, turn their head to the right and place a hand on the left side of their face and ask to push against your hand, test in the opposite direction.
12. Hypoglossal nerve
    a. Ask the child to stick their tongue out and inspect for fasciculation and deviation (tongue deviates to the side of the lesion)

Box 28.3 Cerebellar examination

1. General observation looking for any abnormal movements, abnormal speech and telangiectasias on the conjunctiva
2. Assess speech by asking them some questions, all the while taking note of stuttering or dysarthria
3. Eyes
   a. Look for nystagmus
   b. Assess eye movements, especially on moving the eyes to the extremes of horizontal gaze
4. Upper limbs – essentially you are performing a selected upper limb neurological examination
   a. Assess for tone – hypotonia is usual in cerebellar disorders
   b. Coordination
      i. Dysmetria using finger–nose test (see earlier)
      ii. Dysdiadochokinesia
      iii. Piano-playing – ask the child to pretend to play an imaginary keyboard
   c. Reflexes – hyporeflexia is usual
5. Lower limbs
   a. Assess for tone – hypotonia
   b. Coordination
      i. Heel–shin test
      ii. Toe-tapping – ask the child to tap your hand with the sole of the right foot as quickly as possible
   c. Reflexes
6. Gait – ask the child to walk normally and then heel–toe whilst looking for a broad-based gait

Box 28.4 Upper limb examination

1. General observation – take note of clues such as the child's wheelchair, orthoses or splints, helmet or dysmorphic features
2. Ask the child and parent to expose the chest and arms fully
3. Inspection – with the child standing inspect for:
   a. Posture
   b. Contractures
   c. Muscle bulk, wasting and (pseudo) hypertrophy
   d. Involuntary muscles and fasciculations
   e. Scars
   f. Limb shortening
4. Tone – whilst holding on to their hand passively, move their arm in unexpected, irregular movements
5. Power – compare both sides
   a. Shoulder abduction (C5) and shoulder adduction (C7, 8)
   b. Elbow flexion (C5, 6) and extension (C7, 8)
   c. Hands:
      i. Squeeze my fingers
      ii. Spread your fingers out wide
6. Reflexes – compare both sides
   a. Biceps – C5, 6
   b. Triceps – C7, 8
   c. Brachioradialis – C5, 6

7. Coordination
   a. Finger–nose test (assess for dysmetria) – ask the child to touch their nose with their index finger, and then your finger. You must move your finger to different sites at different arm lengths.
   b. Hand-tapping (assess for dysdiadochokinesia) – get them to tap one hand on the back of another and to alternate tapping between the palm and back of the hand.
8. Sensation may be difficult to perform in children, but it is important to have a rough idea about dermatomes in case you need to assess
   a. C4 – tip of shoulder
   b. C5 – lateral surface of upper arm
   c. C6 – lateral surface of forearm
   d. C7 – radial surface of middle finger
   e. C8 – ulnar border of hand
   f. T1 – medial surface of forearm
   g. T2 – medial surface of upper arm
9. Function is assessed by asking the child to draw/write/pick up objects

Box 28.5 Lower limb examination

It is always important to examine gait as part of a lower limb assessment, and this is described separately.

1. General observation – as mentioned above, take note of clues such as the child's wheelchair, orthoses or splints, helmet or dysmorphic features
2. Ask the child and parent to undress to their underpants only
3. Assess the child's gait
4. Inspection – with the child lying on the bed, inspect the child's legs and spine. Note:
   a. Posture
   b. Contractures
   c. Muscle bulk, wasting and (pseudo) hypertrophy
   d. Involuntary muscles and fasciculations
   e. Scars

5. Assess tone:
   a. Roll the legs from side to side taking note of movement of the foot at the ankle
   b. Place the palmar surfaces of both one's hands underneath the child's thighs and lift the thighs up slightly off the bed and then let them fall
   c. Flex and extend at the hip, knee and ankle joints
   d. Clonus – test both ankles by rapidly dorsiflexing the foot – more than 3 beats of ankle clonus is abnormal
6. Power
   a. Hip flexion (L1 and L2) and extension (L5 and S1)
   b. Knee flexion (L3 and L4) and extension (S1)
   c. Ankle dorsiflexion (L4) and ankle plantar flexion (S1 and S2)

Box 28.5 Lower limb examination—cont'd

7. Reflexes – compare both sides
   a. Knee – L3, L4
   b. Ankle – S1, S2
   c. Plantar reflex – an abnormal reflex (i.e. positive Babinski reflex) is for the great toe to be up-going and therefore the toes to be splayed when stroking the lateral aspect of the sole of the foot and medially across the ball of the foot. (Positive Babinski is a normal finding in infants)
8. Coordination – test both sides by asking the child to run the heel of one foot down the shin of the other (heel–shin test). This is often best demonstrated to them using their foot rather than explaining what you want them to do verbally.

9. Sensation can be difficult to test in children but one needs to know the dermatomes. Test light touch, vibration and joint proprioception (pain sensation is not usually expected to be tested)
   a. L1 – upper outer thigh
   b. L2 – middle anterior thigh
   c. L3 – anterior knee
   d. L4 – medial calf
   e. L5 – lateral calf
   f. S1 – sole of the foot
   g. S2 – strip up posterior and thigh

Box 28.6 Gait examination

1. General observation – again, take note of clues such as the child's wheelchair, orthoses or splints, helmet or dysmorphic features
2. Ask the child and parent to undress the child to their underpants only
3. Inspection – with the child standing inspect for:
   a. Posture
   b. Contractures
   c. Muscle bulk, wasting and (pseudo) hypertrophy
   d. Involuntary muscles and fasciculations
   e. Scars
   f. Limb shortening
   g. Spine for scars or lesions (overlying tuft of hair, for instance, which may suggest spina bifida)
   h. Examine their shoes for evidence of abnormal wear and tear
4. Ask the child to walk across the room
   a. Assess for the normal heel-strike/toe-off phases
   b. Foot position – varus/valgus
   c. Noise of the walk – slapping gait associated with foot drop
   d. Limp
   e. Arm position and swing
   f. Abnormal movements

5. Ask the child to walk heel–toe – assessing cerebellar pathways
6. Ask the child to walk on the outsides of their feet (Fog's test) – this exacerbates the signs of a subtle hemiplegia
7. Ask the child to run across the room – again exacerbating any signs of a subtle hemiplegia
8. Squat–stand – ask the child to stand from the squatting position – assess for proximal myopathy
9. Trendelenburg's sign for proximal (hip) muscle weakness
   a. Ask the child to stand in front of you but facing away
   b. Get them to lift one foot off the ground
      i. Normal is for the pelvis to rise on the side of the lifted leg
      ii. The test is abnormal if the pelvis sags on the side of the lifted leg
10. Gower's sign, by asking the child to stand from lying supine, which again assesses for proximal muscle weakness. Gower's sign is when the child is unable to stand without turning prone and then bracing their hands on their knees or 'walking' their hands up their legs to get upright.

Imaging the nervous system

Cranial ultrasound

This remains the modality of choice in neonates and infants due to the ease of scanning via the open anterior fontanelle. It is quick and non-invasive, but highly operator-dependent. Repeat scans over time allow evolution and progression of lesions to be monitored. It is particularly used for:

- Intraventricular haemorrhage (IVH) and the ischaemic cysts of periventricular leukomalacia (PVL)
- Ventricular dilatation
- A range of cerebral malformations and other lesions, e.g. agenesis of the corpus callosum

However, MRI is much better in detecting ischaemic lesions, e.g. hypoxic–ischaemic encephalopathy (HIE) or PVL and for detailed anatomy of cerebral malformations.

Cranial computed tomography

Cranial computed tomography (CT) is widely available and rapid, so continues to be used for:

- Head trauma
- If clinical condition is unstable
- Intracranial calcification
- Haemorrhage

Table 28.3 Overview of MRI appearances

	T1	T2	FLAIR
Solid mass	Dark	Bright	Bright
Fluid-filled cyst	Dark	Bright	Dark
Subacute blood	Bright	Bright	Bright
Acute and chronic blood	Grey	Dark	Dark
Fat	Bright	Dark	Bright

FLAIR, fluid attenuated inversion recovery.

This technique can be enhanced with the use of contrast. Its use has largely been replaced by MRI, which does not require radiation and is usually more informative.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is the imaging technique of choice for most paediatric neurological disorders, e.g. for demyelination. No radiation is involved. Various different computerized sequences can be used to interrogate the signal to answer particular clinical questions (Table 28.3):

- *T1 sequence* – CSF appears black, grey matter is grey and white matter white or paler grey.
- *T2 sequence* – for assessing tissue fluid content, such as oedema. CSF is white.
- *FLAIR (fluid attenuated inversion recovery)* – similar to T2, and is of value in interrogating lesions close to the ventricles. The signal from CSF is purposely reduced to allow clearer tissue imaging.

Increased availability of MRI scanning in children has helped expand our knowledge about the pathological processes occurring in children with encephalopathy. Questions 28.6 and 28.7 illustrate this point.

Question 28.5

Interpretation of MRI findings

Which of the following patterns best describes the pattern of signal generated by cerebrospinal fluid on MRI? Select ONE answer only.

A. T1 sequence bright, T2 sequence bright, FLAIR* sequence bright

B. T1 sequence bright, T2 sequence dark, FLAIR sequence bright

C. T1 sequence dark, T2 sequence bright, FLAIR sequence bright

D. T1 sequence dark, T2 sequence bright, FLAIR sequence dark

E. T1 sequence dark, T2 sequence dark, FLAIR sequence dark

*Fluid attenuated inversion recovery (FLAIR)

Answer 28.5

D. T1 sequence dark, T2 sequence bright, FLAIR sequence dark.
  See below for discussion.

Questions 28.6 and 28.7

A child with acute neurological loss

A nine-year-old girl presents with acute encephalopathy. In the preceding 24 hours, she was noted to have some fever and vomiting. Her parents also noticed that she was slightly confused the evening prior to her visual loss. Neurological examination revealed no focal deficit and there were no signs of meningism.
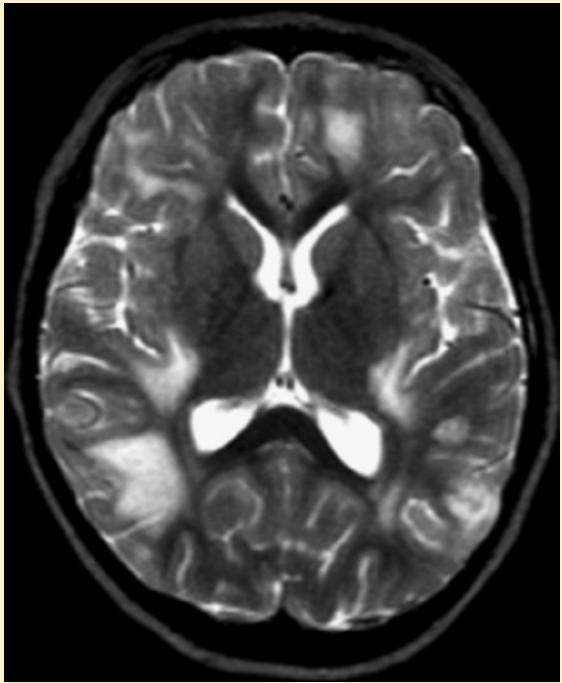
  Investigations revealed the following:

Full blood count unremarkable, CRP 56 and ESR 32.

Blood and urine cultures – negative

CSF studies:

- WCC <3, RCC <3, protein 0.16, glucose/lactate normal
- Culture and virology – negative

MRI brain. Multiple high signal white matter lesions on T2 weighted images around the grey–white matter junction. *(From Swaiman KF, et al. Pediatric Neurology. Mosby 2006.)*

Question 28.6

What is the most likely diagnosis? Select ONE answer only.

A. Acute disseminated encephalomyelitis (ADEM)
B. Cerebral abscess
C. Diffuse astrocytoma
D. Multiple sclerosis
E. Viral encephalitis

Question 28.7

What is the most likely mechanism involved pathologically? Select ONE answer only.

A. Direct spread of virus into white matter of brain
B. Medium vessel vasculitis
C. Perivenular infiltrates of lymphocytes and macrophages
D. Small vessel vasculitis
E. Tumour spread with secondary malignancy

Answer 28.6

A. Acute disseminated encephalomyelitis (ADEM).

Answer 28.7

C. Perivenular infiltrates of lymphocytes and macrophages.

This case described in Question 28.6 highlights a classical presentation of acute disseminated encephalomyelitis (ADEM). The main differential diagnosis for this is multiple sclerosis (MS), although MS is rare in childhood. It is also essential to rule out meningo-encephalitis. It is important to try and differentiate between ADEM and MS based on history, clinical features and investigations.

ADEM, an inflammatory demyelinating condition of childhood, commonly occurs after a viral or bacterial infection. Less commonly, it has been reported to occur post MMR vaccination. Most patients with ADEM have a degree of encephalopathy during the course of illness, which may progress to loss of consciousness. These children may also commonly have fever, vomiting and headache. Seizures may occur in up to a third of patients. All these features are rarely seen in MS and should alert a physician towards a diagnosis of ADEM. Viral encephalitis may have similar presenting features and therefore must be ruled out by performing a lumbar puncture.

MS is a chronic inflammatory demyelinating disease of the CNS characterized by myelin loss and variable degrees of axonal degeneration and gliosis that correlate with progression of neurological disability. In MS, acute demyelination is part of a complex and incompletely understood immunological cascade in which there may be multiple episodes and a relapsing clinical course. CSF studies may show an increased protein and lymphocyte count in ADEM. However, these abnormalities are not exclusive to ADEM.

Brain MRI is crucial in achieving a diagnosis. Both ADEM and MS show predominant white matter changes, which are disseminated. In ADEM, these lesions tend to occur in the deep white matter or around the grey–white matter junction, with periventricular sparing. In contrast, periventricular and corpus callosum white matter changes are highly suggestive of MS. Follow-up scans may also be useful, as in ADEM, new lesions should not occur.

Pathologically, ADEM is characterized by perivenular infiltrates of lymphocytes, macrophages, and occasional plasma cells with oedematous and demyelinated adjacent white matter. Lesions are multifocal or diffuse and may be found in the optic nerves, spinal cord and brain. Characteristically, and in contrast to multiple sclerosis (MS), all lesions are of the same age, and axonal injury is minimal.

Analysis of CSF for oligoclonal bands can be helpful in determining the risk of MS. Intrathecal synthesis of oligoclonal bands occurs in MS in 40–95% of cases, but only in 0–29% of children with ADEM.

In either case of demyelination (ADEM or MS), the first line of management involves steroids,

which have been shown to hasten recovery. It is common practice to give intravenous methylprednisolone for 3 days, followed by a tapering dose of oral steroids over a few weeks. However, as ADEM is a self-limiting condition, some cases start improving spontaneously before the introduction of steroids and may not require treatment. It is imperative that antivirals and antibiotics are continued until CSF culture/virology results are obtained.

Recent scientific advances which have improved clinical practice – functional MRI

Functional MRI allows for visualization of regional oxygen consumption and blood flow, and is used to examine brain activity. It allows creation of maps showing which parts of the brain are involved in a particular task, such as movement or speech. It is increasingly used in presurgical assessment of children being considered for epilepsy surgery and allows more accurate prediction of post-op functional outcome. This has led to the formation of a national paediatric epilepsy surgery service.

It has also enhanced our understanding of other neurological conditions including autistic spectrum disorder.

Magnetic resonance angiography

Magnetic resonance angiography (MRA) permits non-invasive assessment of the intracranial vascular system. It has found particular use in conditions such as intracranial arteriovenous malformations (e.g. Sturge–Weber syndrome) and blockages or stenosis.

Magnetic resonance spectroscopy (MRS)

This newer technique relies upon the individual resonance properties of certain molecules within brain tissue. Known patterns exist of chemicals such as lactate, choline, and creatine. It has many potential uses, as it can detect high levels of metabolites or other target molecules in conditions including HIE, brain injury, epilepsy, metabolic disorders, and multiple sclerosis. For example, a raised lactate signal suggests a metabolic disorder. Perhaps the most promising area of paediatric research at present is in tumours (choline signals are often elevated in tumour tissue). At present, MRS is restricted to larger research centres, and it is not yet widely available.

Positron emission tomography

This functional imaging technique is available in only a few centres. A labelled radioactive tracer is injected into the body, which gives off gamma rays that are detected by a scanner. The information gleaned depends

on what molecule the tracer was attached to. If the target molecule is fluorodeoxyglucose (analogue of glucose), then the images will reflect regional glucose uptake and therefore the metabolic activity of the tissue. The main indication in paediatric neurology is to identify precise areas of seizure onset in focal epilepsy, thus identifying possible targets for epilepsy surgery.

Question 28.8

An infant with abnormal movements

Oliver, a 6-month-old, is referred by his GP to the paediatric day unit because of abnormal movements over the preceding two weeks. His parents initially noticed brief episodes lasting 2–3 seconds, where he would drop his head forward when he is sat up in association with forward tonic flexion of his upper limbs. They initially thought they were due to colic but became concerned when they increased in frequency, now happening 20–30 times daily. He has also been noted to be less responsive over the past few days. Oliver was born at term, with no neonatal problems and his development has been age-appropriate. On assessment, his systemic examination was unremarkable. No abnormal skin pigmentation was noted. He has had a cluster of episodes, which you suspect are infantile spasms.

What would your next plan of action be? Select ONE answer only.

A. Commence urgent treatment before any of the above

B. Discharge with an urgent outpatient referral to paediatric neurology

C. Discharge with outpatient paediatric follow-up

D. Organize an urgent MRI of the brain within 48 hours

E. Organize an urgent EEG within 48 hours

Answer 28.8

E. Organize an urgent EEG within 48 hours.

If there are doubts regarding the diagnosis or if episodes are not witnessed by someone familiar with the condition, video recording by parents can be very useful. The main point to highlight is that any child with suspected infantile spasms should undergo an urgent EEG within 24–48 hours, where possible. Usually, an acute admission is necessary to facilitate this. An awake EEG may be normal in early stages and a period of sleep recording is therefore recommended for this reason. EEG patterns compatible with infantile spasms include hypsarrhythmia, modified hypsarrhythmia, and burst suppression amongst others.

If the EEG is completely normal, including on follow-up, the likely diagnosis is benign myoclonus

of early infancy, which can mimic infantile spams. This non-epileptic condition is harmless and resolves without any intervention.

In many medical conditions, the principle of investigations prior to treatment applies. However, infantile spasms are an exclusion to this. Studies have shown that the longer it takes to control these spasms, the worse the outcome. Treatment should therefore be started within a few days of diagnosis, ideally within 24 hours, where possible.

The International Collaborative Infantile Spasms Study (ICISS) should provide evidence about combined treatment with both hormonal treatment (steroids or ACTH) and vigabatrin compared to hormonal treatment alone.

Roughly 40% of children with tuberous sclerosis complex (TSC) will have infantile spasms. It is important to look for TSC in all children presenting with infantile spasms as treatment differs – vigabatrin is the drug of choice for infantile spasms secondary to TSC.

Neurophysiological investigations

The electroencephalogram

In routine electroencephalogram (EEG) monitoring, electrodes are positioned over the scalp. In invasive monitoring, electrodes are placed inside the skull and dura, but this is only used in quaternary epilepsy centres. Typically, 21 numbered electrodes are placed in defined positions in each of five locations (F – frontal, C – central, P – parietal, T – temporal, O

Question 28.9

Neurophysiological investigation

Following is a list of possible investigations:

A. Electrocardiogram (ECG)
B. Electromyography (EMG)
C. Electroretinogram (ERG)
D. Nerve conduction studies
E. Standard electroencephalogram (EEG) without activation procedures
F. Standard EEG with activation procedures (hyperventilation and photic stimulation)
G. Sleep-deprived EEG
H. Visual evoked potentials (VEP)

From the list above (A–H), select the MOST appropriate investigation to identify the following disorders:

1. Myotonia
2. Optic neuritis
3. Peripheral nerve demyelination

Answer 28.9

1. D. Nerve conduction studies
2. H. Visual evoked potentials
3. D. Nerve conduction studies
   See below for discussion.

– occipital). A channel is the voltage difference measured between pairs of these electrodes.

A standard EEG recording usually lasts around 30 minutes. An experienced neurophysiology technician can usually obtain a good quality recording from even the most resistant of children. Movement causes artefacts making interpretation difficult. The background EEG recording evolves over the course of childhood. The age of the child is therefore crucial in EEG interpretation. The sleep–wake state and any medications can also affect EEG pattern.

EEG wave patterns are classified by frequency into alpha (8–13 Hz), beta (>13 Hz), theta (4–7 Hz) and delta (1–3 Hz). After about the age of 3 years, the predominant EEG rhythm is alpha rhythm. This is most clearly expressed over the posterior regions. Alpha becomes prominent when eyes are closed.

Activation procedures

Several techniques are used to maximize the amount of information gained during an EEG recording.

1. *Hyperventilation* – usually for 3 minutes. This causes significant slowing of background activity and can reveal abnormalities not obvious in the resting record. Classically, this technique provokes an absence seizure in children with childhood absence epilepsy. Hyperventilation is achieved by asking the child to blow on a toy windmill.
2. *Photic stimulation* – involves light flashes at specific frequencies (1–30 Hz) for 5–10 seconds. This can reveal a tendency to photosensitivity, and can allow more careful classification of an epilepsy syndrome.
3. *Sleep deprivation* – can induce seizure activity in some epilepsy syndromes, e.g. juvenile myoclonic epilepsy. Interictal epileptiform discharges can be activated during sleep, especially in benign localization-related epilepsy syndrome (e.g. BECCTS). If epilepsy is suspected and a standard awake EEG does not provide adequate information to allow classification of the epilepsy syndrome, a sleep EEG may help. Sleep may be achieved by depriving a child of sleep the night before a recording or induced by medication, e.g. melatonin.

Peripheral neurophysiology

Most peripheral neuropathies in children present with sensory and motor deficits in a symmetrical distal

pattern. Onset is usually gradual. These children should attend a specialized paediatric neuromuscular clinic.

Investigation techniques used are detailed below.

Electromyography

Electromyography (EMG) involves inserting a needle electrode directly into the muscle under investigation. The muscle action potentials are captured on recording equipment and amplified as a sound. Usually there is no electrical activity heard in a resting muscle. Voluntary effort allows action potentials to be recorded. Nerve injury and myopathic conditions will cause fibrillation potentials and characteristic changes in EMG pattern. Myotonia can also be detected and has a characteristic sound.

Nerve conduction studies

This investigation can confirm a clinical suspicion of a peripheral neuropathy and can allow classification into axonal degeneration or demyelinating conditions. In addition, this study can indicate if both motor and sensory nerve fibres are involved.

An electrode records the compound muscle action potential (CMAP) over the desired muscle group. A stimulating electrode is placed at two measured points along the nerve pathway. The latency, amplitude, wave form and velocity of conduction are all recorded. Normal age-specific values allow for comparison.

In axonal degeneration, the conduction velocity is usually preserved, but the amplitude of the compound action potential will be reduced. Demyelination usually results in reduced conduction velocities.

Visual evoked potentials

Visual evoked potentials (VEPs) are simple, non-invasive tests (see Chapter 30, Ophthalmology, for details). They are sometimes appropriate for younger children who cannot easily communicate their visual symptoms or cooperate with the more standard vision assessment techniques.

They can help detect lesions of the sensory visual pathways, e.g. demyelination of the optic nerve in optic neuritis. They also allow some degree of quantification and can be a useful technique to monitor progression of visual abnormality.

Electroretinogram

Electroretinogram evaluates retinal function by placement of an electrode on or very close to the eye in addition to a reference electrode on the forehead (see Chapter 30, Ophthalmology, for details). This study captures both rod and cone responses, depending on whether the retina is light or dark adapted. Light adapted recordings favour cone responses, while dark adaptation allows rod function analysis.

Headache

Headache is a common symptom, and arises through mechanisms that are not fully understood. Prevalence of headache in children and adolescents is around 50–60%, and that of migraine 7–10%. Below the age of 7 years, headaches are slightly more common in boys than girls, but this ratio reverses with age. In addition, prevalence of headaches also increases with age, reaching adult values in the late teens.

A detailed history is the key to identifying the cause of headaches. As well as asking about the site, severity and duration of the headache, one must determine how often they occur, whether the onset is sudden or gradual and if there is any aura. Associated features such as nausea, visual symptoms and weakness might suggest migraine. Precipitants, relieving factors and family history are vital. Figure 28.6 is a simple clinical guide to approaching a child with a headache.

The International Headache Society divides headaches into three main groups (Table 28.4). Although severe acute headache can be a symptom of meningeal irritation or raised intracranial pressure, it is more commonly associated with a viral 'flu-like' illness. Recurrent and chronic headache can also stem from raised intracranial pressure, but is more commonly due to tension headache or migraine. Rarely, it is a symptom of hypertension.

Tension headaches are the most common type of primary headache. These may be episodic or chronic. Chronic daily headache is a less common problem and may in itself be caused by overuse of analgesics, which are helpful in episodic headache but may provoke chronic headache.

Migraine

Migraine occurs in 10% of children aged 5–15 years. They are slightly more common in boys in early childhood, but by adolescence, girls predominate with a ratio of 3:1. The diagnosis of migraine is based on clinical grounds and summarized in Table 28.5.

Acute migraine headaches usually occur when either external or internal triggers are activated to reach a particular threshold. External triggers may include certain foods, internal triggers may include stress or relief from stress.

Particular phases of migraine are often described:
- Prodrome – prior to onset, vague change in mood.
- Aura – usually involves some focal neurological symptoms, often visual disturbance, lasting less than one hour.
- Headache phase – often unilateral, can be associated with a feeling of nausea or
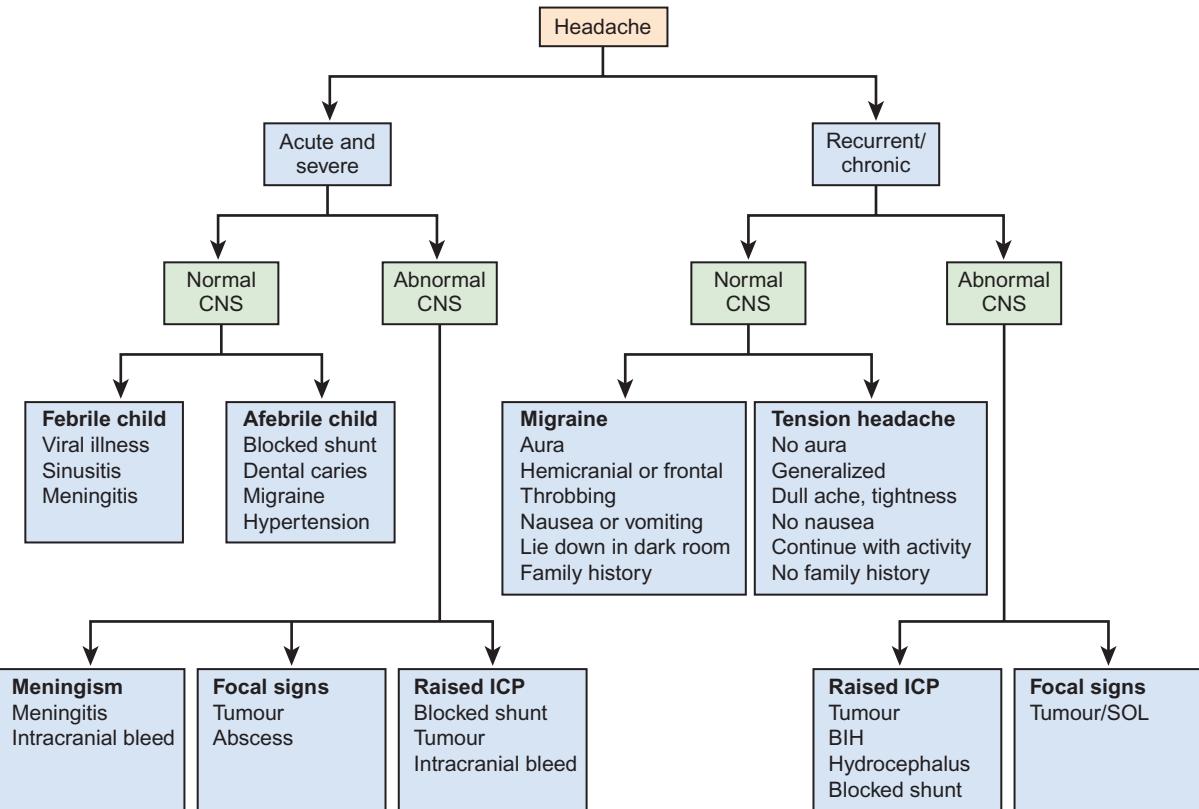
Fig. 28.6 Clinical decision pathway for headache. *(From Levene M. MRCPCH Mastercourse, 2007, Elsevier Churchill Livingstone, with permission.)*

Table 28.4 International classification of headache disorders

Type	Primary headache	Secondary headache	Cranial neuralgias, facial pain and other headaches
Aetiology	Idiopathic	Secondary to another pathology	Nerve-related
Examples	Migraine Tension headache Cluster headache	Drug-induced Infective Raised intracranial pressure Brain tumour Vascular event Hypertensive	Trigeminal neuralgia Optic neuritis

(Source: International Headache Society, 3rd edition.)

vomiting, needing to sleep and photophobia. Can last up to 72 hours, depending on treatment strategies.
- Resolution phase – non-specific feeling of being unwell.

Pathophysiology of migraine

The pathophysiology of migraine is complex, and several theories have been proposed over the years, none of which provides a complete answer. There is a clear genetic component, which has been borne out by twin studies and family histories, and the defect has been isolated for one variant of migraine: familial hemiplegic migraine (FHM). FHM is a rare subtype of migraine with aura that has an autosomal dominance inheritance pattern. The defect has been isolated to chromosome 19, with missense mutations for a subunit of a voltage-gated calcium channel. A linkage to this chromosome also appears to occur in some families with more common migraine types.

The trigeminovascular system

The trigeminovascular system is capable of activating nociceptive neurons on dural blood vessels. This, in turn, releases active substances that affect the vessel wall (including substance P, neurokinin A, calcitonin gene-related peptide, and nitric oxide). These produce dilatation, protein extravasation, and sterile inflammation, thus producing pain. This is unlikely to be the only mechanism of headache, as giving drugs targeting this process does not seem effective in migraine.

Table 28.5 International headache society criteria for diagnosis of migraine

Type	Grade	Criteria
Migraine without aura	A	At least five attacks fulfilling B to D below
	B	Headache lasting 4–72 hours (2–48 hours in children)
	C	Headache characterized by at least two of the following: 1. Unilateral location 2. Pulsating quality 3. Moderate or severe intensity (inhibits or prohibits daily activity) 4. Aggravated by climbing stairs or similar routine physical activity
	D	Headache accompanied by at least one of the following: 1. Nausea or vomiting, or both 2. Photophobia and phonophobia
Migraine with aura	A	At least two attacks fulfilling B below
	B	Presence of at least three of the following: 1. One or more fully reversible aura symptoms indicating focal cerebral cortical dysfunction or brainstem dysfunction or both 2. At least one aura symptom develops gradually over more than 4 mins, or two or more symptoms occur in succession 3. No aura symptom lasts more than 60 mins. When more than one aura symptom is present, accepted duration is proportionally increased 4. Headache follows aura with a symptom-free interval of less than 60 mins (it may also begin before or simultaneously with aura)

Table 28.6 Anti-migraine therapy

Non-pharmacological	Acute attack	Prophylaxis
Relaxation	Paracetamol	Pizotifen
Lifestyle modification	NSAIDs	Propranolol
Avoidance of triggers	(Opiods)	(Topiramate)
Biofeedback	Antiemetics	(Calcium channel
Occipital nerve stimulation	Triptans	blockers)
	(Ergotamine)	
	(Dopamine antagonists)	

smooth muscle cells in meningeal vessels; however, both 5-HT1D and 5-HT1B receptors can be found in both tissues to some extent, and even in coronary vessels. The trigeminal sensory neurons and meningeal blood vessels are both important in headache generation.

Familiar drugs used to treat migraine (the triptans) are selective 5-HT1B/D agonists. They are hypothesized to work by blocking neurotransmission in the trigeminocervical complex and reducing neuropeptide release.

Dopamine

Dopamine pathway stimulation produces symptoms familiar to migraine sufferers: nausea and vomiting, irritability, low blood pressure, and hyperactive behaviour. Dopamine antagonists do have clinical efficacy in relieving many, but not all, of the symptoms of migraines.

Endothelial dysfunction

Nitric oxide is a vasodilator and pro-inflammatory agent, in combination with cyclic-GMP, and is implicated in vascular smooth muscle cell dysfunction. Its levels may be elevated in children with migraine.

Magnesium

Magnesium shows promise as an anti-migraine therapy. Authors have put forward that relative magnesium deficiency triggers a cascade involving platelet aggregation, glutamate release, and vasoconstrictive 5-hydroxytryptamine.

Treatment of migraine

Relaxation, lifestyle modification, and simple analgesia are recommended as first-line therapy, but when this is not successful other agents are indicated (Table 28.6). Headache and food diaries are used to try and identify any potential triggers, such as:

- Sleep deprivation
- Stress
- Oral contraceptive pill
- Menstrual cycle

Cortical spreading depression

Many pathophysiological processes have been implicated in migraine, both vascular and neuronal, and more than one factor may be responsible. The theory of cortical spreading depression represents a wave of neuronal excitation in the cortical grey matter that spreads from its site of origin. This phenomenon is felt to account for the pre-migrainous aura reported by up to 30% of patients.

Serotonin

5-hydroxytryptamine (5-HT) receptor is widely believed to be a central player in migraine. The receptor subtype 5-hydroxytryptamine-1D (5-HT1D) is found in higher numbers in trigeminal sensory neurons, including peripheral projections to the dura and within the trigeminal nucleus caudalis and solitary tract. 5-HT1B receptors are located primarily on

- Vasodilator therapy
- Food (e.g. cheese, chocolate)

Pharmacological therapy for migraine

Acute attacks

Analgesics: Paracetamol and non-steroidal anti-inflammatories (NSAIDs) are first-line therapy, with opiods reserved for resistant cases.

Antiemetics: Domperidone, phenothiazines, and antihistamines may be given separately or in combination with other drugs. They act on receptors including 5-HT3, muscarinic acetylcholine, histamine 1, and dopamine 2 receptors. These receptors are all involved in the areas of the body known to trigger nausea and vomiting: the vestibular nuclei, nucleus of the solitary tract, chemoreceptor vomiting trigger centre, the vomiting centre (lower medulla, reticular formation, dorsal vagal nucleus), and higher brain centres. They act to relieve the nausea associated with migraine attacks.

Ergotamine (not recommended in children): Ergotamine acts via serotonin receptor activation, particularly 5-HT1B and 1D receptors, and to a lesser extent at 5-HT1F receptors. Ergot also is a potent alpha-adrenergic receptor agonist, which triggers arterial and venoconstriction. This vasoconstriction can affect systemic blood vessels, including the coronary arteries. It carries risk of other side effects due to action at 5-HT1A receptors (nausea, mood change), 5-HT2A receptors (peripheral vasoconstriction), and dopaminergic D_2 receptors (nausea and vomiting).

Triptans (not licensed below 6 years): Triptans also are agonists at 5-HT1B and 1D receptors, and to a lesser extent at 5-HT1F receptors. 5-HT1B receptors are preferentially expressed in intracranial extracerebral arteries, whilst in the peripheral arteries there are more 5-HT2A receptors. As the triptans are agonists at 5-HT1B receptors, but not at 5-HT2A receptors, they have less systemic vasoconstrictive impact than ergotamine. They are particularly useful in older children with infrequent migraine, as they act quickly and can be taken orally, by subcutaneous injection or intranasally (unlicensed). A non-oral route is useful if nausea and vomiting are prominent features. If a child does not respond to one agent, a trial of a different triptan is advised. They are, however, *not* indicated for hemiplegic, basilar, or ophthalmoplegic migraine.

Regularly taking agents for acute attacks has limitations, as they can produce rebound headache and take time to abort the headache. In those children where significant time off school is occurring or when headaches are very severe, a trial of prophylaxis is warranted. This approach is also indicated if the acute agents are contraindicated or not tolerated, or if the child is considered too young for use of the available licensed agents.

Migraine prophylaxis

Pizotifen (not licensed below 5 years): Pizotifen is a cycloheptathiophene derivative structurally related to cyproheptadine and the tricyclic antidepressants. It is a serotonin antagonist at 5-HT2A and 5-HT2C receptors, as well as a histamine antagonist and has weak anticholinergic activity. It may act by inhibiting the reuptake of serotonin by blood platelets, preventing loss of tone of extracranial vessels.

Propranolol (licensed for use in 2 years and over): A non-selective beta-1 receptor antagonist, propranolol can reduce both the frequency and severity of attacks. Similar beta blockers that also have intrinsic sympathomimetic properties (e.g. pindolol) are ineffective in migraine prophylaxis. Possible mechanisms or therapeutic action include:

- Alteration of 5-HT synthesis
- Antagonism of 5-HT receptors
- Decreased neuronal firing of noradrenergic neurons in the locus coeruleus
- Alteration of GABA-mediated firing of periaqueductal grey matter neurons

Propranolol should not be given to patients with asthma.

Topiramate (not currently licensed in children): An anticonvulsant, topiramate is a sodium channel blocker (as are many antiepileptics), promotes GABA-A receptor activation, inhibits L-type high-voltage calcium ion channels, and inhibits glutamate receptors. It is not known which of these mechanisms is responsible for its benefit in migraine.

Calcium channel blockers (not currently licensed in children): Drugs such as verapamil or nifedipine act to block calcium channels on the cell wall of arterial blood vessels in the brain. They are also thought to have an impact on the serotoninergic system of the brain.

Secondary headaches

Headache secondary to underlying disease is uncommon, but must not be overlooked. Particular features on history and examination that may suggest pathology are outlined in Table 28.7. Any child presenting with headache should be assessed with these symptoms or signs in mind, particularly those suggesting raised intracranial pressure.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH) is a syndrome characterized by increased intracranial pressure (ICP) of unknown cause. It was previously referred to as benign intracranial hypertension, but this term is no longer used as, although it is usually self-limiting,

Table 28.7 Features suggestive of sinister underlying pathology in a child with headache

History	Examination
Recent onset	Papilloedema*
Increasing in severity	Bitemporal hemianopia
Worse in the morning, on lying down, or on coughing*	(craniopharyngioma) or other visual problems
Associated with vomiting, often without nausea in the early stages*	Endocrine dysfunction (diabetes insipidus, hypothyroid, growth failure, early or late puberty)
Seizures	Abnormal neurological examination
Deterioration in school performance*	Ptosis, gaze palsy
Change in personality or behaviour*	Abnormal head position
Lethargy/drowsiness	Raised blood pressure, slow pulse and widened pulse pressure*
'Irritability'	A 'tense' or 'full' fontanelle (infants)*
	Rapidly increasing head circumference (infants)*

*Particularly associated with raised intracranial pressure of any cause.

it can last several months and it may lead to permanent visual loss.

The pathophysiology of this condition remains unclear. By definition, the elevated ICP is not related to an intracranial disorder, a meningeal process, or cerebral venous thrombosis. Many theories have been suggested, including: increased brain water content, excess CSF production, reduced CSF absorption, and increased cerebral venous pressure. A fundamental problem is our lack of understanding of the mechanism for control of normal CSF volumes and pressures.

The condition is particularly encountered in overweight or obese teenage girls and young women. The role of excess fat tissue in modifying endocrine function is under investigation and may contribute at least in part to this disorder.

It causes headache, nausea, and visual disturbance, with blurred vision, visual loss or diplopia, which can be irreversible. Papilloedema is present on fundoscopy. Brain imaging is normal, but the opening CSF pressure on lumbar puncture is raised.

Management may involve therapeutic CSF removal by repeat lumbar punctures, taking off enough fluid each time to reduce intracranial pressure. Other options include use of the drug acetazolamide, as this is a carbonic anhydrase inhibitor that alters flow of hydrogen, sodium, potassium, bicarbonate, and water. It is also used as a diuretic, glaucoma treatment, and metabolic acidifying agent; it works in IIH to reduce CSF production. Cases non-responsive to the above measures may progress to surgery for CSF shunt insertion or optic nerve sheath fenestration.

Cranial neuralgias, facial pain and other headaches

Trigeminal neuralgia is characterized by sudden, sharp 'electric shock' pain that is severe and affects one side of the face in the distribution of the trigeminal nerve. It can occur several times per day, and be triggered by movement or by light touch of the face, even a gust of wind. Commoner in women and those over 50 years of age, it can be treated using carbamazepine. Pathogenesis is thought to be related to vascular compression at the trigeminal nerve entry into the pons, resulting in focal trigeminal nerve demyelination. Surgery to release the pressure can be effective but requires detailed consideration.

Epilepsy

Neuronal transmission occurs via the neuronal action potential and dysfunction in this most basic of physiological mechanisms is the fundamental basis of epilepsy and seizure disorders.

Action potentials occur due to depolarization of the neuron cell membrane, with the wave of depolarization propagating along the axon to cause release of neurotransmitters at the axon terminal. Action potentials occur in an all-or-none fashion as a result of local changes in membrane potential caused by a net positive influx of ions. Membrane potential thus varies with activation of various ligand-gated channels. These are affected by binding to neurotransmitters or by changes in transmembrane potentials.

A cellular hyperexcitable state can result from increased excitatory factors, decreased inhibition, an alteration in voltage-gated ion channels, or a change in ion concentrations, all of which favour membrane depolarization. Neurotransmitters are released by the presynaptic terminal at the synapse. They then bind to specific receptors on the postsynaptic membrane for that ligand. Ligand binding causes channel activation and movement of ions in or out of the cells.

The major neurotransmitters in the brain include glutamate, gamma-aminobutyric acid (GABA), acetylcholine (ACh), noradrenaline (norepinephrine), dopamine and serotonin. Other molecules including neuropeptides and hormones are also thought to modify neurotransmission but over longer time periods. The major excitatory neurotransmitter is glutamate. There are several subtypes of glutamate receptors (e.g. AMPA and NMDA) which are permeable to sodium and potassium. It is the movement of Na^+ and K^+ through the channels which leads to depolarization and generation of an action potential.

The complex mechanism of channel function regulating neuron action potentials is the fundamental

basis of epilepsy (and other neurological conditions). Situations leading to altered brain tissue physiology, such as infection, inflammation or vascular compromise, will lead to channel dysfunction, thus seizure activity often results with various other neurological symptoms.

Similarly, there are an increasing number of recognized genetic channelopathies causing malfunction of particular ion channels. Such conditions often have epilepsy as part of the phenotypical presentation. A good example is the SCN1A sodium channelopathy. Mutations in this gene often present with troublesome seizures. The range of seizure presentations is variable, from frequent febrile seizures, the syndrome of generalized epilepsy with febrile seizures plus (GEFS+), as well as severe myoclonic epilepsy of infancy. In addition, mutations in some genes (e.g., CACNA1A – a calcium channel subunit) are associated with migraine disorders such as hemiplegic migraine.

Pharmacological treatment of epilepsy

Choice of anticonvulsant therapy is dependent upon seizure type and epilepsy syndrome (Table 28.8). Monotherapy at the lowest dose to achieve seizure frequency is the aim of treatment. Therapy is usually continued for a minimum period of two years after achieving seizure freedom. The availability of a palatable liquid, granules, or dissolvable preparation is of prime importance among the paediatric population.

Some antiepileptic medications such as sodium valproate, phenytoin and carbamazepine have been in use for a great many years. More recently, some

Table 28.8 Recommended anticonvulsants by seizure type

Seizure type	First line	Adjunct	May worsen seizures
Generalized tonic–clonic	Lamotrigine Sodium valproate Levetiracetam	Clobazam Lamotrigine Levetiracetam Sodium valproate Topiramate	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Tonic or atonic	Sodium valproate	Lamotrigine	Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin
Absence	Ethosuximide Lamotrigine Sodium valproate		Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Myoclonic	Levetiracetam Sodium valproate Topiramate	Clobazam Clonazepam Piracetam	Carbamazepine Lamotrigine Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Focal	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Lacosamide Sodium valproate Topiramate	
Status epilepticus	Buccal midazolam Rectal/intravenous diazepam Intravenous lorazepam	Intravenous phenobarbital Phenytoin	

(Adapted from NICE guidance.)

newer drugs have become available. The mechanism of action of most medications is reasonably well understood.

Knowing how a particular antiepileptic drug (AED) works can be helpful in determining an alternative treatment if an effective medication is not tolerated, or deciding upon a therapeutic strategy if a particular class of AED has not been clinically effective.

Question 28.10

Mechanism of action of AEDs

Concerning the mechanism of action of antiepileptic medications, which of the following agents does NOT work on the voltage-dependent sodium channel? Select ONE answer only.

A. Carbamazepine
B. Ethosuximide
C. Lacosamide
D. Lamotrigine
E. Phenytoin

Answer 28.10

B. Ethosuximide.
See below for discussion.

Medications acting at voltage-dependent sodium channels

Carbamazepine – binds to voltage-dependent sodium channels extending the inactivated phase and thus preventing the generation of rapid action potentials. It is usually well tolerated but may cause systemic upset in the form of nausea, vomiting and diarrhoea. Central side effects include drowsiness, headache and dizziness. A Stevens–Johnson type adverse reaction is possible and more likely in certain ethnic groups.

Phenytoin – has been widely used for a great many years. It acts on both voltage-dependent sodium channels and on sodium–potassium ATPase and thereby reduces synaptic transmission. Phenytoin is an integral step in the management of status epilepticus in Advanced Paediatric Life Support (APLS) guidelines. Drug interactions are common. Very few children will be maintained on long-term phenytoin due to the side-effect profile, which includes gum hypertrophy, rash and excess hair growth.

Lamotrigine – also acts at voltage-dependent sodium channels, but is believed to have other modes of actions. The major side effect of this drug is development of a rash, which can progress to a Stevens–Johnson syndrome. The risk can be reduced by very gradual titration of dose. This slow introduction does, however, limit its usefulness in the acute setting. Plasma levels are significantly elevated by sodium valproate, so doses must be reduced appropriately.

Oxcarbazepine – a compound with a similar chemical structure to carbamazepine and likely a similar mechanism of action.

Zonisamide – derived from the sulfonamide group of drugs and is unrelated to other anticonvulsants. The main mechanism of action seems to be at voltage-dependent sodium channels as well as calcium channels. Side effects include behavioural change, drowsiness and dizziness. Renal stones have also been reported.

Lacosamide – a newer drug that enhances slow inactivation of voltage-dependent sodium channels resulting in the inhibition of repetitive neuronal firing. This medication is usually well tolerated but experience is more limited at present.

Rufinamide – structurally unrelated to other epilepsy drugs and modulates the activity of sodium channels, prolonging their inactivation phase. The most common side effects are sleepiness and vomiting.

Medications acting on calcium currents

Ethosuximide – reduces calcium channel currents in thalamic neurons, which are thought to have a role to play in absence type seizures. The major side effects include nausea, vomiting, sleep disturbance, drowsiness, and hyperactivity. Because of its distinctive taste, compliance can be an issue.

Medications affecting GABA systems

Gamma-aminobutyric acid (GABA) is a neurotransmitter that is widely distributed throughout the central nervous system and exerts postsynaptic inhibition.

Phenobarbitone – among the oldest AEDs still in current use. It is effective for the management of both generalized and partial seizures. The main side effect, which limits its use, is sedation.

Tiagabine – a second generation AED that is indicated as adjunctive treatment for partial seizures. Its use in the paediatric setting is limited to date.

Vigabatrin – an irreversible inhibitor of GABA-transaminase, which increases the concentration of GABA in the central nervous system. It is particularly effective for infantile spasms in children with tuberous sclerosis. The major and significant side effect is an irreversible visual field loss on prolonged use. Therefore, it is rarely used for more than 6 months. Assessing visual fields is very difficult in younger children.

Benzodiazepines – enhance GABA inhibition by increasing the frequency of GABA-mediated chloride channel openings. This group of medicines is often associated with the development of tolerance, which significantly limits their use in the longer term. Sudden discontinuation may lead to withdrawal seizures and significant behavioural change in children.

Diazepam and lorazepam – often used in the acute setting. Clobazam, clonazepam and nitrazepam are sometimes used in the longer term, or for repeated short courses, either when seizures are troublesome or when background medications are being altered. Common side effects include sedation, as well as drooling, insomnia, and behavioural change.

Medications acting at glutamate receptors

Glutamate is the most prevalent excitatory neurotransmitter.

Perampanel – a relative newcomer, which targets post-synaptic AMPA receptors, and is only licensed in children over 12 years. Experience is limited. Mood change, fatigue and headache have been reported as side effects.

Medications with other mechanisms of action

A number of AEDs have multiple mechanisms by which they prevent seizures.

Sodium valproate – a broad-spectrum AED used alone and in combination for the treatment of generalized and partial seizures. It has been in mainstream use for many years. It is known to act at voltage-dependent sodium channels, as well as increasing gamma-aminobutyric acid (GABA). It is also thought to act against certain calcium channels. Side effects include nausea, vomiting, hair loss and weight gain. Use of this medication is teratogenic. This must therefore be taken into account in teenage girls.

Topiramate – blocks voltage-dependent sodium channels, promotes activity of GABA receptors, and antagonizes an NMDA–glutamate receptor. It

also weakly inhibits carbonic anhydrase in the central nervous system. Weight loss is a common side effect.

Levetiracetam – a broad-spectrum drug. The mechanism of action for this medication is unknown. It is generally well tolerated. Oral and intravenous administration is possible, with relatively fast escalation. Side effects include behavioural change and sleepiness.

Non-pharmacological treatment of epilepsy

Vagus nerve stimulation

Vagus nerve stimulation (VNS) is an alternative management strategy for patients with refractory epilepsy. Initial animal studies indicated that stimulation of the vagus nerve could be used to terminate seizures. Although the exact mechanism of vagus nerve stimulation is not well understood, it probably relates to the complex connections between the vagus nerve and various regions of the brainstem, midbrain and cortex. The device is implanted on the chest wall with electrodes attached to the left vagus nerve in the neck. Onset of benefit can take many months to emerge. MRI scanning is not possible with VNS *in situ*.

Ketogenic diet

The ketogenic diet is a high-fat, low-carbohydrate, adequate protein diet that has been used in the treatment of difficult epilepsy for many years. This diet regime causes production of ketone bodies (β-hydroxybutyrate, acetone and acetoacetate) – from fatty acid oxidation by the liver – and reduced blood glucose levels. The ketogenic diet is also the treatment of choice for a small number of other neurometabolic conditions, including GLUT1 deficiency, and PDH deficiency.

Elevated free fatty acids lead to chronic ketosis and increased concentrations of polyunsaturated fatty acids in the brain. Chronic ketosis is predicted to lead to increased levels of acetone; this may activate potassium channels to hyperpolarize neurons and limit neuronal excitability.

Chronic ketosis is also felt to alter brain biochemistry to promote inhibitory neurotransmitter levels. This actual scientific basis is not fully understood but is likely to involve many pathways, including free radical generation, interleukin and cytokine balance, and various mitochondrial pathways, ultimately leading to reduced membrane hyperexcitability, and thus improved seizure control.

Careful dietetic planning and monitoring is required, and all children need an individualized care plan in case of illness or hospital admission.

Recent scientific advances which have improved clinical practice – epilepsy

Whilst drug treatments for epilepsy tend to filter down through adult neurology prior to being introduced in children, the introduction of the ketogenic diet and vagal nerve stimulation (VNS) has permitted previously intractable cases to achieve a measure of control. Stereotactic surgery is now potentially curative for certain focal epilepsies, and wider experience and availability of specialist scanning techniques such as positron emission technology (PET) offers hope of understanding much more about the human brain and its disorders.

Further reading

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Elisabeth Jameson

CHAPTER

29

Metabolic medicine

Introduction

Intermediary metabolism is the term given to the biochemical reactions that degrade, synthesize or interconvert molecules within the cells. There are numerous metabolic pathways, which serve the following aims:

- Generation of energy
- Catabolism of organic molecules
- Synthesis of cellular building blocks
- Excretion of harmful substances.

These pathways require enzymes, which, if absent or deficient, can give rise to an inborn error of metabolism (IEM). This chapter describes the key metabolic pathways and links them with their associated diseases.

Acid–base disturbance

Definitions

The key terms are outlined in Table 29.1.

Biochemistry

Acid–base balance is essential for correct cellular functioning. Blood gas measurement can identify the primary disturbance (Table 29.2). In general:

- Metabolic disturbances are compensated acutely by changes in ventilation and chronically by renal responses
- Respiratory disturbances are compensated by renal responses.

In the case of metabolic acidosis, calculation of the anion gap will determine if there is the presence of an unmeasured anion such as an organic acid, e.g. methylmalonic or propionic acid (Table 29.3 and Fig. 29.1). Acidosis with a normal anion gap is often associated with hyperchloraemia because the loss of base is buffered by an increase and/or retention of chloride.

Clinical

Metabolic acidosis is a common finding. In the majority of cases, it reflects severe illness rather than an inborn error of metabolism (IEM). The latter should be considered if the acidosis is out of keeping with the clinical picture, is persistent despite standard management and there is no identifiable acid present, e.g. lactate or ketones.

Presentation

Metabolic acidosis is typically non-specific in presentation. Signs may include a reduced conscious level,

Table 29.1 Acid–base definitions

Terminology	Definition
Acid	A proton or hydrogen ion donor. It can dissociate to yield H^+ and the corresponding base.
Anion gap (see Fig. 29.1)	$[Na^+ + K^+] - [Cl^- + HCO_3^-]$. Normal $= 10 - 16$ mmol/L. Reflects concentration of those anions not routinely measured, e.g. organic acids (see Question 29.1).
Base	A proton or hydrogen ion acceptor. Can accept H^+ to form corresponding undissociated acid.
Base excess	Measures the change in the concentration of a buffer base from the normal value. Normal range $= +/- 2$ mmol/L.
Buffer	Consists of a weak acid in the presence of its base. A buffer serves to minimize changes in H^+ concentration in response to the addition of an acid or base. Examples of buffers in: Plasma – bicarbonate, proteins, inorganic phosphate (Pi) Erythrocytes – haemoglobin, bicarbonate, Pi Kidneys – bicarbonate, Pi, ammonium
pH	The logarithm to the base 10 of the reciprocal of the hydrogen ion concentration. $pH = -\log [H^+]$
pKa	The pH of a buffer at which half the acid molecules are undissociated and half are associated.

vomiting or those associated with the underlying aetiology, e.g. non-blanching rash in the case of meningococcal sepsis. Many patients will display an increased respiratory rate, Kussmaul respiration, reflecting the compensatory hyperventilation that occurs to promote removal of carbon dioxide.

Diagnosis

The blood gas is key to identifying the primary disturbance in acid–base balance. In addition to calculating the anion gap, ketones and lactate should be measured as potential causes of acidosis. When investigating for an IEM, urine organic acids and plasma amino acids and acylcarnitines are required. It is important to measure an ammonia level as this can be elevated in an organic acidaemia due to the metabolites inhibiting the urea cycle.

Management

The underlying aetiology, when known, should be treated. If acidosis is severe, normalization of acid–base balance can be achieved with administration of sodium bicarbonate.

Lactic acidosis

Normal plasma lactate is <2 mmol/L. A raised level has a wide differential (Table 29.4). In terms of IEM, mitochondrial disorders are classically associated with a raised lactate, with levels often fluctuating. When considering the possibility of mitochondrial disease, measuring cerebral spinal fluid for a raised level can be helpful. However, a normal lactate does not exclude a mitochondrial disorder.

Table 29.2 Acid–base disturbance

Abnormality	Primary disturbance	Effect on		Base excess	Compensatory response
		pH	pCO_2		
Respiratory acidosis	↑ pCO_2	↓	↑	Negative	↑ $[HCO_3^-]$
Metabolic acidosis	↓ $[HCO_3^-]$	↓	N or ↓	Negative	↓ pCO_2
Respiratory alkalosis	↓ pCO_2	↑	N or ↓	Positive	↓ $[HCO_3^-]$
Metabolic alkalosis	↑ $[HCO_3^-]$	↑	N or ↑	Positive	↑ pCO_2

Table 29.3 Metabolic acidosis and anion gap

With normal anion gap	With raised anion gap
• Intestinal loss of base, e.g. diarrhoea, fistulae • Renal loss of base, e.g. renal tubular acidosis (RTA) types 1 and 2, pyelonephritis • Carbonic anhydrase inhibitors	• Diabetic ketoacidosis • Renal failure • Poisoning with: salicylate, methanol, propylene glycol, iron, isoniazid, ethylene glycol • Inborn errors of metabolism, e.g. organic acidaemia, lactic acidosis

Table 29.4 Causes of a raised lactate

Metabolic	Non-metabolic
Respiratory chain disorder Pyruvate dehydrogenase deficiency Pyruvate carboxylase deficiency Disorders of gluconeogenesis Glycogen storage disorders Organic acidaemia Fatty acid oxidation disorder	Hypoxic–ischaemic encephalopathy Severe illness Cardiac disease Sampling artefact
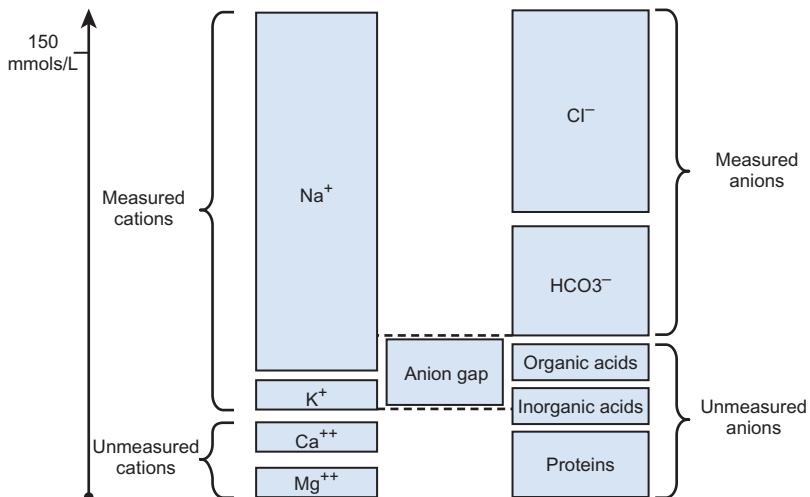
Fig. 29.1 Representation of the anion gap, an estimate of the osmolar difference between measured cations and anions.

Question 29.1

A 6-day-old baby with tachypnoea

A 6-day-old 3 kg term baby boy, born after a normal pregnancy and delivery, presents with reduced feeding and tachypnoea (respiratory rate 80/minute) over the last 24 hours. On examination, he is encephalopathic.

Investigations:

Blood:

Full blood count	mild pancytopenia
Sodium	136 mmol/L
Potassium	3.6 mmol/L
Chloride	110 mmol/L
Lactate	8 mmol/L (1–2.8)
Ammonia	60 µmol/L (normal <100)
C-reactive protein	6 mg/L

Blood gas:

pH	7.29
pCO_2	2.0 kPa (15 mmHg)
pO_2	13 kPa (98 mmHg)
Bicarbonate	10 mmol/L
Base excess	−18 mmol/L

Which of the following is the most likely diagnosis? Select ONE answer only.

A. Group B streptococcal septicaemia

B. Hypoxic–ischaemic encephalopathy

C. Organic acid disorder

D. Surfactant protein B deficiency

E. Urea cycle defect

Answer 29.1

C. Organic acid disorder.

There is a marked anion gap. The anion gap = (136 + 3.6) − (110 + 10) = 31.6 mmol/L.

In this patient, the gas normalizes with intravenous 10% dextrose and two half corrections of sodium bicarbonate. Further investigations: urine organic acid analysis reveals methylmalonic acidaemia (MMA).

Group B streptococcal septicaemia is possible, but is more likely to present with shock and a much more abnormal blood count, including low or high white blood cell count and thrombocytopenia. The low CRP in spite of being ill for 24 hours is also against this diagnosis. Hypoxic–ischaemic encephalopathy would present before 6 days. Surfactant protein B deficiency would present with increasing respiratory distress from birth. A urea cycle defect is possible, but the ammonia level is normal for a neonate.

Key points – organic acid disorders

- Methylmalonic and propionic acidaemia are the most common organic acidaemias
- Can cause pancytopenia because of effects on the bone marrow at times of decompensation
- pH can be maintained with hyperventilation
- A lactate of 8 mmol/L would not by itself generate such a large anion gap
- To calculate a half correction (using this case as an example):

$$\frac{\text{Base deficit} \times \text{weight (kg)} \times 0.3}{2}$$
$$= \frac{18 \times 3 \times 0.3}{2}$$
$$= 8.1 \, \text{mmol NaHCO}_3^-$$

The urea cycle and hyperammonaemia

Biochemistry

Ammonia

Ammonia is a highly neurotoxic chemical detoxified by the urea cycle (Fig. 29.2), which principally occurs in the liver. Ammonia is formed from:

- Nitrogen produced from amino acid metabolism
- Glutamate by the action of glutamate dehydrogenase
- Glutamine by the action of glutaminase.
- Alanine and glutamine produced by muscle turnover
- Urease-positive gut bacteria
- Ingested protein not utilized in biochemical processes

The urea cycle

The urea cycle (see Fig. 29.2) consists of six enzymes, with each full cycle disposing of two nitrogen atoms:

one from ammonia and one from aspartate. The cycle progresses as:

- *N*-acetylglutamate forms from the condensation of glutamate with acetyl-CoA catalysed by *N*-acetylglutamate synthetase
- Condensation of ammonia with bicarbonate forms carbamoyl phosphate catalysed by carbamoyl phosphate synthetase. The latter is only active in the presence of *N*-acetylglutamate.
- Carbamoyl phosphate condenses with ornithine to form citrulline
- Citrulline is transferred into the cytoplasm and combines with aspartate to form argininosuccinate, catalysed by argininosuccinate synthase.
- Argininosuccinate lyase cleaves argininosuccinate to arginine
- Arginine is hydrolysed to urea, which is excreted in urine. Each urea molecule contains two nitrogen atoms and one carbon atom. Ornithine is transported back into the mitochondrion by the ornithine transporter.
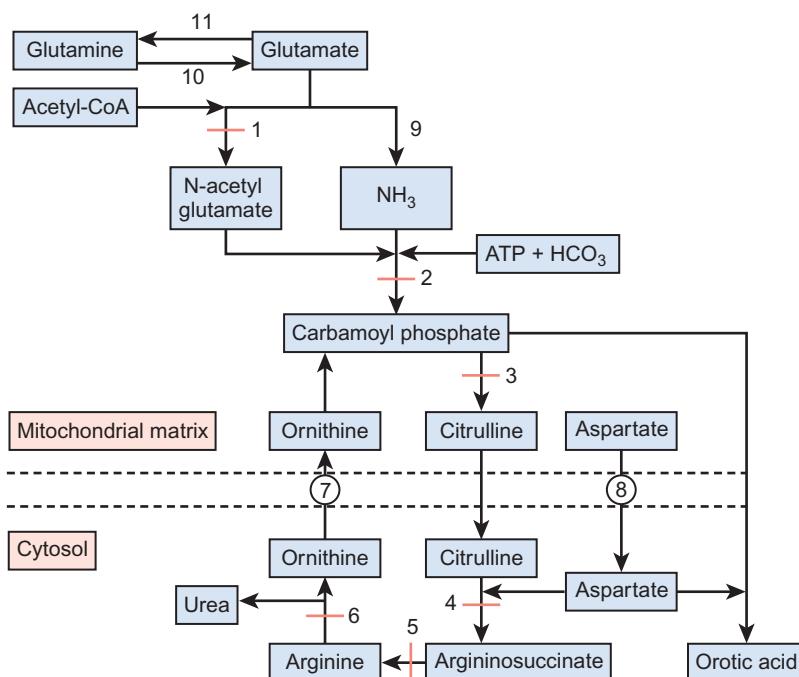
Fig. 29.2 The urea cycle. 1, *N*-acetylglutamate synthetase (NAGS); 2, carbamoyl phosphate synthetase 1 (CPS1); 3, ornithine transcarbamoylase (OTC); 4, argininosuccinate synthetase (ASS); 5, argininosuccinate lyase (ASL); 6, arginase; 7, mitochondrial ornithine transporter; 8, mitochondrial aspartate–glutamate carrier (citrin); 9, glutamate dehydrogenase; 10, glutaminase; 11, glutamine synthetase.

Ammonia is also buffered by the conversion of glutamate to glutamine via the action of glutamine synthetase. At times of hyperammonaemia, the glutamine concentration increases and thus can be used as an indicator of insufficient urea synthesis and is indicative of longer term metabolic control.

Clinical

Hyperammonaemia (normal plasma ammonia levels are <100 μmol/L in neonates and <50 μmol/L thereafter) has a wide differential (Table 29.5). Urgent measurement of ammonia should therefore take place in any baby, child or adult presenting with unexplained encephalopathy or illness. The urea cycle disorders (UCD) arise due to deficiency of one of the six main urea cycle enzymes.

Presentation

The classic presentation is the term baby who becomes increasingly sleepy and encephalopathic on day 3–5 of life with poor feeding and vomiting (see Question 29.2). Ammonia levels can rise rapidly. Urgent investigation is required to clarify the diagnosis and guide management.

The urea cycle disorders are inherited in an autosomal recessive manner, except for ornithine transcarbamylase (OTC) deficiency, which is X-linked

(see Genetics of metabolic disorders, below). Male infants are severely affected and many do not survive the neonatal period. Female carriers have a varied phenotype; the majority remain asymptomatic but approximately 15% will require treatment.

Diagnosis

Diagnosis of urea cycle disorders (Table 29.6) is based upon plasma amino acid analysis and the presence or absence of urine orotic acid, which is produced when carbamoyl phosphate passes into the pyrimidine pathway. The absence of orotic acid in a urea cycle disorder implies N-acetylglutamate synthetase (NAGS) or carbamoyl phosphate synthetase (CPS) deficiency. Orotic acid is classically very elevated in OTC because of the accumulation of intracellular carbamoyl phosphate. The remaining defects are associated with a much smaller or negligible amount of orotic aciduria.

Management

This can be thought of in terms of acute and long term.

Acute:

- Stop feeds and commence 10% dextrose to reduce nitrogen load on the cycle
- Commence intravenous ammonia scavenging medications (see Principles of pharmacological treatment, below)
- Commence intravenous arginine to replenish the urea cycle
- Transfer to specialist centre in preparation for haemofiltration

Chronic:

- Low protein diet to reduce nitrogen load on the cycle
- Ammonia scavenging medications to aid excretion of excess nitrogen
- Arginine (except in arginase deficiency) to replace arginine not produced by the urea cycle

Table 29.5 Differential diagnosis of hyperammonaemia

Inborn errors of metabolism	Acquired
Urea cycle disorder	Transient hyperammonaemia of newborn
Organic acidaemia	
Fatty acid oxidation disorders	Severe illness
Pyruvate carboxylase deficiency	Herpes simplex infection
Ornithine aminotransferase deficiency	Cardiac disease
	Medications (sodium valproate, asparaginase)
HHH syndrome (hyperammonaemia, hyperornithinaemia, homocitrullinuria)	Reye-like illness
	Liver disease
	Porto-systemic shunts
	Artefactual from poor sampling

Table 29.6 Diagnosis of urea cycle disorders

Enzyme	Disorder	Plasma amino acid concentrations relative to reference range					Urine orotic acid
		Alanine	Glutamine	Citrulline	ASA	Arginine	
NAGS	NAGS def	↑	↑				Normal
CPS	CPS def	↑	↑	↓		↓	Normal
OTC	OTC def	↑	↑	↓		↓	↑↑↑
ASS	Citrullinaemia	↑	↑	↑↑		↓	↑
ASL	ASA def	↑	↑		↑	↓	↑
Arginase	Arginase def				↑		↑

ASA, argininosuccinic aciduria; ASL, argininosuccinate lyase; ASS, argininosuccinate synthetase; CPS, carbamoyl phosphate sythetase; def, deficiency; NAGS, N-acetylglutamate synthetase; OTC, ornithine transcarbamylase.

A 5-day-old baby with drowsiness and poor feeding

A 5-day-old baby girl is born at term after a normal pregnancy and delivery. She presents with a 24-hour history of increasing sleepiness and poor feeding. On examination, she is encephalopathic with an irritable cry.

Investigations:

Blood:

Haemoglobin	136 g/L
White cell count	10.0×10^9/L
Platelets	360×10^9/L
CRP	10 mg/L
Glucose	4.0 mmol/L
Ammonia	875 µmol/L (<100)
Lactate	5 mmol/L (1–2.8)
Urea and electrolytes	normal
Liver function tests	normal
Calcium, phosphate, ALP	normal

Blood gas:

pH	7.5
pCO_2	2.5 kPa
pO_2	11.3 kPa
Base excess	–5 mmol/L
Bicarbonate	22 mmol/L

Which of the following is the most likely diagnosis? Select ONE answer only.

A. Hyperinsulinaemia of the newborn

B. Intrapartum hypoxia

C. Pyridoxine dependency

D. Septicaemia

E. Urea cycle defect

Answer 29.2

E. Urea cycle defect.

A urea cycle defect is the most likely because of the elevated lactate level and the extremely high ammonia. Hyperinsulinaemia is possible but ruled out by the normal blood glucose. Intrapartum hypoxia would have presented earlier with seizures and possibly renal failure. Pyridoxine dependency would result in intractable seizures. Septicaemia is unlikely with the virtually normal blood count.

Intravenous sodium benzoate and sodium phenylbutyrate are commenced. She is transferred to the paediatric intensive care unit (PICU) for haemofiltration. Ammonia normalizes over 6 hours. While on PICU she suffers a seizure. Investigations: High plasma citrulline and absent urine orotic acid suggest citrullinaemia, subsequently confirmed

with mutation analysis. She subsequently recovers and is discharged on a low protein diet, sodium benzoate and arginine.

Key points – urea cycle defects

- Ammonia is a respiratory stimulant and can cause respiratory alkalosis
- Seizures can be seen in the acute phase due to cerebral oedema secondary to the effects of hyperammonaemia
- Early referral to PICU for haemofiltration is essential
- High ammonia levels (>1000 µmol/L) are associated with poor prognosis in terms of survival and long-term neurological outcome

Glucose and glycogen metabolism

Definitions

There are a number of key processes in this pathway, as defined in Table 29.7.

Glucose biochemistry (Fig. 29.3)

Glucose

Glucose provides an immediate energy source via its conversion into pyruvate with the net production of 2 molecules of ATP and NADH (nicotinamide adenine dinucleotide) per glucose molecule. Excess glucose can be converted into glycogen, which can be utilized

Table 29.7 Definitions in relation to glucose and glycogen metabolism

Term	Definition
Hypoglycaemia	A true blood glucose of <2.6 mmol/L.
Gluconeogenesis	Synthesis of glucose from non-glucose precursors, i.e. amino acids (except leucine and lysine) and glycerol in the liver, kidney or intestinal epithelium. Glucose can also form from intermediates of glycolysis, the Krebs cycle and fructose.
Glycolysis	Oxidation of glucose to pyruvate with generation of adenosine triphosphate (ATP).
Glycogenesis	Conversion of excess glucose to glycogen. Key enzymes are glycogen synthase and the branching enzymes.
Glycogenolysis	Degradation of glycogen to glucose. Phosphorylase is the controlling enzyme.

at times of fasting or increased glucose demand, e.g. aerobic exercise.

Clinical

Hypoglycaemia is a common finding in children and is seen in many clinical scenarios. It is common in the immediate newborn period (see Chapter 11, Neonatal medicine), particularly in infants who are preterm or growth restricted, or who have mothers with maternal diabetes or who are seriously ill, e.g. sepsis or hypoxic–ischaemic encephalopathy. If severe or recurrent, or if it occurs in older infants and children, investigations should be undertaken to identify a serious underlying pathology (see Chapter 26, Diabetes and endocrinology). A hypoglycaemia screen should be performed at the time of low blood glucose (Table 29.8). It is essential to establish the presence or absence of ketones, as their absence is an abnormal physiological response. Figure 29.4 gives a diagnostic guide to metabolic causes.

Prolonged fasts can be performed to provoke hypoglycaemia in order to permit investigations to be completed. However, this should only be done under strict supervision and once a fatty acid oxidation disorder has been excluded, as a prolonged fast could result in metabolic decompensation.
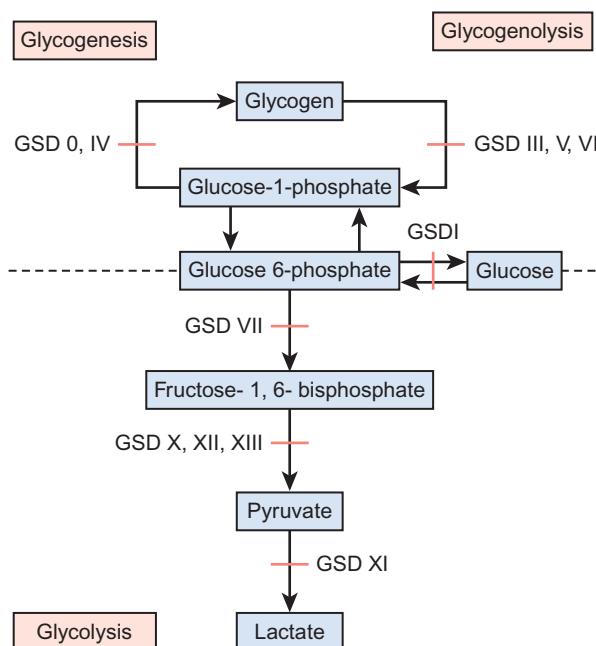
Fig. 29.3 Overview of glucose and glycogen metabolism.

Table 29.8 Tests comprising a hypoglycaemia screen

Bloods	Urine
Blood glucose – confirm severity	Organic acids
Blood gas	Ketones
Free fatty acids	Reducing substances
3-hydroxybutyrate	
Insulin and C-peptide	
Cortisol and growth hormone	
Lactate	
Ammonia	
Acylcarnitines	
Plasma amino acids	
Urea and electrolytes, liver function tests	
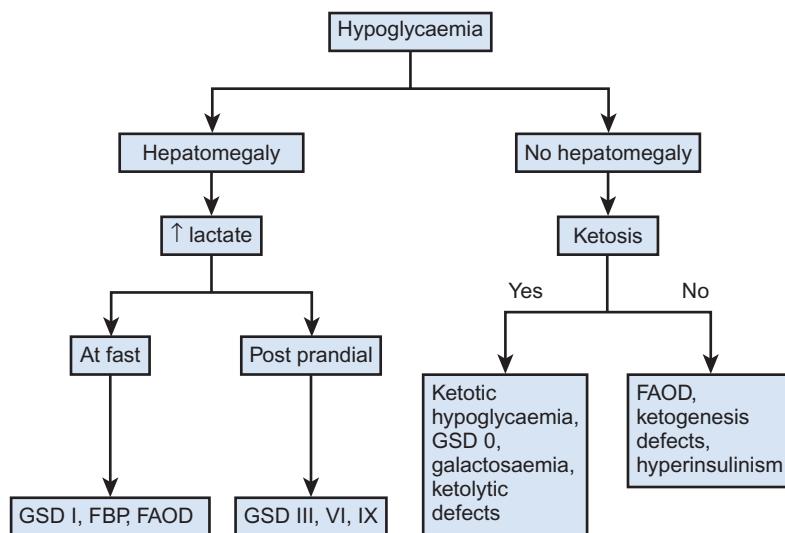
Fig. 29.4 Diagnostic guide to hypoglycaemia. GSD, glycogen storage disease 0, I, III, IV, IX; FAOD, fatty acid oxidation disorder; FBP, fructose-1,6-bisphosphatase deficiency.

Table 29.9 Classification of the glycogen storage disorders (GSDs)

Presentation	GSD
Hepatic	Ia, Ib, III, IV, VI, IX, 0
Muscle	V, VII, X, XI, XII, XIII
Cardiac	II, III

Glycogen biochemistry (see Fig. 29.3)

Glycogen is a macromolecule found in the liver and muscles. It is the primary energy source between meals. It is composed of up to 60,000 glucose molecules joined by α-1,4 linkages with branching points formed by α-1,6 linkages at intervals of 4–10 glucose residues.

Glycogenesis

Glycogenesis occurs when excess glucose is available. The key enzyme is glycogen synthase. This exists in a dephosphorylated active (synthase a) and a phosphorylated inactive (synthase b) form.

Glycogenolysis

Glycogenolysis releases glucose from glycogen by two steps:

- Phosphorylase splits the α-1,4 linkage, releasing glucose-1-phosphate. Like glycogen synthase, it has active and inactive forms. Glucose is the major inhibitor of its active form.
- Debranching enzyme splits the α-1,6 bond, producing free glucose.

Clinical

The glycogen storage disorders (GSDs) are a diverse group and can be divided into hepatic, muscular and cardiac sub-groups (Table 29.9). Figure 29.3 broadly outlines their position within the pathway. The clinical phenotype is dependent upon the site of abnormal glycogen metabolism.

Glycogen storage disorder I (GSD-I)

Type I exemplifies the hepatic form. It is due to deficiency of glucose-6-phosphatase and leads to severe hypoglycaemia because of the inability to mobilize glucose from glycogen or to utilize glucose from gluconeogenesis. The children have hepatomegaly due to glycogen storage and a characteristic cherubic facies. Management is with regular feeds during the day and a continuous overnight feed to maintain normoglycaemia (see Principles of dietary treatment, below).

Glycogen storage disorder V (GSD-V)

Question 29.3

Glycogen storage disorder type V (McArdle's disease)

A fifteen-year-old girl presents with symptoms of muscle pain and cramps and fatigue during brief, intense exercise. She has also noted episodes of dark-coloured urine accompanying these episodes. She is often able to resume exercise following a brief rest. Glycogen storage disease type V (McArdle's disease), the most common muscle glycogenosis, is suspected.

Which of the following statements about the disease are true (T) and which are false (F)?

A. Hepatomegaly is a clinical feature.

B. Her symptoms during vigorous exercise are due to the lack of pyruvate available for production of acetyl-CoA for the Krebs cycle.

C. It is caused by a deficiency of the myophosphorylase enzyme, which leads to reduced glycolysis in muscle fibres and reduced production of pyruvate.

D. She can resume exercise after rest because of the onset of free fatty acid oxidation within the muscle.

E. The dark-coloured urine is from bilirubin.

Answer 29.3

A. False. This form of glycogen storage disease affects muscles rather than the liver.

B. True.

C. True.

D. True. The Krebs cycle is dependent on free fatty acid oxidation for production of acetyl-CoA. This process takes longer than pyruvate formation, which explains the 'second wind' phenomenon.

E. False. Myoglobin (an oxygen and iron binding protein found in muscle tissue) is released into the blood due to muscle damage during intensive exercise and is responsible for her dark-coloured urine.

The Krebs cycle and mitochondrial respiratory chain

The Krebs cycle, also known as the tricarboxylic acid cycle (Fig. 29.5), is found in all cells except red blood cells, which lack mitochondria. It links the pathways of intermediary metabolism with the mitochondrial
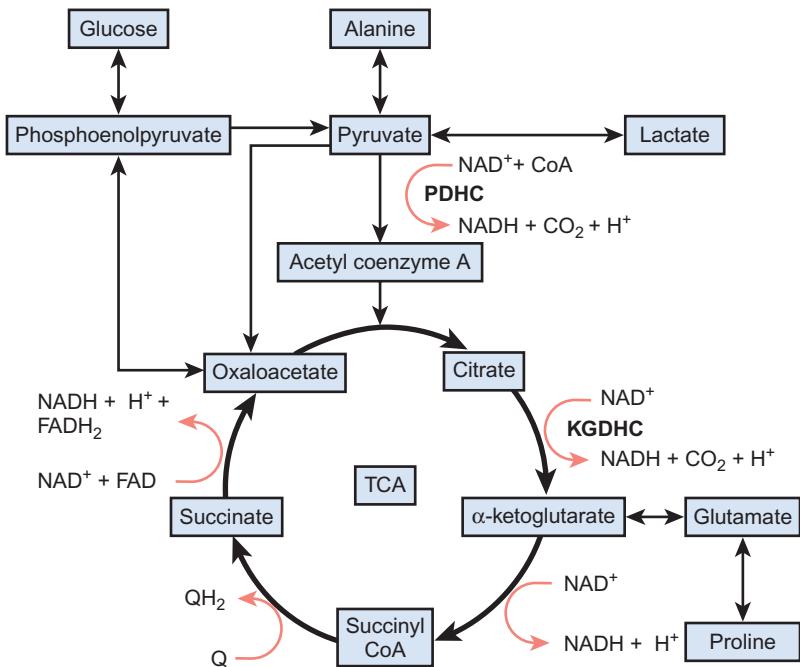
Fig. 29.5 The Krebs cycle. CoA, coenzyme A; NAD^+, nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; KGDHC, α-ketoglutarate dehydrogenase; Q, coenzyme Q; FAD, flavin adenine dinucleotide; $FADH_2$, reduced flavin adenine dinucleotide.
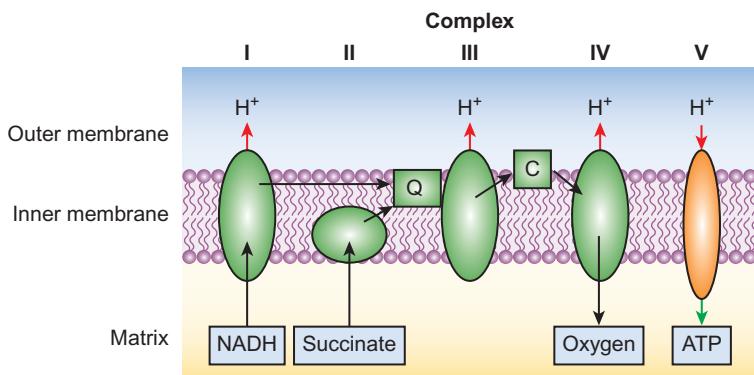
Fig. 29.6 The mitochondrial respiratory chain. NADH, reduced nicotinamide adenine dinucleotide; ATP, adenosine triphosphate; Q, coenzyme Q; C, cytochrome c; →, electron flux; →, proton flux.

respiratory chain (Fig. 29.6). The pyruvate dehydrogenase (PDH) complex regulates the cycle's activity.

Biochemistry

Pyruvate dehydrogenase (PDH) complex

The complex is formed from three enzymes (E1, E2, E3), and E1 requires the co-factor thiamine diphosphate. The complex provides substrate for the Krebs cycle in the form of acetyl-CoA by facilitating the

conversion of pyruvate to acetyl CoA. The pyruvate is derived from glucose, lactate and alanine. Pyruvate also undergoes conversion to oxaloacetate by pyruvate carboxylase, which also feeds into the Krebs cycle.

Krebs cycle

The primary function is to oxidize acetyl-CoA generated from metabolism of carbohydrates, ketone bodies, fatty acids and amino acids into reduced nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide ($FADH_2$). These are then

utilized in oxidative phosphorylation. The cycle also provides intermediates for other pathways and has links with gluconeogenesis, lipogenesis and amino acid metabolism.

Mitochondrial respiratory chain

The mitochondrial respiratory chain (MRC), also known as the electron transport chain, is present in all mitochondria-containing cells. The chain is composed of five complexes (I to V) and two link molecules (ubiquinone and cytochrome c) embedded within the mitochondrial membrane (see Fig. 29.6). It is the site of ATP production. This occurs though two coupled processes:

1. Electron transport: Complexes I–IV comprise a series of redox reactions utilizing NADH and $FADH_2$ from the Krebs cycle. Ubiquinone shuttles electrons form complexes I and II to III. Cytochrome c shuttles electrons from complex III to IV. This flow of electrons is used to pump protons across the inner mitochondrial membrane to the intermembrane space, so creating a proton (H^+) gradient.
2. Oxidative phosphorylation: Complex V (ATP synthase) channels the protons back into the mitochondrial matrix with the generation of ATP.

Clinical

Strictly speaking, mitochondrial disorders are those directly resulting from deficits in energy production by oxidative phosphorylation. Disturbances of this complex system result in disrupted supply of ATP. Those organs with the greatest energy demands are most severely affected, i.e. brain, heart, kidney, retina, skeletal muscle.

Presentation

Clinical presentation is very varied and while clinical syndromes are recognized (Table 29.10), mitochondrial disease should be considered in the following instances:

- Multi-system disease
- Elevated lactate, though differential is wide and raised lactate is not a compulsory requirement (see Acid–base disturbance, above)
- Leigh syndrome with its characteristic cranial magnetic resonance imaging findings of symmetrical changes of the basal ganglia and the brainstem.

Diagnosis and management

Investigation is difficult (see Investigations used in screening and diagnosis, below) and often only symptomatic treatment is possible, e.g. seizure management, gastrostomy feeding.

Thiamine has been used in patients with PDH deficiency in order to increase the efficiency of the reactions undertaken by E1. Effects have been variable. The use of a ketogenic diet (see Principles of dietary treatment, below) in patients with PDH deficiency has been marginally more successful, as it serves to provide an alternative source of acetyl-CoA for use by the Krebs cycle.

Table 29.10 Common mitochondrial disorders

Syndrome	Clinical features	Onset (years)	Common mutations
MERRF	**M**yoclonic **e**pilepsy with **r**agged **r**ed **f**ibres	5–15	m.8344G>A
NARP	**N**europathy, **a**taxia, **r**etinitis **p**igmentosa	5–30	m.8993T.G/C
Barth	Cardiomyopathy, cyclical neutropenia, myopathy, short stature	Neonate or infancy	*TAZ* gene
Ethylmalonic encephalopathy	Developmental delay, acrocyanosis, petechiae, diarrhoea	Neonatal or infancy	*ETHE1* gene
GRACILE	**G**rowth **r**etardation, **a**minoaciduria, **c**holestasis, **i**ron overload, **l**actic acidosis and **e**arly death	Neonatal or infancy	*BCS1L* gene
MELAS	**M**itochondrial **e**ncephalopathy, **l**actic **a**cidosis, **s**troke-like episodes. Myopathy, migraine, vomiting, seizures, visual and hearing disturbance	5–15	80% m.3243A>G
Alpers	Intractable seizures and liver involvement	Early childhood	POLG
Kearns–Sayre	Triad: onset <20 years, progressive external ophthalmoplegia, pigmentary retinopathy plus at least 1 of cardiac conduction block, cerebellar ataxia, CSF protein >0/1 g/L	<20	90% due to large mtDNA deletions +/– duplications

Fatty acid metabolism and ketone synthesis

Fat is an important stored energy source, especially at times of fasting, when fatty acid oxidation provides up to 80% of cellular energy. Fatty acids are used preferentially by the heart and by muscles during sustained exercise. The brain is unable to directly metabolize fatty acids but can use ketone bodies generated during fatty acid oxidation.

β-Hydroxybutyrate and acetoacetate are the principal ketone bodies. They are generated from acetyl-CoA by β-oxidation of fatty acids. Their conversion to acetyl-CoA allows their use as an alternative fuel. Disorders of ketogenesis resemble that of fatty acid oxidation disorders; in contrast to defects of ketolysis, where severe ketosis predominates.

Biochemistry

Fatty acid metabolism has three stages (Fig. 29.7):

- Entry of fatty acids into mitochondria. Fatty acids are mobilized by lipase. Medium- and short-chain fatty acids permeate the mitochondrial membrane and are activated to CoA esters in the matrix in preparation for β-oxidation. Long-chain fatty acids (those with 16–20 carbon atoms) must be activated to coenzyme A esters in the cytoplasm. They join with carnitine to form a fatty acylcarnitine via CPT 1 (carnitine palmitoyltransferase I) and transferred into the mitochondrial matrix via the carnitine:acylcarnitine translocase transporter. Once in the matrix, CPT II converts the fatty acylcarnitine back to a fatty acyl-CoA and carnitine, the latter exported back into the cytosol.
- β-Oxidation occurs via a spiral pathway. Each turn shortens the acyl-CoA by two carbons. There are four cycles; each catalysed by a carbon chain length specific enzyme:
  - Acyl-CoA dehydrogenase (irreversible)
  - Long-chain acyl-CoA dehydrogenase (C14–20)
  - Medium-chain acyl-CoA dehydrogenase (C8–12)
  - Short-chain acyl-CoA dehydrogenase (C4–6)
- The net effect is production of:
  - Electrons, which are transferred to the respiratory chain
  - Acetyl-CoA, which is either oxidized in the Krebs cycle or used by the liver to create ketone bodies.

Clinical

Presentation

Fatty acid oxidation disorders have three classic presentations:

1. Hypoketotic hypoglycaemia. If left untreated, encephalopathy ensues, often accompanied by liver dysfunction and hepatomegaly, leading eventually to coma and death.
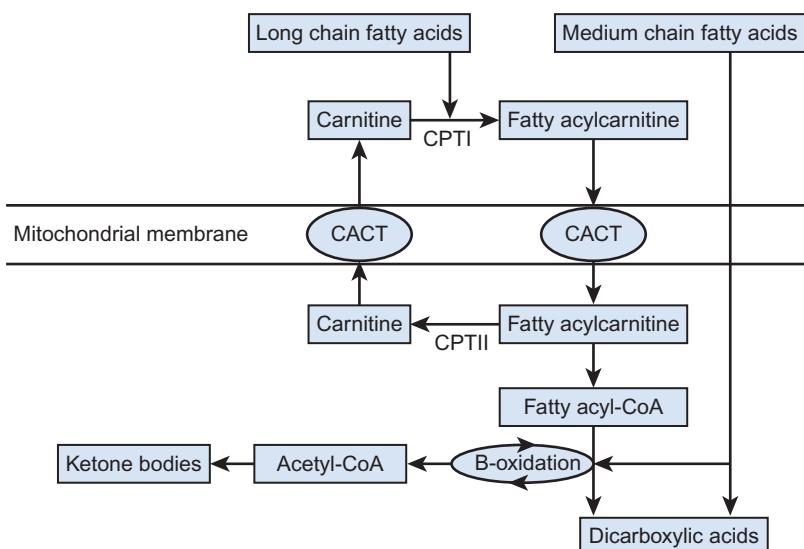
Fig. 29.7 **Fatty acid oxidation. CPT 1, carnitine palmitoyltransferase I; CPT II, carnitine palmitoyltransferase II; carnitine acylcarnitine translocase (CACT).**

Table 29.11 Summary of disorders of fatty acid metabolism

Disorder	Presentation	Diagnosis	
		Carnitine/acylcarnitine	Urine organic acid
CTD	Cardiomyopathy, muscle weakness, liver disease Asymptomatic	↓↓↓ free/total carnitine	No dicarboxylic aciduria
CPT I	Liver disease, renal tubular acidosis	N–↑ total/free carnitine ↓C_{16}, C_{18}, $C_{18:1}$	No dicarboxylic aciduria
CPT II	Early onset: cardiomyopathy, liver disease Attenuated: exercise intolerance, rhabdomyolysis	↓ total carnitine ↑ ratio $C_{16} + C_{18:1}/C_2$	No or non-specific dicarboxylic aciduria
CACT	Severe cardiomyopathy, arrhythmias, liver disease	↓↓ total carnitine ↓ free carnitine	↑ C_{16}, C_{18}, $C_{18:1}$ May have dicarboxylic aciduria
VLCAD	Severe: cardiomyopathy, liver disease, hepatomegaly, sudden death in infancy Attenuated: late-onset rhabdomyolysis, exercise intolerance	↑ $C_{14:1}$ and ratio $C_{14:1}/C_{12:1}$	C_6–C_{14} dicarboxylic aciduria
LCHAD	Cardiomyopathy, liver disease, hypotonia, neuropathy, retinopathy; late-onset rhabdomyolysis Mother with affected fetus may have steatosis or HELLP syndrome in pregnancy	↑ lactate and hydroxyl-compounds $C_{14\text{-OH}}$, $C_{16\text{-OH}}$, $C_{18:1\text{-OH}}$	C_6–C_{14} dicarboxylic acids
MCAD	Reye-like rapidly progressive crisis after 8–16 hours fasting, during ordinary illness or after surgery Now identified by newborn screening (see Investigations used in screening and diagnosis, below)	↑ C_8, C_6, ratio C_8:C_{10}	C_6–C_{14} dicarboxylic aciduria, suberylglycine, hexanoylglycine.

CACT, carnitine translocase deficiency; CPT I/II, carnitine palmitoyltransferase I/II deficiency; CTD, carnitine transporter defect; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; MCAD, medium-chain acyl-CoA dehydrogenase deficiency; VLCAD, very-long-chain acyl-CoA dehydrogenase deficiency.

2. Cardiomyopathy, arrhythmias or conduction defects.
3. Myopathy or acute rhabdomyolysis.

Diagnosis

Diagnosis is based upon clinical presentation and measurement of carnitine and acylcarnitine levels and urine organic acids (Table 29.11). The majority of episodes are triggered by intercurrent illness or fasting. Management is therefore avoidance of fasting and reduction of catabolic stress at times of intercurrent illness by use of an emergency regimen (see Principles of dietary treatment, below). Those with carnitine transporter defect require carnitine.

Case history

Early neonatal death

Term baby observed on postnatal ward for 24 hours in view of prolonged rupture of membranes. Discharged home on day 2, breastfeeding. On day 3 he became apnoeic and required resuscitation and transfer to paediatric intensive care. He was encephalopathic and a CT head was consistent with hypoxic–ischaemic encephalopathy. Care was withdrawn. Cause of death was presumed to be sepsis; however, post-mortem acylcarnitine and urine organic acid analysis were consistent with MCAD deficiency. Mutation analysis confirmed

baby was homozygous for the common mutation c.985A>G.

Key points:

- MCAD deficiency can present in the first few days of life before screening results are available
- If there are older siblings, they should be tested if they were born prior to newborn screening
- Future pregnancies should be managed prospectively in accordance with national guidelines (see www.bimdg.org.uk)

Vitamin-responsive disorders

Vitamins act as co-factors and co-enzymes in many biochemical systems. Consequently, there are a number of vitamin-responsive disorders (Table 29.12). The following case history highlights the role of active and inactive co-factors.

Case history

Metabolic epileptic encephalopathy

A newborn, term male baby born after a normal pregnancy and delivery presents with seizures on day 1 of life, which become intractable despite standard anti-convulsant therapy. The possibility of pyridoxine-responsive seizures is raised. Pyridoxine is given intravenously at 100 mg/kg with no effect. Pyridoxal phosphate is given orally

with immediate effect. Investigations confirm pyridoxal phosphate deficiency with a mutation found in the *PNPO* gene.

Key points:

- Pyridoxine must be given in controlled circumstances as it can cause apnoea
- If pyridoxine is ineffective, a trial of the biologically active pyridoxal phosphate should be given. Only available as an oral preparation.

Genetics of metabolic disorders

The full spectrum of inheritance modes are seen in IEM (Table 29.13). The most common pattern is autosomal recessive. While consanguineous parentage increases the risk of IEM, it is not obligatory.

Table 29.12 Vitamin responsive disorders

Vitamin	Used in
B$_1$ (thiamine)	Thiamine-responsive variants of maple syrup urine disease, PDH def, complex I def
B$_2$ (riboflavin)	Glutaric aciduria type II, complex I
B$_6$ (pyridoxine)	Pyridoxine-responsive homocystinuria, pyridoxine-dependent seizures
B$_6$ (pyridoxal phosphate)	Pyridoxamine-5-phosphate oxidase def
B$_7$ (biotin)	Biotinidase def, multiple carboxylase def, biotin responsive basal ganglia disease
B$_9$ (folic acid)	Methylenetetrahydrofolate reductase (MTHFR) def
B$_{12}$ (hydroxycobalamin)	B$_{12}$-responsive MMA (methylmalonic acidaemia), MTHFR def
Vitamin E	Abetalipoproteinaemia, glutathione synthase def

def, deficiency; PDH, pyruvate dehydrogenase.

Table 29.13 Modes of inheritance

Inheritance mode	Examples
Autosomal recessive	Organic acidaemias, UCD (except OTC), MPS (except type II), aminoacidopathies, glycogen storage disorders
Autosomal dominant	GLUT1, familial hypercholesterolaemia
X-linked	OTC deficiency, Barth syndrome, MPS type II, creatine transporter deficiency, Lesch–Nyhan
Maternal	MELAS, Leber's hereditary optic atrophy, Pearson syndrome, MERRF, NARP, MIDD

GLUT1, glucose transporter 1; MELAS, mitochondrial encephalopathy, lactic acidosis, stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibres; MIDD, maternally-inherited diabetes and deafness; MPS, mucopolysaccharidosis; NARP, neuropathy, ataxia, retinitis pigmentosa; OTC, ornithine transcarbamylase; UCD, urea cycle disorder.

Mitochondrial genetics

Mitochondrial genome (mtDNA) is inherited exclusively from the mother as, after fertilization of the ovum, the sperm-derived mitochondria disappear in early embryogenesis. In any one cell there are hundreds of copies of mtDNA because there are many copies in each mitochondrion and many mitochondria per cell. An mtDNA mutation may affect all (homoplasmy) or a proportion (heteroplasmy) of copies of the mtDNA in a cell. Clinical disease only occurs once a threshold of heteroplasmy is exceeded. The threshold is dependent upon the severity of the mutation and the susceptibility of the tissue to the effects of the mutation. Above this threshold, the severity of the clinical phenotype will depend upon the level of heteroplasmy. For example, m.3243A>G causes MELAS syndrome in people with high levels of the mutation, but those with lower levels may only suffer diabetes mellitus and deafness. The level of heteroplasmy and hence phenotype can vary from mother to child (see Chapter 9, Genetics, for further details).

Newborn screening

This is offered to all newborn babies on day 5–7 of life (see Chapter 11, Neonatal medicine). The conditions tested for are cystic fibrosis, congenital hypothyroidism, haemoglobinopathies, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, phenylketonuria (PKU), maple syrup urine disease (MSUD), isovaleric aciduria (IVA), glutaric aciduria type I (GA1) and homocystinuria (HCU). The last six are inborn errors of metabolism.

MCAD deficiency

MCAD deficiency is a disorder of fatty acid oxidation (see Fatty acid metabolism and ketone synthesis, above). It has an incidence in the UK of approximately 1 in 10,000 births. It is detected on newborn screening by measuring the octanoylcarnitine (C8) level. If elevated, the test is repeated. Screen positive patients are referred to the nearest specialist metabolic centre for confirmation with repeat acylcarnitine testing, mutation analysis and urine organic acid analysis looking for dicarboxylic aciduria. Management is with the avoidance of fasting and the use of an emergency regimen at times of illness to prevent metabolic decompensation (see Principles of dietary treatment, below).

Phenylketonuria

Phenylketonuria (PKU) is an aminoacidopathy due to a deficiency of phenylalanine hydroxylase, which

converts phenylalanine to tyrosine. Accumulation of phenylalanine, if untreated, causes microcephaly, seizures and learning difficulties. Newborn screening aims to detect a raised phenylalanine (Phe) level. If the level is increased, the test is repeated and the tyrosine level is measured. Screen positive patients are referred to the local metabolic service for confirmation with repeat testing. If the phenylalanine level is markedly raised and the tyrosine level is low, PKU is confirmed. However, 1% of patients with raised Phe levels will not have PKU but will have a disorder of pterin metabolism. This group of disorders leads to disturbances in central nervous system amines and results in a neurological phenotype, requiring treatment with L-dopa, tetrahydrobiopterin and/or 5-hydroxytryptophan. All PKU-positive patients are therefore tested for pterin defects when reviewed by the specialist centre.

PKU is treated with a low protein diet, so restricting intake of phenylalanine in conjunction with a phenylalanine-free amino acid supplement. The latter is vital to ensure nutritional requirements for all non-essential and essential amino acids (Table 29.14) are met to allow optimal growth. The amount of natural protein allowed is calculated using an exchange system whereby one food can be exchanged for another of equivalent phenylalanine content. The number of allowed exchanges is variable and depends upon blood phenylalanine level, severity of enzyme deficiency, energy intake, compliance with protein substitute and age and weight of the child. Phe levels are monitored by the patients sending in regular blood spots for analysis and altering the diet according to the level in relation to target range.

Investigation of suspected metabolic disease

If a diagnosis is clear, then specific diagnostic investigations can be performed, including genetic testing.

Table 29.14 The amino acids

Essential	Non-essential
Histidine	Alanine
Isoleucine	Arginine
Leucine	Asparagine
Lysine	Aspartate
Methionine	Cysteine
Phenylalanine	Glutamate
Threonine	Glutamine
Tryptophan	Glycine
Valine	Proline
	Serine
	Tyrosine

Often the diagnosis is unclear, with many children presenting with chronic, non-specific signs such as developmental delay (DD), faltering growth, dysmorphism or seizures. Even those presenting acutely with metabolic acidosis or hyperammonaemia will need multiple investigations to elucidate the aetiology. Investigations are often staged (Tables 29.15–29.16), except in the moribund child, when efforts must be made to obtain samples peri-mortem to minimize post-mortem artefact. Routine pathology samples should be sent concurrently, i.e. full blood count, urea and electrolytes, coagulation, as many of these profiles are deranged in metabolic disease. Discussion with a specialist centre is vital to guide the process.

Table 29.15 Typical first-line investigations (guided by clinical picture)

Sample	Test	Indication
Blood	Amino acids and acylcarnitines	Possible UCD, organic acidaemia or aminoacidopathy, DD, seizures, faltering growth, dysmorphism
	Beutler test	Galactosaemia
	Very-long-chain fatty acids	Possible peroxisomal disorder
	White cell enzymes	Dysmorphism, organomegaly, learning difficulties, developmental regression
	Lactate	Mitochondrial disease, GSDs
Urine	Organic acids	Possible organic acidaemia, FAOD
	Amino acids	Tubulopathy, cystinosis
	MPS and oligosaccharides	MPS disorder or oligosaccharidosis

DD, developmental delay; FAOD, fatty acid oxidation disorder; GSDs, glycogen storage disorders; MPS, mucopolysaccharidosis; UCD, urea cycle disorder.

Table 29.16 Second-line investigations (guided by clinical picture)

Sample	Test	Indication
Cerebral spinal fluid	Neurotransmitters Amino acids, glucose and lactate (paired with plasma samples)	Neurotransmitter disorders, GLUT1 deficiency, non-ketotic hyperglycinaemia
Skin biopsy	Fibroblast culture	PDH deficiency, flux studies, filipin staining
Muscle biopsy	Histochemistry and respiratory chain enzymes	Mitochondrial disease
Liver biopsy	Histochemistry and mitochondrial studies	GSD, mitochondrial disease

GSD, glycogen storage disorder; PDH, pyruvate dehydrogenase.

Mitochondrial disease testing

This is notoriously difficult and often no diagnosis is reached, though recent technological advances have improved diagnostic rates. A general guide to investigation:

- If there is a characteristic clinical syndrome, proceed straight to testing for the common mutation.
- If there is no characteristic clinical syndrome, proceed to muscle biopsy for histochemistry and respiratory chain biochemical analysis and progress to molecular genetics.

Principles of pharmacological treatment

Many conditions are managed using symptomatic therapies, e.g. anti-convulsants. Table 29.17 summarizes the main medications used in metabolic disease.

Table 29.17 Medications used in inborn errors of metabolism

Medication	Indication	Mode of action
Arginine	Urea cycle disorders	Replenishes arginine. Substrate for nitrous oxide.
Carglumic acid	Hyperammonaemia due to NAGS or CPS deficiency	Artificial activator of CPS1 thereby promoting the urea cycle.
Carnitine	Organic acidaemias, carnitine transporter defects	Replenishes body stores. Removes toxic acyl-CoA intermediates from within the mitochondria.
Citrulline	CPS and OTC deficiency	Replenishes citrulline and arginine.
Sodium benzoate	Hyperammonaemia	Conjugates with glycine to form hippuric acid, which is excreted in the urine.
Sodium phenylbutyrate	Hyperammonaemia	Conjugates with glutamine to form phenylglutamine, which is excreted in the urine.

CPS, carbamoyl phosphate synthetase; NAGS, *N*-acetylglutamate synthetase; OTC, ornithine transcarbamylase.

Enzyme replacement therapy

Lysosomes can be thought of as the 'recycling centres' of our cells. They contain a large number of enzymes required for the intracellular breakdown of various molecules. A deficiency of one of these enzymes leads to a specific lysosomal storage disorder (LSD) (Table 29.18). They are termed 'storage disorders' because the loss of the enzyme results in the accumulation (or storage) of the incompletely metabolized substance within the lysosome. This leads to swelling of the lysosome and cellular dysfunction. Clinically, this manifests with the typical features of storage, such as organomegaly and dysmorphism. Some LSDs predominantly affect the central nervous system and are primarily neurological diseases, e.g. Krabbe disease.

Lysosomal enzymes are synthesized via the endoplasmic reticulum. They are then processed in the Golgi apparatus, where a mannose-6-phosphate residue is added. The latter identifies it as a lysosomal enzyme. The lysosome 'picks up' the enzyme via its mannose-6-phosphate receptor and transports the enzyme inside. Enzyme replacement therapies (ERTs) have been developed for some of the LSDs which exploit this natural process (Table 29.19). In summary, in ERT a recombinant enzyme is produced with a mannose-6-phosphate residue added to it; thus, allowing the manufactured deficient enzyme to be imported into the lysosome.

Principles of dietary treatment

Many inborn errors of metabolism are treated by dietary modification (Table 29.20). Specialist dietetic advice is essential to ensure nutritional requirements are met. There are four key dietetic strategies, as detailed below.

Supplying a deficient product

An example would be the need for a regular supply of glucose in a hepatic GSD, such as type I. Children with GSD-I are unable to metabolize glycogen or utilize glucose from gluconeogenesis due to a deficiency of glucose-6-phosphatase (see Glucose and glycogen metabolism, above). They are at risk of hypoglycaemia

Table 29.18 Classification of lysosomal storage disorders

Group	Deficient breakdown of:	Disorders
Mucopolysaccharidoses (MPS)	Glycosaminoglycans	MPS I, II, III, IV, VI, VII
Oligosaccharidoses	Carbohydrate side-chains from glycoproteins	Fucosidosis, α and β mannosidosis
Sphingolipidoses	Ceramide-containing membrane lipids	Gangliosidosis 1 and 2, Niemann–Pick disease A and B, Gaucher types 1, 2 and 3, Fabry, Krabbe

Table 29.19 Lysosomal storage disorders and their available enzyme replacement therapies

Disorder	Licensed enzyme replacement therapy
Gaucher disease types 1 and 3	Imiglucerase, velaglucerase, taliglucerase
Fabry disease	Agalsidase alfa, agalsidase beta
Mucopolysaccharidosis type I	Laronidase
Mucopolysaccharidosis type II	Idursulfase
Mucopolysaccharidosis type VI	Galsulfase
Pompe disease	Alglucosidase alfa

Table 29.20 Inborn errors of metabolism treated with a specialist diet

Disorder	Conditions treated with diet
Amino acid metabolism	Phenylketonuria, maple syrup urine disease, homocystinuria, tyrosinaemia, lysinuric protein intolerance
Organic acid metabolism	MMA (methylmalonic acidaemia), propionic acidaemia, isovaleric acidaemia, glutaric aciduria type I
Carbohydrate metabolism	Galactosaemia, hereditary fructose intolerance, glycogen storage disease I

even when well. Management involves the supply of glucose delivered by regular feeds over the day and a continuous feed overnight. The length of time between feeds varies between patients, with some requiring daytime feeds as often as every 1½ hours. In older patients and those with less severe disease, uncooked cornstarch can be used as a slow release glucose substrate. This reduces the number of feeds during the day and may allow cessation of overnight feeding.

Preventing accumulation of a toxic substrate by restricting intake

This has already been exemplified in the case of PKU (see Neonatal screening, above). Another example is that of galactosaemia (see Chapter 21, Hepatology) which is due to a deficiency of galactose-1-phosphate uridyltransferase. This is required for the metabolism of the monosaccharide galactose. Presentation is classically in the neonatal period with prolonged jaundice, liver dysfunction, cataracts and sepsis (typically *E. coli*). The patient is treated with a minimal-galactose diet and due to the extremely limited dairy intake, many require calcium supplementation. Despite strict dietary adherence, outcomes remain sub-optimal due to the endogenous production of galactose in the gastrointestinal tract. Long-term complications include ovarian dysfunction (in females) and learning difficulties.

The urea cycle disorders, organic acidaemis and other amino acidopathies, such as tyrosinaemia, require dietary protein restriction. It is crucial that, despite the restriction, the diet provides sufficient protein and essential amino acids to meet the safe levels of protein intake specified by the World Health Organization. To achieve this, many patients will require protein substitutes and vitamin/mineral supplementation.

Supplying adequate energy and preventing catabolism

At times of illness metabolic demands are increased. If these demands are not met, the body enters a state of catabolism. This is also seen during starvation. Certain groups of patients are at risk of metabolic decompensation:

- Fatty acid oxidation disorder: at risk of hypoglycaemia
- Hepatic GSD: at risk of hypoglycaemia
- Urea cycle disorders: at risk of hyperammonaemia
- Organic acidaemias: at risk of metabolic acidosis and hyperammonaemia

To prevent such a situation arising, patients are provided with an emergency regimen. This involves stopping the normal diet and providing a supply of glucose orally or intravenously with the aim of increasing insulin secretion and reducing catabolism. Oral glucose is preferred during minor illness as it can be given at home. The common glucose polymers used are Caloreen®, Polycose®, Maxijul®, Polycal®, Vitajoule®. The concentration and volume are adjusted according to the patient's age. The drinks are continued every two hours during the day and three hourly overnight until the child is on the road to recovery. Patients who vomit or refuse to take their emergency regimen, or who deteriorate despite taking it, require hospital admission for intravenous glucose with the aim to supply 6–12 mg/kg/minute of glucose, depending on age. The fluid used should generally be 10% glucose and 0.45% saline with electrolytes added as determined by the plasma electrolytes. If patients become hyperglycaemic, an insulin infusion should be started with appropriate monitoring rather than reducing the concentration of the glucose infusion as it promotes anabolism.

Ketogenic diet

The brain relies on glucose to provide its energy. GLUT1 is a glucose transporter responsible for facilitating the transport of glucose across the blood–brain barrier. Defects in this system result in low cerebral spinal fluid (CSF) glucose levels with resultant

neurological disease. Patients classically present with an early-onset epileptic encephalopathy resistant to standard anti-convulsant medications. Unrecognized, the patient suffers developmental delay and evolution of a movement disorder. Non-classical forms have a varied phenotype but remain neurological in nature. Diagnosis is based on a low plasma to CSF glucose ratio of <0.5 with normal CSF cell count, protein and lactate. Confirmation is with mutation analysis. Treatment is with a ketogenic diet, as the brain is able to use ketones as an alternative energy source (see Fatty acid metabolism and ketone synthesis, above). While the diet can alleviate some of the neurological problems, patients often have residual cognitive problems.

The classical ketogenic diet is based on four grams of fat being consumed for every one gram of protein and carbohydrate. Side effects include constipation, mild hyperlipidaemia, platelet dysfunction and, very rarely, kidney stones or pancreatitis. The medium-chain triglyceride (MCT)-based diet is an alternative to the classical diet. MCT provides 60% of the energy with saturated fat, with carbohydrate and protein providing the remaining 40%. If patients on the diet become unwell, they must not be given dextrose-containing solutions (unless hypoglycaemic) as this shuts off ketosis and can cause recurrence of seizures.

Summary

Individually, inborn errors of metabolism are rare but, collectively, they are not uncommon. They have a multitude of presentations and, unless thought about, will be missed, as standard investigation of the unwell child will not detect them. Diagnosis is important not just for management of the affected child but also to allow family genetic counselling, as all are inherited conditions. Investigation is central to diagnosis and can be difficult. Management is multi-disciplinary and early discussion with a specialist metabolic centre is vital. A solid understanding of their pathophysiology is essential to understanding these complex disorders.

Further reading

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Louise Allen

Ophthalmology

Although ophthalmology may seem a fairly minor topic to the generalist, paediatric eye and visual disorders are common in both primary and secondary care settings. The eyes, their visual pathways and higher visual processing mature throughout early childhood. Good visual function depends on all these factors. These stages of normal visual development and the way we assess them are covered in Chapter 4, Normal child development.

Epidemiology of childhood visual impairment

Visual impairment in childhood impacts all areas of a child's development and influences their future prospects. In the UK, nearly 4% of the childhood population are registered severely visually impaired or blind (compared to 12% in developing countries) and half these children will have additional motor, sensory, learning impairments or systemic disease. Our screening programmes and access to specialist paediatric ophthalmic care prevent many cases of severe visual impairment, and the majority (75%) of children registered blind in the UK have an unpreventable and untreatable cause. The registration process facilitates the educational and social support these children need. The level of visual impairment is based on corrected binocular visual acuity (using a Snellen chart) and visual fields. The definitions of sight impairment are shown in Box 30.1.

Applied embryology of the eye

The developing eye

The eye develops from a complex, coordinated interaction between surface ectoderm, neuroectoderm and the mesenchyme (comprising mesoderm and neural crest cells), mediated by many developmental genes (Fig. 30.1). The optic fissure closes in the sixth week of gestation and, by the beginning of the second trimester, the rudimentary eye has developed, although subsequent differentiation and maturation occur beyond term.

Abnormal ocular development

Anophthalmos, microphthalmos and coloboma

This is a spectrum of early ocular malformation and may be unilateral or of varying severity in each eye. The most severe manifestation is anophthalmos, where no globe is present (incidence 2/100,000 live births). In microphthalmos, a small globe, which may or may not have visual potential, is present (incidence 19/100,000 live births). An absent or very small globe will fail to stimulate orbital growth; orbital expanders and conformers should be fitted within weeks of birth in order to prevent permanent orbital asymmetry. Ocular coloboma is a more common malformation (incidence 1/20,000 live births), resulting from failure of closure of the optic fissure in the sixth gestational week. This is often an isolated anomaly but may also characterize a syndrome (e.g. CHARGE: *C*oloboma, *H*eart abnormalities, *A*tresia choanae, *R*etardation of *G*rowth and development and *E*ar/hearing abnormalities). The coloboma can affect the inferonasal iris (Fig. 30.2A), and/or the inferior choroid and retina and the optic nerve, the latter two resulting in visual impairment (Fig. 30.2B).

Aniridia

Although the name suggests otherwise, this is a malformation of the whole eye, usually causing partial or total absence of the iris, cataract, corneal stem cell

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Box 30.1 Definitions of sight impairment

Severely sight impaired (SVI)/blind:

- Less than 3/60 (the top letter can only be read at 3 metres) with a full visual field
- From 3/60–6/60 accompanied by severe visual field restriction
- Better than 6/60 but a visual field restricted to 10 degrees or less

Sight impaired/partially sighted:

- From 3/60–6/60 with full visual fields
- Up to 6/24 with a moderate visual field defect
- 6/18 or better with a gross visual field defect, e.g. homonymous hemianopia

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Week 3:
The first step in eye development is the development of the optic sulci. Genes: PAX6, PAX2, SOX2, SOX3, FOXE2

Week 4:
Cross-section through forebrain (red dashed line). The invaginating lens placode comprised of surface ectoderm forms the optic vesicle. The neuro-ectoderm lines the vesicle.

Week 6:
Cross section through optic vesicle. The lens placode (ectodermal thickening) begins to separate from the surface forming the lens. The inferiorly located optic fissure is starting to close.

Week 7:
The neuro-ectoderm forms the retina and optic nerve. The surrounding mesenchyme forms the hyaloid vasculature, vitreous and inner layers of the cornea. Extra-ocular muscles begin to form. Genes: PITX2, FOXC1, CYP1B1

Fig. 30.1 Stages of eye development and some of the genes that control it.
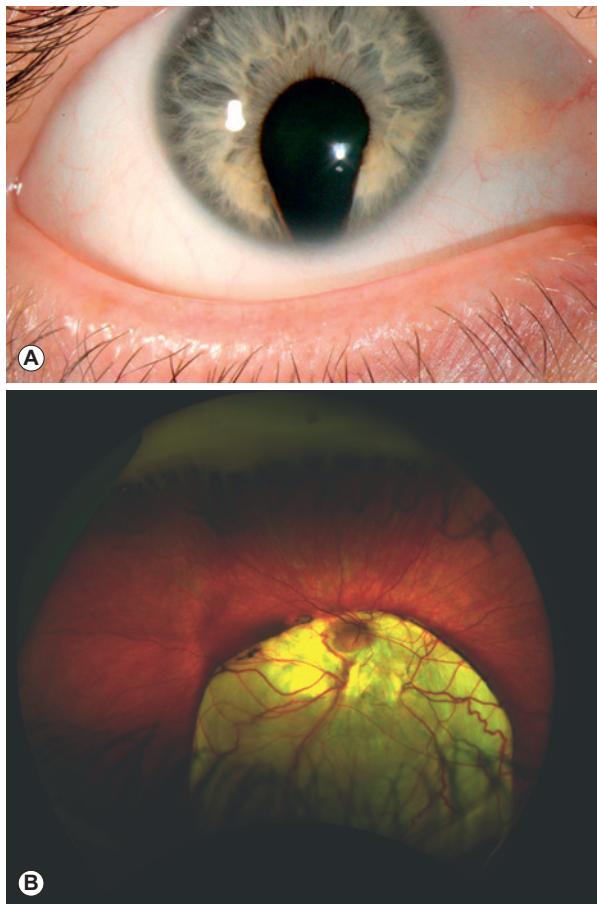
Fig. 30.2 **A. Iris coloboma causes a defect in the inferonasal iris. B. A chorioretinal coloboma affects the inferonasal fundus; severe forms can cause deep excavation of the optic disc and macula, severely impairing vision and causing leukocoria (white reflex on direct ophthalmoscopy).**

failure and absence of the fovea (foveal hypoplasia), which causes poor vision and nystagmus. Most cases are autosomal dominant (due to inherited point mutations in *PAX6*). However, in sporadic aniridia, a novel micro-deletion can involve *PAX6* and a neighbouring tumour suppressor gene causing WAGR syndrome (*W*ilm tumour, *A*niridia, *G*enito-urinary abnormalities and *R*etardation): newborns with sporadic aniridia require urgent investigation for renal tumours.

Albinism

Melanin has several important functions in the developing eye. It mediates the complex organization of the fovea and guides the axons of the retinal ganglion cells distally through the optic chiasm. Children born with the more severe forms of autosomal recessive oculocutaneous albinism will have translucent irides, foveal hypoplasia and abnormal axonal decussation at the optic chiasm (a useful diagnostic feature demonstrated by visual evoked potentials). X-linked ocular albinism causes the ocular features of albinism without significant cutaneous involvement.

Vitreo-retinal dysplasia

This is thought to be caused by abnormal retinal vasculogenesis. At its most severe, the retina is an unrecognizable funnel of neurovascular tissue projecting from the optic disc into the vitreous cavity at birth. In less severe cases, there are localized areas of retinal non-perfusion and ischaemia; early recognition and laser treatment to these areas can prevent neovascularization and subsequent retinal detachment. Babies with incontinentia pigmenti (*IKBKG* gene mutation, X-linked dominant, lethal in males) are at risk of developing abnormal retinal vasculature and require regular retinal examination from birth in order to prevent retinal detachment with laser treatment.

Optic nerve hypoplasia

Optic nerve hypoplasia causes a small optic nerve head on fundoscopy, often associated with tortuous retinal veins and a variable level of visual impairment. Maternal risk factors include young age, maternal diabetes and a history of excessive alcohol or use of illicit drugs during pregnancy. There are many systemic associations of optic nerve hypoplasia, including fetal alcohol syndrome and Dandy–Walker syndrome. More commonly, optic nerve hypoplasia is associated with endocrine abnormalities due to panhypopituitarism (may present as neonatal jaundice, hypoglycaemia and seizures) or specific mid-line CNS malformations, such as septo-optic dysplasia, characterized by absence of the septum pellucidum and thinning or agenesis of the corpus callosum.

Applied anatomy of the eye

The developed eye (Fig. 30.3)

The axial length of the eye at birth is around 17 mm. The globe grows particularly rapidly in the first six months, reaching the adult axial length of 22 mm by 5 years. The volume of the neonatal eye is approximately 2.8 cm^3 compared to the adult volume of 7 cm^3. Orbital volume doubles in the first year of life and is dependent on the presence of the globe.

The eye is described as having an anterior segment (including conjunctiva, episclera and the externally visible portion of sclera, cornea, anterior chamber, iris and lens) and a posterior segment (including vitreous cavity, retina, retinal pigment epithelium and choroid and posterior sclera). The ophthalmic artery (a branch of the internal carotid artery) supplies the eyelids and orbit. The central retinal artery branches off the
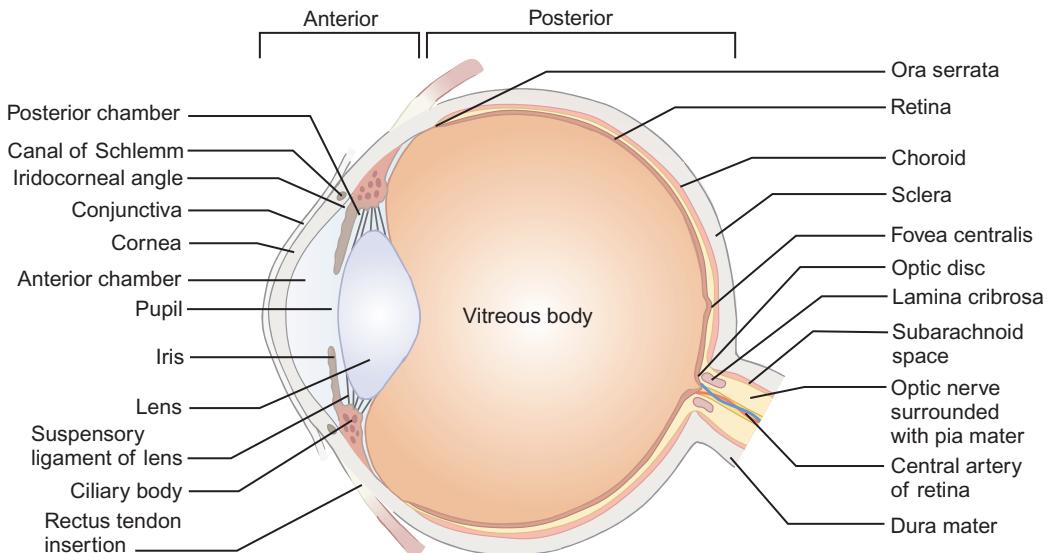
Fig. 30.3 Anatomy of the developed eye.

ophthalmic artery to enter the eye via the optic nerve head, supplying the inner layers of the retina (and, in the fetus, the lens via the hyaloid artery system). The posterior ciliary arteries, derived from the ophthalmic artery, anastomose within the choroid to supply the retinal pigment epithelium and outer layer of the retina, including the photoreceptors. A blood–ocular barrier exists to protect the eye from toxic substances: the blood–retina barrier is maintained by the tight junctions in the retinal capillary bed and between retinal pigment epithelial cells, and the blood–aqueous barrier by the tight junctions of the ciliary epithelial cells. Inflammation, as seen in uveitis, breaks down the blood–ocular barrier, allowing inflammatory cells and proteins to enter the aqueous and vitreous from the circulation.

The eye is also immunologically isolated (privileged): if antigens from the eye enter the systemic circulation, for example following penetrating eye injury, this can result in an autoimmune attack on the other eye – a devastating, potentially blinding condition called sympathetic uveitis.

Sensation from the orbit is conveyed via the ophthalmic division of the trigeminal nerve. Neuronal connections exist between the trigeminal nucleus and the parasympathetic dorsal nucleus of the vagus nerve. Pressure on the eye(s) during retinopathy of prematurity screening or the traction on the muscles during squint surgery can result in bradycardia and respiratory depression. Immediate cessation of the stimulus combined with administration of an antimuscarinic agent, such as atropine, can reverse the effect. Motor innervation of the orbit is discussed later in this chapter.

The structure of the retina

The retina is a complex, multi-layered neural structure lining the posterior segment of the globe. It is continuous with the optic nerve posteriorly and fuses anteriorly with the epithelium of the ciliary body at the ora serrata. The retina and retinal pigment epithelium (RPE) are derived from two neuroectodermal layers separated by a potential space. A retinal detachment occurs when fluid enters this space, peeling the retina from the underlying RPE. The retina itself is made up of many layers of neural cells: the outermost layer of the retina is made up of the photoreceptors, rods and cones, which receive metabolic and nutritional support from the underlying RPE and choroid. Central and colour vision is provided by the macular retina, the centre of which is called the fovea.

Rods are sensitive to low levels of light and are most numerous in the retinal periphery, giving peripheral and night vision. Cones are classified according to the sensitivity of their photo-pigment: long (red), medium (green) and short (blue) wavelengths. The fovea is responsible for visual acuity; cell bodies and axons of the inner retina are displaced peripherally at the fovea, making it the thinnest area of the retina and affording its tightly packed cone photoreceptors (147,000/mm^2) optimal exposure to incident light. The photoreceptors are the sensory receptors of the retina, the bipolar cells, situated in the inner retina, are the first order neurons and the retinal ganglion cells (RGC), situated in the innermost layer, are the second order neurons. The RGC axons traverse the surface of the retina in the nerve fibre layer on the surface of the retina and then travel within the optic nerve to synapse

in the lateral geniculate body. For optimal light transference to the underlying photoreceptors, the RGC axons are only myelinated distal to the optic disc, so that they remain transparent. Sometimes the myelination process occurs anterior to the optic disc, giving a white appearance to the nerve fibre layer; although striking in appearance, myelinated nerve fibres rarely cause visual problems unless they involve the macula.

Methods of visualizing the fundus

- Direct ophthalmoscope
- Indirect ophthalmoscope
- Retcam imaging
- Ocular coherence tomography
- Standard retinal photography
- Fluorescein angiography

Although portable and cheap, the direct ophthalmoscope is the most difficult method of visualizing the fundus in children: it gives a real, magnified image but small field of view with no depth, making fundoscopy difficult in young children. In this situation, the head-mounted indirect ophthalmoscope is the instrument of choice, giving a stereoscopic, less magnified image with a much wider field of view. The virtual nature of the image, inverted both vertically and horizontally, can be confusing for the novice and the technique can take years to master. The Retcam is a wide-angle camera, which can usefully document the fundus appearance and is particularly useful for retinopathy of prematurity and retinal haemorrhages secondary to inflicted head injury. Its drawback is that the camera lens makes contact with the cornea, making it poorly tolerated in alert babies and toddlers. Most children over 5 years of age are able to sit still for standard retinal photography.

Ocular coherence tomography has been a great advance in retinal imaging, enabling a detailed cross-sectional image of the retina and optic disc to be constructed. This can be particularly helpful when macular pathology is suspected or to document changes over time, for instance, serial nerve fibre layer thickness analysis in papilloedema. Intravenous fluorescein angiography is useful for demonstrating the vascular network of the retina, particularly areas of ischaemia or vascular leakage. Once visualized by fluorescein angiography, the areas of retinal ischaemia can be lasered to prevent secondary neovascularization.

Prematurity and the eye

Retinopathy of prematurity

Vascularization of the retina begins at about 14 weeks' gestation and is not complete until term. It is stimulated by vascular endothelial growth factor (VEGF-A) and insulin-like growth factor (IGF-1), which work synergistically. VEGF production is induced by physiological fetal retinal hypoxia, whilst IGF-1 is oxygen independent, with rising levels stimulating retinal angiogenesis during the second and third trimesters.

Retinopathy of prematurity (ROP) is a neovascular disorder affecting infants born at less than 32 weeks' gestational age. Extremely low birth weight (<1000 g) and early supplemental oxygen requirement and acidosis are additional important risk factors. About 50% of premature babies born <1000 g birth weight will develop ROP and 15% will reach the threshold for treatment. In the UK, guidelines specify that all babies under 32 completed weeks' gestation and less than 1500 g should be screened by an ophthalmologist.

ROP develops in two distinct phases:

- The *hyperoxic phase*: premature delivery into a high oxygen environment causes down-regulation of VEGF, halting the normal progression of vascular tissue into the developing anterior retina
- The *hypoxic phase*: the unvascularized anterior retina becomes increasingly ischaemic as it matures, VEGF is up-regulated and leads to neovascularization from the ridge of mesenchymal spindle cells at the anterior border of the vascularized retina. Untreated, the abnormal new vascular network creates a tractional retinal detachment and blindness.

The international classification of ROP includes stages of ROP development and zones of location in the retina (Fig. 30.4). Zone 1 and posterior zone 2 ROP is the most aggressive. The threshold for treatment is based on the zone of the disease, its stage, and the presence of retina vascular dilatation and tortuosity – 'plus' disease. Timely treatment can prevent progression to retinal detachment and blindness. Recently, a correlation between a drop-off in postnatal weight gain (which mirrors a fall in IGF-1 levels) and the subsequent development of ROP has been identified. A computer-based algorithm based on postnatal weight gain (WINROP) is being developed, which may help future identification of those babies most at risk.

Currently, laser ablation of the avascular, ischaemic anterior retina is the preferred treatment for severe ROP. A promising new treatment is the intra-vitreal injection of an anti-VEGF agent (bevacizumab or ranibizumab). Although this treatment is easier and quicker to perform than laser, systemic absorption depresses serum VEGF levels for several weeks, which may have systemic consequences. The resultant prolonged absence of VEGF within the eye also delays the

Stages of retinopathy of prematurity (ROP)	Zones of ROP (left eye)
Stage 1: Demarcation line at anterior edge of vascularized retina Stage 2: The line becomes a thickened ridge Stage 3: The ridge develops neovascularization Stage 4: Localized tractional retinal detachment Stage 5: Funnel retinal detachment	
Plus disease: Dilatation and tortuosity of the retinal vessels **Aggressive posterior ROP (APROP):** Zone 1 disease, neovascularization is not localized to a ridge	
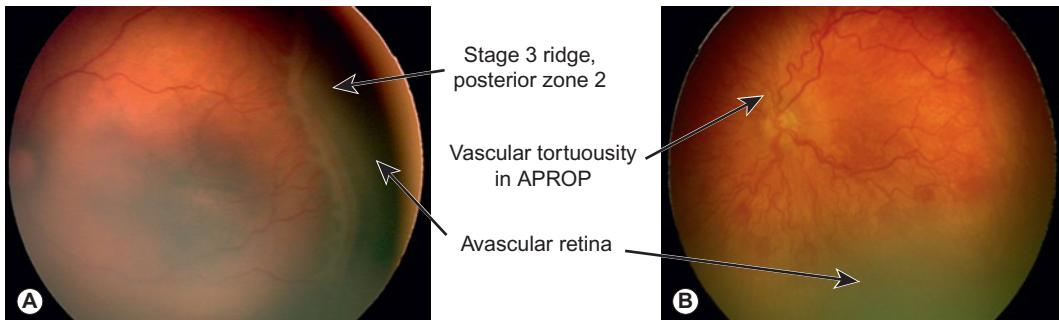
Fig. 30.4 Stages and zones in retinopathy of prematurity. A. This Retcam image shows stage 3 ROP with a neovascular ridge in the temporal retina of a left eye; the avascular, ischaemic retina lies anteriorly. B. This Retcam image shows aggressive posterior ROP (APROP) in zone 1 of a left eye. The neovascular tissue in APROP lies flat on the retina rather than forming a ridge, which can make identification difficult. Note the vascular tortuosity and dilatation signalling 'plus' disease.

Question 30.1

Ocular structures
The following (A–J) are ocular structures:
A. Aqueous
B. Ciliary body
C. Cornea
D. Lens
E. Optic nerve head
F. Retina
G. Retinal pigment epithelium
H. Trabecular meshwork
I. Uveal tract
J. Vitreous gel

Which tissue is the primary site of pathology in the following conditions? Select ONE answer for each. Each answer may be used once, more than once or not at all.
1. Toxoplasma choroiditis
2. Infantile glaucoma
3. Accommodative insufficiency

Answer 30.1

1. I. Uveal tract. The choroid is part of the uveal tract and is the site of ocular toxoplasma infection.
2. H. Trabecular meshwork. The primary cause of infantile glaucoma is a congenital anomaly of the trabecular meshwork; eventually breaks in Descemet's membrane of the cornea and optic nerve damage in addition to globe enlargement occur.
3. B. Ciliary body. Accommodation is centrally mediated and stimulated by vision de-focus. Insufficient contraction of the ciliary body prevents the lens from becoming more globular and powerful. In adults, accommodative insufficiency occurs beyond the age of 45 years due to the aging lens losing its malleability, but this is not the case in children.

normal vascularization of the anterior retina, leaving it non-perfused and ischaemic for months beyond term. In the UK, anti-VEGF treatment is currently reserved for the most severe cases in which laser treatment is not possible or sufficiently effective. Randomized, controlled trials are planned to determine the safety of this new treatment.

Congenital and developmental eye conditions

Childhood cataract

Cataracts may be present at birth or develop and become visually significant with time. The lens grows in size throughout life as layer upon layer of lens fibres are laid down, encircling the fetal and embryonic nucleus like layers of an onion. The lens has the highest protein content of any tissue in the body and is transparent because of the accurate organization of the proteins (called crystallins) in fibres within it; disorganized protein fibre structure or the accumulation of abnormal metabolic products within the lens causes opacification.

Congenital cataract

Cataracts occur in 2/10,000 live births and are usually identified at screening. Although the majority are idiopathic, 20% of children with isolated bilateral congenital cataracts will have a family history or parental consanguinity; the cataracts are often secondary to point mutations (in genes such as *MAF, CRYA1*). Cataracts are common features of many different syndromes, particularly Down's syndrome (1.5% prevalence); they may also complicate other ocular malformations, such as aniridia. Babies with sporadic bilateral congenital cataracts should have a TORCH and galactosaemia screen and a referral for genetic evaluation. Males should additionally have a urinary amino acid assessment to exclude Lowe syndrome.

Unilateral congenital cataracts most commonly result from abnormal regression of the embryological hyaloid vascular system, which supplies the posterior lens during development (persistent fetal vasculature). Unilateral cataracts are usually associated with mild microphthalmia and are not generally investigated.

Cataracts developing after the critical period of neuroplasticity (see Chapter 4, Normal child development) are usually associated with a better visual prognosis. These may be genetic in aetiology but may also be secondary to uveitis, steroid therapy and radiation.

Management of childhood cataract

Visually significant congenital cataracts require early surgery within the first two months of life to achieve good visual function. Less dense cataracts may be managed conservatively with close observation and refractive correction. If the cataracts are unilateral or asymmetrical, occlusion therapy (patching) of the better-seeing eye may be prescribed.

Infants and children develop especially severe ocular inflammation and fibrotic changes following intra-ocular procedures. To prevent re-opacification of the visual axis with scar tissue, the posterior capsule and anterior vitreous are removed during the lensectomy procedure and an intensive topical steroid regimen is prescribed postoperatively. Some paediatric ophthalmologists elect to implant the eye with an acrylic intra-ocular lens (IOL) at the time of lensectomy if the globe is otherwise normal; others leave the eye aphakic (without a lens) and replace the refracting power of the lens with a contact lens until the child is older. Since they are not exchangeable, an IOL refractive power is selected to leave the eye hypermetropic, to allow for the physiological myopic shift which occurs during ocular growth. This residual hypermetropia is usually corrected with an extended wear contact lens for the first year and glasses thereafter.

Childhood glaucoma

Childhood glaucoma is a rare, potentially blinding condition characterized by raised intra-ocular pressure and optic disc cupping. In the normal optic nerve head, the retinal ganglion cell (RGC) axons are concentrated around the circumference of the optic disc, leaving a pale central area relatively devoid of axons, called the optic cup. The raised intra-ocular pressure of glaucoma causes RGC death and, as the number of axons passing through the optic nerve head opening dwindles, the relative size of the optic cup (the cup : disc ratio) gradually enlarges. Uncontrolled glaucoma will result in peripheral visual field loss, which is difficult to detect in children. The RGCs serving the macula are the last to be damaged; this is why the optic neuropathy associated with glaucoma is not characterized by the early loss of visual acuity or colour vision that is seen with optic neuritis or optic atrophy.

The normal intra-ocular pressure in children is usually between 6 and 18 mmHg and can usually be measured in the eye clinic. Raised intra-ocular pressure is the result of impaired aqueous outflow through the trabecular meshwork rather than overproduction of aqueous by the ciliary body. Children under 3 years of age have low scleral rigidity, and raised intra-ocular pressure will result in globe expansion (buphthalmos); the increase in axial length causes a shift towards

myopia (or loss of hypermetropia) and an increasing corneal diameter (normal corneal diameter is 11 mm).

Primary congenital glaucoma

Presenting within the first year of life, this is usually bilateral, and results from abnormal development of the drainage angle. Incidence is 1/10,000 live births and the majority are due to a gene mutation (in the *CYP1B1* gene). The globe enlarges due to the raised pressure and splits occur in the deeper layers of the cornea (Haab's striae) leading to photophobia and corneal opacification. Treatment is by the early surgical division of the abnormal 'Barkan membrane' which obstructs fluid flow to the drainage angle.

Secondary glaucoma

Causes of secondary glaucoma are:

- Anomalies of the anterior segment, e.g. aniridia
- Sturge–Weber syndrome: if the capillary malformation involves the eyelids, the episcleral venous pressure may be raised, reducing aqueous outflow and causing glaucoma in 50%
- Following congenital cataract surgery (30% lifetime risk), possibly due to the release of vitreous derived factors or inflammatory cells into the drainage angle in infancy
- Topical, inhaled or oral steroid therapy: due to the increased accumulation of glycosaminoglycans or trabecular meshwork-inducible glucocorticoid response protein (TIGR) in the trabecular meshwork.

Retinal pathology due to non-accidental head injury

The tangential acceleration/de-acceleration injury to which an infant may be subjected in non-accidental injury can result in vascular shearing – in the brain, this results in subdural haemorrhage; in the retina it causes multiple, multi-layer haemorrhages and retinoschisis (splitting of the layers of the retina). Multiple retinal haemorrhages, especially when associated with subdural haemorrhage, are characteristic of (but not specific to) non-accidental head injury. Clotting and metabolic conditions, such as glutaric aciduria, should be excluded. The presence of retinoschisis and perimacular folds indicate significant vitreous traction, which may be the result of severe accidental or non-accidental head injury.

Patterns of retinal injury (Fig. 30.5) are:

- Dark, round sub-retinal haemorrhages, often with a white centre, occur in the potential space between the retina and RPE (resolve within months)
- Dot- and blot-shaped intra-retinal haemorrhages (resolve within weeks)
- Flame-shaped nerve fibre layer haemorrhages (resolve within days)
- Pre-retinal (sub-hyaloid) haemorrhages lie in the potential space between the posterior hyaloid (vitreous) surface and the retina. The retina beneath is obscured by the haemorrhage and there is often a blood fluid level.

Sub-retinal haemorrhages

Deep retinal haemorrhages

Perimacular folds

Nerve fibre layer haemorrhages
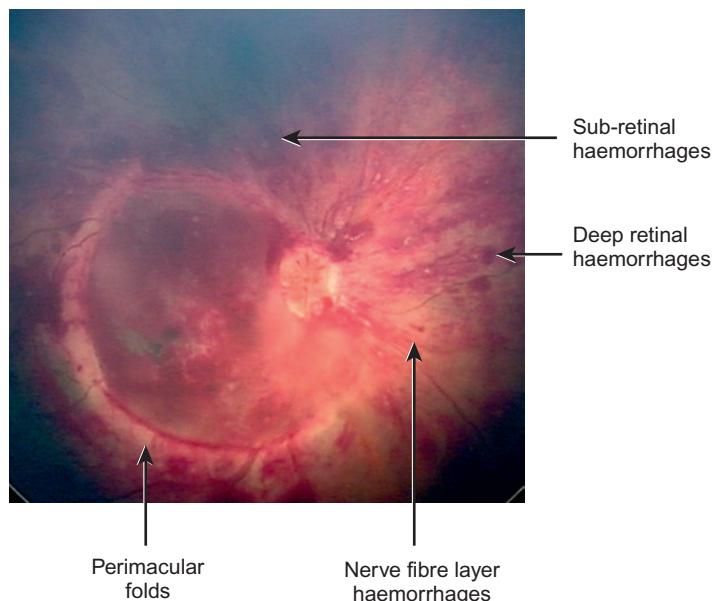
Fig. 30.5 Retinal findings in severe non-accidental head injury. This Retcam photo of the right eye shows severe multi-layer retinal haemorrhages and a marked perimacular fold with retinoschisis (retinal splitting) at the macula.

- Vitreous haemorrhage, caused by the rupture of a pre-retinal haemorrhage into the vitreous
- Retinoschisis and perimacular folds: infant vitreous is viscous and strongly adherent to the retina; severe vitreous traction causes a splitting of the inner retinal layers, elevating the retina into folds encircling the macula.

Retinal dystrophies

The phototransduction cascade

Phototransduction is the process by which light is converted into electrical signals. The electrical transmission of the light response can be assessed using an electrodiagnostic test called an electroretinogram. This investigation first tests the rod pathway after dark adaptation using a dim light to which cones are insensitive, then the cone pathway after light adaptation to a bright flash and flicker light stimulus (to which rods are unable to respond).

The phototransduction pathway relies on many proteins, and therefore retinal dysfunction due to mutation or deletion of genes encoding these proteins is common. Eight per cent of males are affected by mutations of the cone pigments, which alter their spectral sensitivity (congenital colour blindness). More significantly, hundreds of different gene mutations have been implicated in the development of retinal and macular dystrophy, which are currently untreatable and responsible for a quarter of all childhood blindness in the UK.

Retinal dystrophies can develop at any stage in childhood. In general terms, they can be non-progressive, for instance due to a channelopathy, or progressive, for instance due to ongoing cell death from the accumulated toxic metabolic products, e.g. *RDS* gene mutation in autosomal dominant retinal dystrophy. Rod dystrophies cause poor peripheral and night vision (nyctalopia), cone dystrophies cause poor colour vision and visual acuity, often with photophobia (due to defective light adaptation). Macular dystrophies affect the macula only, causing poor central and colour vision but sparing the peripheral visual field.

The visual pathway

The anterior visual pathway

Isolated damage to the optic nerves, optic chiasm and optic tract produce characteristic visual field defects (Fig. 30.6): bitemporal hemianopia caused by chiasmal lesions, homonymous hemianopia caused by lesions of the optic tract, optic radiation and occipital cortex. In practice, however, the visual field deficit is

Light reflex pathway

Light reflex
Ciliary ganglion
Midbrain
Lateral geniculate body
Edinger-Westphal nucleus
Pretectal nucleus
Visual cortex

Lesions of the visual pathway and expected visual field deficit

Lesion 1: Right optic nerve lesion
Poor vision right eye, central scotoma

Lesion 2: Chiasmal lesion
Bitemporal hemianopia

Lesion 3: Right optic tract lesion
Incongruous left homonymous hemianopia

Lesion 4: Right optic radiation lesion
Congruous left homonymous hemianopia

Fig. 30.6 The visual pathway. The temporal retina of the right eye and nasal retina of the left eye serve the left visual field. Axons from the nasal retina decussate at the optic chiasm and thereafter axons serving the left visual field travel together in the optic tract and radiation. Visual field deficit resulting from pathology at each point in the pathway is shown on the right. Posterior lesions produce more congruous (similar) homonymous field deficit than anterior lesions. The anatomy of the pupillary light reflex is illustrated on the left. Pupillary fibres leave the optic tract and synapse in the pretectal nuclei of the midbrain. The parasympathetic nucleus of the IIIrd nerve receives bilateral innervation and its fibres supply the pupil sphincter after synapsing in the ciliary ganglion.

rarely so clear cut. For instance, a child with an optic chiasmal glioma may have a bitemporal hemianopia due to chiasmal involvement, but anterior extension into the optic nerve may leave the child with functional vision in the contralateral nasal hemifield only.

The posterior visual pathway

The optic radiations originate in the neurons of the lateral geniculate nucleus (LGN); neurons from the lateral portion of the LGN, conveying the homonymous superior visual field, fan out laterally and inferiorly around the tip of the inferior horn of the lateral ventricle and *s*wing posteriorly, terminating in the inferior lip of the calcarine fissure of the occipital cortex. Neurons from the medial portion of the LGN, conveying the homonymous inferior visual field, pass almost directly posteriorly, in the retrolentiform part of the internal capsule before terminating in the superior lip of the calcarine fissure of the occipital cortex.

The visual cortex consists of the primary and secondary visual area situated, for the most part, on the deep calcarine sulcus on the posteromedial surface of the hemisphere. The macular area is represented in the most posterior third of the visual cortex.

Dorsal and ventral streams of visual processing

Visual processing and cognitive visual function occur via white matter connections linking visual cortex with the posterior parietal cortex (the dorsal stream) and the inferotemporal cortex (the ventral stream).

Functions of the dorsal stream are:

- Visual searching
- Attention to detail in a complex visual environment
- Visual guidance of actions

Parietal lesions cause inaccuracy of voluntary saccadic and pursuit eye movements (visual ataxia).

Functions of the ventral stream are:

- Route finding
- Word/letter face recognition
- Recognizing expression

Right temporal lobe injury causes poor recognition of people (prosopagnosia). Left temporal lobe injury causes impaired shape recognition (dyslexia).

Cerebral visual impairment

Cerebral visual impairment (CVI) accounts for 30% of SVI registrations in the UK and is usually associated with other developmental and motor deficits. The term encompasses impaired visual acuity, visual field deficit and abnormalities of perceptual and cognitive visual function secondary to brain pathology.

CVI can result from:

- CNS developmental defects such as holoprosencephaly (failed or incomplete separation of the forebrain)
- Perinatal insults
  - Prematurity, e.g. periventricular leukomalacia (PVL), intraventricular haemorrhage
  - Term infants: hypoxic–ischaemic encephalopathy
- Older children: hypoxia, trauma, visual pathway tumours, metabolic encephalopathy

Ex-premature babies with PVL have visual ataxia and poor processing of complex visual environments (damage to the dorsal stream) and also bilateral inferior homonymous hemianopia (damage to the superior fibres of the optic radiation). These children often have bilaterally pale, cupped but normal sized optic nerve heads due to trans-synaptic, retrograde degeneration of the RGCs secondary to axon injury within the optic radiation.
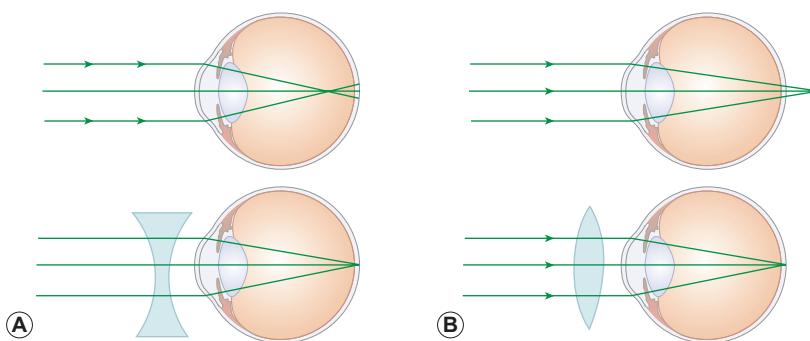
Fig. 30.7 **The optics of the eye with refractive error. A. Myopia: image focused anterior to the retina, corrected with concave (minus) lens. B. Hypermetropia: image focused posterior to the retina, corrected with convex (plus) lens.**

Question 30.2

Diplopia and headaches after reading

A 7-year-old systemically well child with good visual acuity and no refractive error has developed intermittent horizontal diplopia associated with headaches after reading over the last few months. Eye movement testing shows a full range of eye movements, with no movement on cover testing for distant targets but an exotropia (divergent squint) for near targets.

Which diagnosis is the more likely? Select ONE answer only.

A. Bilateral sixth nerve palsy
B. Convergence insufficiency
C. Dyslexia
D. Myasthenia gravis
E. Uncorrected hypermetropia (long sight)

Answer 30.2

B. Convergence insufficiency.

Convergence insufficiency is a relatively common problem in school-aged children and refers to a reduced ability to converge the eyes on near targets. This causes symptoms of eye strain and diplopia when reading. Bilateral sixth nerve palsy would cause an esotropia (eye turns inwards) for distance targets. Uncorrected hypermetropia is excluded by the normal refraction. Myasthenia gravis causes variable ptosis and diplopia with fatiguability; the absence of ptosis in this case makes this diagnosis unlikely. Dyslexia does not cause squint.

Optics

The normal refractive state of the eye

Focusing a distant image in an optical system of 22 mm requires 50 dioptres (D) of refractive power. In the human eye, about 44D is provided by the cornea and the rest is provided by the lens. The lens is malleable and becomes more globular with accommodation, thereby increasing its power and allowing near objects to be focused on the retina. Most infants are hypermetropic, a gradual process of emmetropization occurring in the first 5 years. Amblyopia is poor vision in one or either eye which persists once any existing ocular or refractive anomaly is corrected. It is usually unilateral and results from visual deprivation (e.g. congenital cataract), strabismus or refractive error. Amblyopia may occur and be treated within the period of visual neuroplasticity (see Chapter 4, Normal child development).

Refractive error

Myopia (short-sightedness) occurs when either the refracting power of the lens is too strong or, more commonly, when the eye is long in proportion to the refracting power of the lens (Fig. 30.7). A concave lens is required to achieve a focused image on the retina.

Hypermetropia (long-sightedness) occurs when either the power of the lens is too weak (or absent – aphakia) or the eye is short in proportion to the refractive power of the eye (see Fig. 30.7).

Astigmatism occurs usually because the cornea has a steeper curvature and refractive power in one meridian, which leads to a blurred focal point.

Anisometropia refers to presence of unequal refractive states in each eye.

Accommodation

The triad of the near reflex includes accommodation, miosis (pupil constriction) and convergence. Near image de-focus causes parasympathetic stimulation of the ciliary muscle and the sphincter pupillae, releasing zonular tension on the lens and allowing it to become more globular and powerful. Accommodation is temporarily paralysed using topical antimuscarinic agents

Question 30.3

Abnormal ocular findings

The following (A–J) is a list of ocular findings:

A. Anisocoria
B. Buphthalmos
C. Enophthalmos
D. Incomitant strabismus
E. Keratitis
F. Lagophthalmos (poor or incomplete lid closure)
G. Microphthalmia
H. Proptosis
I. Ptosis
J. White blood cells in the anterior chamber

Choose the most likely ocular finding which accompanies the following pathologies. Select ONE answer for each. Each answer may be used once, more than once or not at all.

1. Bilateral sixth nerve palsy
2. Unilateral seventh nerve palsy
3. Positive anti-nuclear antibody

1. D. Incomitant strabismus. Bilateral sixth nerve palsies cause an esotropia (one or both eyes turn inward) in primary position and poor abduction of each eye. This is a common false localizing sign of raised intracranial pressure in children.
2. F. Lagophthalmos (poor or incomplete lid closure). The VIIth nerve innervates orbicularis oculi – this causes incomplete lid closure and corneal exposure.
3. J. White blood cells in the anterior chamber. Juvenile idiopathic arthritis with positive anti-nuclear antibody may cause a painless chronic anterior uveitis, which allows white cells to leak into the aqueous humour.

in order to objectively measure refractive error. The ability to accommodate decreases exponentially with age and requires virtually no effort in infancy whilst being irretrievably lost at the age of about 45 due to increasing lenticular rigidity.

Innervation of the eye and ocular motility

Six extra-ocular muscles control eye movement and these are supplied by cranial nerves III–VI. An aide memoir is $LR_6(SO_4)$ (Table 30.1). Conjugate movement of each eye is necessary so that the image falls on identically corresponding positions on each retina. This necessitates fine coordination of all 12 muscles within the CNS. Visual feedback of de-focus and transient diplopia permits fine adjustments to be made, a cerebral process called fusion.

Laws of innervation

Hering's law

During purposeful eye movement, equal and simultaneous stimulation of the yoke muscles is required. There are six sets of yoke muscles, as shown in Figure 30.8. For instance, a boy with a right sixth nerve palsy will tend to use the left eye to fixate the examiner and the right eye will have a convergent squint. If asked to fixate with the paretic right eye, additional stimulation will flow to the right lateral rectus to try to keep the eye straight. The yoke muscle, the left medial rectus, will similarly receive additional stimulation causing additional overaction and a larger squint angle.

Sherrington's law of reciprocal innervation

In the eye, stimulation of the agonist muscle must be accompanied by inhibition of its antagonist to allow movement.

Table 30.1 The cranial nerves supplying the orbit

Cranial nerve	Structure innervated	Main action on the eye	Result of dysfunction
III Oculomotor			'Down and out' eye with ptosis
Superior division	Levator palpebrae superioris Superior rectus (SR)	Upper lid elevation Elevation	Ptosis Poor elevation
Inferior division			
	Medial rectus (MR) Inferior rectus (IR) Inferior oblique (IO)	Adduction Depression Elevates the adducted eye, outward rotation	Poor adduction Poor depression
IV Trochlear	Superior oblique (SO)	Depresses the adducted eye, inward rotation	Problems reading/going downstairs Reduced depression in the adducted eye, head tilt
V Trigeminal sensory	Conjunctival, cornea, iris and uveal tissue, facial skin	Provides sensation	Corneal anaesthesia, facial numbness
VI Abducens	Lateral rectus	Abduction	Poor abduction, convergent squint
VII Facial	Orbicularis oculi	Lid closure	Poor lid closure, paralytic ectropion
Parasympathetic (via III)	Pupillary sphincter Ciliary muscle	Miosis (small pupil) Accommodation	Adie pupil: Poorly reacting large pupil, poor near vision
Sympathetic (via VII)	Pupil dilators, iris melanosomes	Mydriasis (large pupil), iris pigmentation	Horner syndrome: Small pupil which dilates poorly in dark Lighter iris (heterochromia) if congenital
	Müller muscle of lids	Mild upper and lower lid retraction	Mild upper and lower lid ptosis, pseudo-enophthalmos
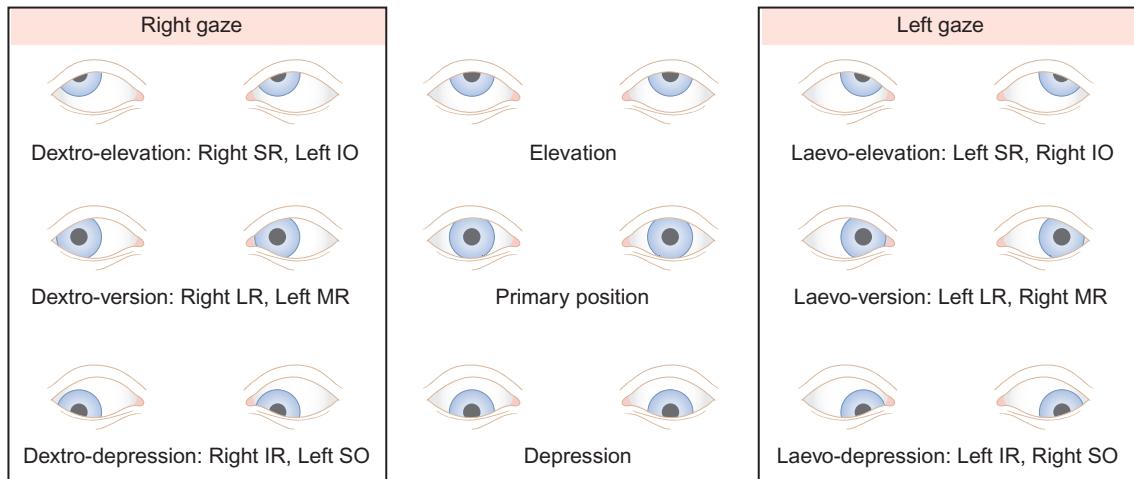
Fig. 30.8 The nine positions of gaze and six pairs of yoke muscles. SR: Superior Rectus; IO: Inferior oblique; LR: Lateral Rectus; MR: Medial Rectus; IR: Inferior Rectus; SO: Superior obleque.

Concomitant squints

Most childhood ocular misalignment is concomitant, i.e. the squint angle is the same in all positions of gaze and is due to refractive error, accommodation issues or poor cortical fusional mechanisms.

Hypermetropic children accommodate when not wearing glasses in order to keep targets focused. The power of accommodation declines exponentially from birth and, at the age of 2–3 years, when the child is doing more detailed close viewing, the resultant accommodative strain stimulates over-convergence and a convergent squint (esotropia). In order to prevent diplopia, the child sacrifices binocularity for clarity and a process of cerebral visual suppression in one eye occurs, subsequently leading to amblyopia. Early correction with glasses can restore binocularity and prevent amblyopia.

Myopic children tend to have weaker accommodation; their problem is too much refracting power in their eyes. This weakened accommodation can lead to poor accommodative convergence and they have a tendency to develop a divergent squint (exotropia).

Children with poor vision in one eye, for instance due to retinoblastoma or cataract, will tend to develop an early squint. For this reason, fundoscopy should be attempted in all children who present with a squint. Children with developmental delay and cerebral palsy have poor cortical fusion mechanisms and are at high risk of developing a squint and amblyopia.

Incomitant squints

Cranial nerve palsy will cause an incomitant squint, i.e. the squint angle changes depending on the position of gaze. This may occur due to a congenital dysinnervation syndrome (e.g. Duane syndrome), or may be acquired though trauma or tumour. Raised intracranial pressure commonly causes VIth nerve paresis in children; a recent onset squint and diplopia in a child merits fundoscopy.

Children with cranial nerve palsies are at risk of developing strabismic amblyopia and those young enough to be in their neuroplastic period need referral to an ophthalmologist for amblyopia management.

Clinical investigation of squint

Ocular misalignment can be detected using the cover test. Manifest deviations can be identified by studying the corneal light reflections, which will appear displaced to the nasal side of the pupil in an exotropic eye and towards the lateral side of the pupil in an esotropic eye. Covering the fixating eye (cover test) will cause a corrective movement in the squinting eye (inwards in exotropia and outwards in esotropia) to enable it to take up fixation. Latent squints are more difficult to identify and require interruption of binocular fusion by the uncover and alternating cover test. When either eye is covered, the covered eye will drift into misalignment and the recovery motion will be seen when the cover is removed.

Management of squint

Optical correction of refractive error and amblyopia therapy are central to squint management in children. Once amblyopia is treated, surgical management of the squint can proceed. The main techniques involve weakening muscles by moving the insertion of the muscle posteriorly (recession) or tightening muscles by making them shorter (resection). The majority of squint operations are cosmetic; about 20% are functional, aimed at restoring a child's binocularity. Sometimes, particularly in the complex incomitant squints seen with CNS tumours, surgery is not helpful and prismatic glasses or the occlusion of one eye may be the only solution to intractable diplopia.

Inter-nuclear control of conjugate horizontal eye movement

The horizontal gaze centre – the paramedian pontine reticular formation (PPRF) – receives supra-nuclear stimulation from the eye movement centres and co-ordinates the innervation between the ipsilateral VIth nerve nucleus and the contralateral medial rectus sub-nucleus of the IIIrd nerve. The inter-nuclear fibres travel within the medial longitudinal fasciculus (MLF) and may be damaged by Arnold–Chiari malformation (downward displacement of the cerebellar tonsils), hydrocephalus, fourth ventricle and brain-stem tumours and trauma.

- PPRF lesions cause a palsy of conjugate horizontal gaze towards the side of the lesion.
- MLF lesions cause ipsilateral absence of adduction and nystagmus in the abducted contralateral eye (aide memoir: iPAD – *i*psilateral *p*oor *ad*duction).
- PPRF and ipsilateral MLF lesions cause one-and-a-half syndrome, an ipsilateral absence of adduction and an ipsilateral horizontal gaze palsy (the only horizontal movement is abduction with nystagmus of the contralateral eye).

Supra-nuclear control of eye movements

Horizontal gaze

Voluntary saccadic eye movements

Conjugate saccades towards one side are mediated by the contralateral fronto-mesencephalic pathway (from the frontal eye field via the superior colliculus to the PPRF). Frontal lesions cause tonic deviation of the eyes *towards* the side of the lesion due to the unbalanced input from the other hemisphere.

Voluntary pursuit eye movements

Conjugate pursuit movements towards one side are mediated by the ipsilateral parieto-occipital mesencephalic pathway via the PPRF. Deep parietal lesions cause disrupted pursuit *towards* the side of the lesion.

Vestibular eye movements

These are mediated by the contralateral labyrinthine–pontine pathway and can be useful for assessing brain-stem and VIth nerve function:

- *Doll's head manoeuvre*: sudden rotation to the left stimulates the left horizontal semicircular canal causing slow conjugate eye movement to the right.
- *Rotational testing*: hold the baby at arm's length with his/her head tipped forward slightly, if possible. As the infant is slowly rotated, the eyes will deviate towards the direction of the spin, with a re-fixational jerk nystagmus to the opposite side.

Vertical gaze

Projections from the frontal eye fields, vestibular apparatus and PPRP innervate the rostral interstitial nucleus of the MLF, which lies dorsomedial to the red nucleus in the midbrain. From here, control of upward saccades passes dorsally through the posterior commissure to the IIIrd nerve nuclei. Control of downwards saccades passes dorsally and caudally to the IIIrd and IVth nerve nuclei.

Transient benign tonic downgaze deviation of both eyes (with normal upward movements on doll's head testing) can be seen in normal neonates and resolves within months. The 'sun-setting' sign is a tonic downward deviation of the eyes secondary to aqueductal distention from hydrocephalus; upward saccades cannot be generated by doll's head movement. Dorsal midbrain (Parinaud's) syndrome causes a supra-nuclear paresis of vertical gaze, often with light–near dissociation and convergence–retraction nystagmus.

Question 30.4

Lack of eye contact at 9 weeks

An infant is seen at the 9-week baby check and her mother is concerned that her baby is not maintaining eye contact with her. There is no family history of eye problems and, in other respects, the infant is developing normally. During your examination, the baby stares at light but does not follow a large target well; horizontal nystagmus is present but the red reflex is normal.

What is the most appropriate management plan? Select ONE answer only.

A. Advise the mother that you will organize an optometric assessment

B. Arrange a routine orthoptic assessment

C. Arrange for the child to attend the emergency eye clinic

D. Reassure the mother and arrange a review in a month to reassess the visual development

E. Refer the baby for an urgent appointment for paediatric ophthalmic assessment

Nystagmus

Descriptive terms used in documenting nystagmus

Nystagmus is a rhythmic oscillation of the eyes and may be described using the following terms:

- Type:
  - Pendular: phases of equal velocity
  - Jerk: phases of unequal velocity
- Direction: the direction of the fast component
- Plane: horizontal, vertical, rotatory
- Amplitude: coarse, medium, fine
- Rate: slow, fast
- Conjugacy: both eyes demonstrate the same movement
- Null zone: a point of gaze in which the nystagmus intensity is minimal

Physiological nystagmus

Nystagmus can be physiological; types include optokinetic nystagmus, rotational nystagmus, caloric nystagmus or end-point nystagmus (seen at extremes of gaze or after sustained deviation of the eyes). Gaze-evoked nystagmus can often be seen as a consequence of therapeutic doses of anti-convulsants.

Pathological nystagmus

Causes of nystagmus fall into three major categories:

- Infantile sensory nystagmus (due to poor vision/afferent system problems, e.g. aniridia, albinism)
- Infantile idiopathic motor nystagmus (the most common form with otherwise normal ocular and neurological function)
- Acquired nystagmus secondary to neurological disease
- Acquired vestibular nystagmus

Infantile nystagmus

Infantile nystagmus is often noticed by the parents in the first few months of life. It has several characteristic features:

- Usually horizontal (but can be vertical or rotatory), uniplanar, i.e. does not change plane in different positions of gaze
- Usually jerk but may be pendular
- Conjugate and similar in amplitude in both eyes
- May have associated head oscillation
- Null point of gaze where the nystagmus is less marked. The child will often adopt a head posture to put his/her eyes in that position of gaze
- Nystagmus is usually dampened by convergence, so near vision is better than distance vision
- Nystagmus worsens when one eye is covered

Infants with nystagmus should be seen by an ophthalmologist to exclude a causative ocular abnormality. If the child's visual development, eye examination, visual electrodiagnostics and general development are normal, idiopathic motor nystagmus (IMN) is diagnosed. X-linked IMN may result from gene mutations in *FRMD7*.

Acquired nystagmus due to neurological disease

Disconjugate nystagmus should trigger concern about potential neurological disease. The pattern of nystagmus can help to localize the pathology.

- *See-saw nystagmus*: pendular, one eye elevates and rotates inwards while the other eye depresses and rotates outwards. Causes: supra-sellar and rostral midbrain lesions.
- *Upbeat nystagmus*: jerk, vertical with fast phase upwards. Causes: lesions of the cerebellar vermis and brainstem
- *Downbeat nystagmus*: jerk, vertical with fast phase downwards. Causes: lesions of the cervico-medullary junction at the level of the foramen magnum, e.g. Arnold–Chiari malformation.
- *Periodic alternating nystagmus*: jerk, horizontal with fast phase alternating from one side to the other after a short rest period. Causes: Arnold–Chiari malformation, spinocerebellar degeneration, trauma, posterior fossa tumours.
- *Spasmus nutans*: triad of head turn, head nodding and nystagmus. Benign form occurring within first 18 months and resolves by 3 years. Nystagmus can be horizontal, vertical, pendular and dysconjugate.

These features can be mimicked by chiasmal, suprachiasmal or third ventricle tumours.

- *Convergence–retraction nystagmus*: jerk convergence–eye retraction movements on attempts of upgaze. Usually associated with defective upgaze and light–near dissociation as part of dorsal midbrain syndrome.
- *Opsoclonus*: bursts of rapid, multivectorial, chaotic and conjugate eye movement abnormality. May be associated with myoclonus: 'dancing eyes and dancing feet'. May occur after infectious encephalopathy but can be a presenting non-metastatic feature of occult neural crest tumours, e.g. neuroblastoma.
- *Ocular bobbing*: fast conjugate vertical movements with fast phase downwards. May be seen in metabolic encephalopathy or obstructive hydrocephalus.
- *Cerebellar system disease*: gaze-evoked nystagmus, ocular dysmetria and visual fixation instability.

Acquired vestibular nystagmus

This is usually associated with other symptoms such as deafness, tinnitus and vertigo. Vestibular disease causes a horizontal-rotatory primary position uni-directional jerk nystagmus. The fast phase beats away from the diseased vestibular system.

Pupil light responses

Pupil size is dependent on an afferent stimulus (light and/or accommodative convergence) and on the efferent sympathetic and parasympathetic innervation pathways.

Afferent pathway

Approximately 10% of the axons in the optic tract synapse in the midbrain. There, they innervate both the ipsilateral and contralateral Edinger–Westphal nucleus. This arrangement leads to consensual pupil reactions to light, i.e. anisocoria (unequal pupils) *cannot* result from a defect in the afferent pathways (see Fig. 30.6).

A defect in the afferent pathway can be the result of retinal disease or pathology affecting the optic nerve and/or anterior optic tract. A very useful test in clinical practice is the Marcus Gunn (or swinging torch) test, which compares the afferent pathway of each eye. For this test, the child should be looking at a distant target (to prevent miosis due to the near reflex). Both pupils will be the same size due to the consensual light response. If a complete afferent pupillary defect is present in one eye, both pupils will constrict equally when light is directed towards the normal eye but neither pupil will constrict when light is shone in the eye with no perception of light (this situation is rare in practice). If there is a relative afferent pupillary defect (RAPD), both pupils will still constrict consensually, but this constriction will be less marked when the light is directed towards the eye with afferent pathway pathology compared to the normal eye. As the light is swung from normal eye to the eye with afferent pathology, a relative dilatation of both pupils will be seen.

Efferent pathway

Parasympathetic innervation of the pupil

The parasympathetic autonomic system is the efferent pathway of the light and near response. A unilateral defect in the parasympathetic innervation of the pupil will lead to anisocoria (unequal pupils). The affected pupil is larger than its partner and unresponsive to light and accommodation, e.g. Adie pupil, complete third nerve palsy. The efferent outflow from the Edinger–Westphal nucleus is under cortical inhibition; pupils are relatively miosed during sleep and sedation but arousal and seizure activity increase the inhibitory tone, resulting in larger pupils.

Sympathetic innervation of the pupil

The sympathetic autonomic system innervates the dilating muscle of the pupil. Horner syndrome results from ipsilateral injury to the sympathetic chain. The unbalanced action of the pupil sphincter results in a small pupil and a mild upper and lower lid ptosis. If the injury occurs in the perinatal period, e.g. due to forceps injury to the neck, the affected eye will be lighter in colour than its partner (heterochromia). If the lesion is pre-ganglionic, there will be accompanying anhydrosis.

Sympathetic innervation occurs via a three neuron chain:

- First order neuron: from hypothalamus to cilio-spinal centre of Budge (syringomyelia, cerebrovascular accident)
- Second order neuron: from cilio-spinal centre of Budge to superior cervical ganglion (chest and neck lesions including neuroblastoma)
- Third order neuron: from superior cervical ganglion via the ophthalmic division of the trigeminal nerve to the pupil dilator muscle and Müller muscle of the eyelids (cavernous sinus lesion, migraine variants)

Ptosis at 6 months

The parents of a 6-month-old infant are concerned about a unilateral partial ptosis, which has been present since birth. The baby was born at term after a complicated vaginal delivery. Your assessment shows no significant facial bruising, a 4 mm right ptosis with no evidence of anisocoria (unequal pupils) or strabismus. The child is otherwise developing well and there is no family history of note.

What would be the most likely diagnosis? Select ONE answer only.

A. Congenital dystrophy of the levator muscle
B. Facial nerve palsy
C. Forceps injury during birth
D. Myasthenia gravis
E. Partial third nerve palsy

Answer 30.5

A. Congenital dystrophy of the levator muscle.

Forceps delivery can result in Horner syndrome or a mechanical ptosis due to bruising, but there was no anisocoria or significant bruising in this case. Facial nerve palsy will cause lagophthalmos, not ptosis. Third nerve palsy would cause the eye to have a divergent squint. Neonatal myasthenia can cause ptosis but it is rare and usually bilateral. The most likely diagnosis is a congenital dystrophy of the levator muscle. This is a relatively common cause of ptosis and requires referral for amblyopia management and eventual surgery to improve the lid height.

Pharmacology and the eye

The blood–ocular barrier prevents many systemic medications from reaching the intra-ocular tissues. Most chemotherapeutic agents cannot enter the eye, making it a sanctuary site for cancer, particularly acute lymphoblastic leukaemia.

Absorption of topical therapy through the cornea is good and most anterior segment problems can be treated with drops (*guttae – g*)/ointment (*oculentum – oc*), with systemic therapy reserved for posterior segment disease. Many drops have preservatives which cannot be tolerated when applied intensively or when contact lenses are worn. The majority of commercial topical therapies are not licensed for use in children, but are regularly prescribed and have a historical safety record.

When a drop is instilled in the eye, only 10% of the active drug is absorbed into the eye, the remainder spills or enters the systemic circulation via the conjunctival vessels or the nasal mucosa via the nasolacrimal duct. Peak plasma concentration occurs within 30 minutes of instillation and can lead to systemic side effects, particularly in neonates. To limit systemic absorption, the lowest concentration of active ingredient should be used and the nasolacrimal duct occluded with a fingertip for a couple of minutes after drop instillation.

Drugs used for diagnosis

Topical anaesthetics

Severe eye pain and blepharospasm can prevent adequate examination. Topical anaesthetics are helpful but should *never* be prescribed on a routine basis for analgesia, since corneal anaesthesia prevents epithelial healing and risks infection. Topical anaesthetics in common use are:

- Proxymetacaine 0.5%: excellent choice for children, effect lasts 10 minutes, does not sting
- Tetracaine 0.5%: longer-acting anaesthetic, useful for surgical procedures, severe stinging on instillation

Fluorescein

Fluorescein absorbs blue light and re-emits it in the green spectrum. It will light up areas of corneal and conjunctival epithelial loss if illuminated with *blue* light. It is available either as a Fluoret impregnated strip or eye drop.

Refraction

Anti-muscarinic drops block the parasympathetic innervation of the ciliary muscle and pupil sphincter, and are commonly used to allow accurate objective refraction in clinic. Side effects include stinging, blurred vision, photosensitivity, flushing and dry mouth.

- Tropicamide 1%: onset in 15 minutes, lasts 3–6 hours
- Cyclopentolate 0.5% (for infants) or 1%: onset in 20 minutes, lasts 24 hours
- Atropine 1%: onset in 30 minutes, lasts 7 days

Sympathomimetics are used synergistically with anti-muscarinics for the intense mydriasis needed for intra-ocular surgery or ROP screening and treatment. Side effects include stinging, blurred vision, sensitivity to light. Rarely, tachycardia and hypertension can occur.

- Phenylephrine 2.5%: onset in 20 minutes, lasts 12 hours

Investigation of pupil abnormalities

Adie pupil

Viral infection can disrupt the ciliary ganglion causing parasympathetic dysinnervation. Denervation hypersensitivity develops and can be clinically tested by using a diluted *parasympathomimetic* such as pilocarpine. This will have no effect on a normal pupil after 30 minutes, but a pupil with denervation hypersensitivity will become miosed.

Horner pupil

Interruption of sympathetic innervation to the eye decreases the concentration of noradrenaline (norepinephrine) around the synapse with the pupil sphincter. Cocaine drops prevent the re-uptake of noradrenaline at the synapse and will cause dilatation of a normal pupil within 30 minutes. The absence of noradrenaline around the synapse in Horner syndrome prevents pupillary dilatation. More recently, apraclonidine 1%, an alpha adrenergic receptor agonist which is routinely available in eye clinics, has been used to demonstrate denervation hypersensitivity of the pupil dilator muscle with Horner syndrome. A drop will cause a dilatation of the pupil in eyes with Horner syndrome and no appreciable difference in the normal eye after 30 minutes.

Drugs used for glaucoma

Improvement of aqueous outflow:

- Parasympathomimetics modify the anatomy of the drainage angle by causing miosis: pilocarpine 1%
- Alpha 2 adrenergic agonists: apraclonidine. Brimonidine is contraindicated for use in children since, unlike apraclonidine, it crosses the blood–brain barrier and causes cardiorespiratory depression.
- Prostaglandin analogues: latanoprost, bimatoprost – these can darken iris colour and enhance eyelash growth

Decreased aqueous production:

- Topical beta blockers: timolol 0.1% or 0.25%. Side effects include bronchospasm, bradycardia, hypotension
- Carbonic anhydrase inhibitors can be used topically or systemically: dorzolamide 2% or acetazolamide. Systemic use can commonly cause fatigue, depression, headache, paraesthesia and electrolyte disturbance.

Drugs used for ocular inflammation and infection

Allergic eye disease is usually treated with topical antihistamines and mast cell stabilizers, which are available over the counter. Olopatadine is licensed for use in childhood allergic eye disease and stings less than others. Topical steroids are required for more severe types of allergy and uveitis but should only be started after an ophthalmological examination. High frequency topical steroid use can cause reduced plasma cortisol, steroid-induced glaucoma and risks ocular surface infection.

Antibiotics and antivirals

Bacterial conjunctivitis is extremely common and microbiological investigation is not required unless the conjunctivitis is chronic or occurring in the neonatal period. Although there are many different topical antibiotic preparations available, many are restricted to specialist use for treating infective keratitis and should be used after attempting culture of the affected site. The following topical antibiotics are suitable for use in a primary care setting:

- Chloramphenicol (cheap, often used for postoperative prophylaxis, broad-spectrum agent)
- Fusidic acid (cheap, good for staphylococcal infections)
- Ofloxacin (useful first-line treatment if chlamydia is suspected)

Topical antivirals such as aciclovir ointment are useful in herpes simplex keratitis but not effective in herpes zoster keratitis, which requires systemic treatment. Fortunately, fungal keratitis is extremely rare but it is devastating when it occurs. *Candida* keratitis can occur in immune-suppressed children and filamentous fungi (e.g. *Aspergillus*) can complicate trauma; amphotericin is the first-line topical antifungal.

Drugs which can cause ocular toxicity

Some systemic therapy can cause ocular toxicity. Children on the following drug treatments should have ophthalmic screening:

- Ethambutol – optic neuropathy
- Vigabatrin – retinal toxicity leading to visual field constriction
- Hydroxychloroquine – causes maculopathy
- Desferrioxamine – retinal toxicity
- Amiodarone – corneal deposits and possible optic neuropathy

Paediatric conditions which require ophthalmic screening

Many childhood conditions are associated with ophthalmic problems. Sometimes the ophthalmic

examination can help diagnostically, but for others screening and early treatment to prevent sight-threatening disease is important.

Ophthalmic examination is required in the following settings:

Neonate:

- Prematurity: screening for ROP
- Family history of early visual impairment: especially cataract, glaucoma, aniridia and retinoblastoma
- Facial capillary malformation involving the eyelids: glaucoma screening

Infant:

- Syndromes/global developmental delay: ocular malformations, cataract, refractive error, cerebral visual impairment
- Sensorineural hearing loss: screening for retinal dystrophy
- Hydrocephalus: monitoring of optic nerve function
- Potential non-accidental injury: screening for retinal haemorrhages
- Incontinentia pigmenti: regular screening for retinal ischaemia and neovascularization

Childhood:

- Juvenile idiopathic arthritis: regular screening for chronic anterior uveitis
- HLA B27-mediated arthropathy: screening for uveitis
- Visual pathway tumours: monitoring of optic nerve function, visual fields
- Diabetes: initial retinopathy screening 3–5 years after diagnosis, then annually
- Marfan's syndrome: screening for lens subluxation, myopia

- Von Hippel–Lindau disease: annual screening for retinal angiomata
- Post irradiation: screening for dry eye, cataract, radiation retinopathy
- Neurofibromatosis type 1: screening for Lisch nodules and monitoring for visual pathway gliomas
- Sickle cell/thalassaemia: screening for retinal ischaemia
- Possible neurometabolic disease: corneal clouding, cataract, retinal dystrophy, cherry-red spot
- Possible Wilson's disease: screening for Kayser–Fleischer ring (copper deposition within the cornea)
- Possible Alagille syndrome: screening for anterior segment anomalies (posterior embryotoxon), optic disc anomalies and retinal pigmentary changes
- Possible Fabry disease: screening for corneal verticillata (whirl-like opacities in the cornea and retinal vascular tortuosity)

Further reading

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Kaukab Rajput, Maria Bitner-Glindzicz

CHAPTER

Hearing and balance

31

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Know the anatomy of the outer, middle and inner ear
- Understand how the structure of the ear is related to function
- Understand the process of hearing and how it may be impaired
- Understand the process of ear development
- Be aware of the genetic and environmental causes of hearing loss
- Know how to investigate hearing loss
- Understand about the assessment of hearing
- Be aware of the treatment of hearing loss – medical management and use of hearing aids and cochlear implants

Anatomy of the ear

The ear is divided into the outer (external) ear, the middle ear and the inner ear. The outer ear consists of the auricle (pinna) and external auditory canal; the middle ear cavity is bordered by the tympanic membrane and contains the three ossicles; the inner ear (or labyrinth) consists of the cochlea (the organ of hearing) and the vestibular system (the organ of balance).

The external ear

Sound waves are collected by the pinna and channelled by the external auditory canal to the tympanic membrane, causing it to vibrate (Fig. 31.1). The shape and resonance of the pinna and external canal results in passive amplification of mid- and high-frequency sounds.

Comparison of the inputs from both ears allows localization of the sound source. Children with unilateral hearing loss find it hard to localize sound or to understand speech in spatially separated background noise.

The middle ear

The middle ear is an air-filled cavity containing the malleus, incus and stapes. It transfers sound energy from air compression waves to pressure waves in the fluids of the cochlea. Normally, the loss of energy when sound waves in air hit a fluid medium is around 99.9%, equivalent to about 30 dB, but the function of the middle ear is to offset this energy loss. The footplate of the malleus rests on the tympanic membrane, and detects vibrations from sound. This in turn is transmitted via the incus to the stapes, whose footplate rests on the oval window of the cochlea. The piston-like movement of the stapes footplate on the oval window sets up a travelling sound wave in the cochlear fluid (see below). The lever system of the ossicles and the difference in surface area of the large eardrum at one end, and the small stapes footplate at the other, means that sound is amplified more than twentyfold between the outer ear and the inner ear, offsetting the loss of energy between air and fluid.

Clinical relevance – conductive hearing loss

When a child has a conductive hearing loss, either due to the presence of fluid in the middle ear, or because of congenital ossicular malformation or trauma, the hearing loss is likely to be around 30 dB. It occurs predominantly in the low frequencies. Thus children with 'glue ear' can still hear speech as long as the speaker is close and clear.

CHAPTER THIRTY-ONE
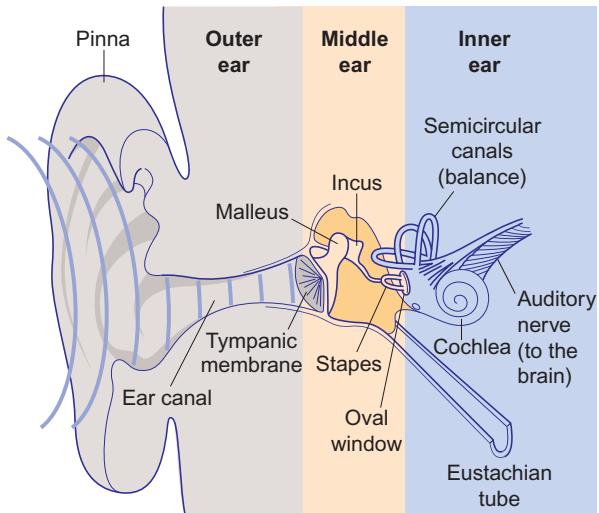
Fig. 31.1 **External, middle and inner ear.** *(From Levene M. MRCPCH Mastercourse, 2007, Elsevier Churchill Livingstone, with permission.)*

The middle ear also contains two small muscles, the stapedius muscle, innervated by the facial nerve (VII) and the tensor tympani, innervated by a branch of the trigeminal nerve (V). These contract in response to loud sounds, reducing transmission of sound to the cochlea and protecting inner ear structures from damage. This response is known as the stapedial or acoustic reflex, and involves the VIIIth nerve, the brainstem nuclei and the VIIth nerve. Clinical measurements of the stapedial reflex can help to differentiate between certain types of hearing loss, and the possible location of the lesion.

Connecting the middle ear to the nasopharynx is the Eustachian tube, which regulates the air pressure in the middle ear. Most of the time this is closed (collapsed), but swallowing, yawning and positive pressure may force it open transiently.

Clinical relevance – external and middle ear abnormalities

Abnormalities of the external and middle ears may result in conductive hearing loss. In children, Eustachian tube dysfunction is common, resulting in an increased tendency to otitis media with effusion ('glue ear'). As the child grows, the Eustachian tube becomes more vertical in orientation and the problems generally resolve. Congenital abnormalities of the external or middle ears, such as external auditory canal atresia, or fixed or missing ossicles, cause conductive hearing loss.

The inner ear

The cochlea

The normal cochlea is a coiled structure with two and a half turns. It is divided lengthways into three fluid-filled compartments by two membranes, the basilar membrane and Reissner's membrane. The scala tympani is the lower compartment, the cochlear duct (scala media) is the middle one and the scala vestibule is the upper compartment (Fig. 31.2). The scala vestibuli and the scala tympani are filled with perilymph, which has a composition similar to extracellular fluid, while the cochlear duct contains endolymph, which is unique, having a high potassium and low sodium concentration.

The specialized sensory hair cells, responsible for converting sound energy into electrical impulses, and their supporting cells are known as the organ of Corti. The organ of Corti runs along the entire length of the basilar membrane.

The vestibular system

The vestibular part of the inner ear (labyrinth) is responsible for balance. It is divided into two functionally separate parts: the semicircular canals and the vestibule (Fig. 31.3). It contains an internal compartment (membranous labyrinth) containing endolymph which is surrounded by perilymph and these fluids are continuous with those of the cochlea. The membranous labyrinth is encased in bone.

The three semicircular canals (SCCs) include the lateral (horizontal) canal, anterior (superior) canal and a posterior (inferior) canal, at approximately right angles to each other. The anterior and posterior canals detect rotation in the vertical planes (i.e. when the head is nodding or rolling), and the lateral canal detects horizontal movements (turning the head to the left or right). At the end of each semicircular canal is a dilatation called the ampulla, containing a patch of sensory hair cells called the cristae ampullares (see Balance and the vestibular system, below).

The vestibule has two parts, containing the utricle and the saccule. These both contain an area (macula) of sensory hair cells. The areas are at right angles to each other and detect gravity and linear acceleration, such as when going up in a lift (vertical), or stopping and starting in a car at traffic lights (horizontal). Together, the utricle and saccule are called the otolith organs.
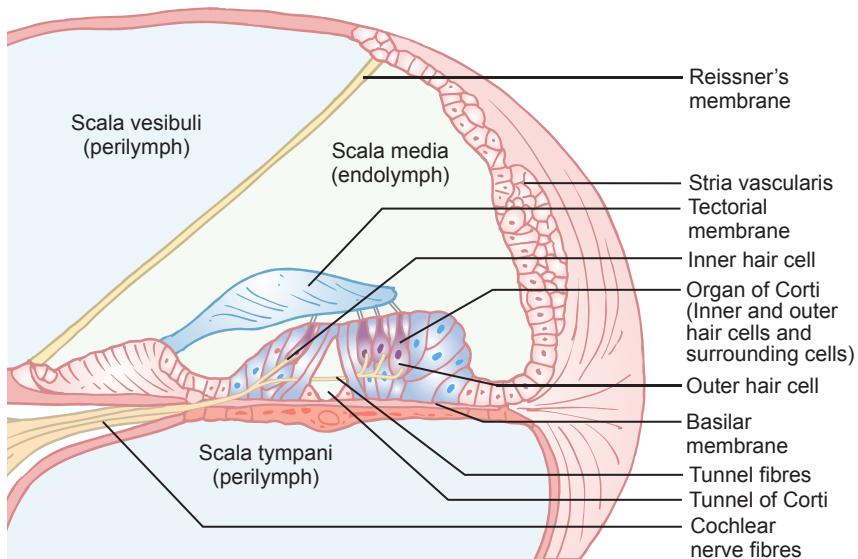
Fig. 31.2 Section through cochlea.
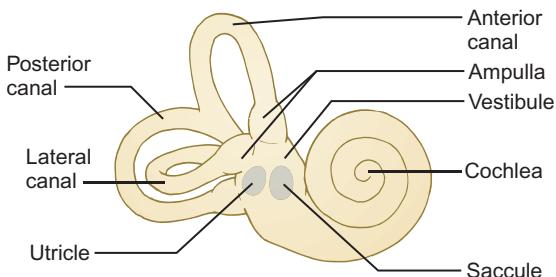
Fig. 31.3 The vestibular system.

Structure and function

When the stapes footplate moves as a result of vibrations transmitted from the tympanic membrane, pressure waves in the cochlear fluid produce movement of the basilar membrane. On the basilar membrane is the organ of Corti (see Fig. 31.2), which detects this movement and converts it into electrical energy (auditory transduction).

The organ of Corti consists of sensory cells (hair cells) and supporting cells. The hair cells are so called because they have hair-like, actin-filled projections on their apical surface, called stereocilia. There are three rows of outer hair cells and one row of inner hair cells. The stereocilia are arranged in rows of increasing height in a 'W' shape on the top of the outer hair cells, whereas the inner hair cells have a linear arrangement of stereocilia. The tallest stereocilia are embedded in an overlying gelatinous membrane, the tectorial membrane, and adjacent stereocilia of each hair cell are connected to each other by thin links, to form a hair bundle.

The process of hearing: converting sound into electrical energy

Inward movement of the stapes in response to sound transmitted through the middle ear produces deflection of the stereocilia towards the tallest row. This increases tension in the links between the tip and the side of the adjacent taller stereocilium. This causes physical opening of ion channels at the top of the stereocilia (like the pulling open of a trap door). Ions from the potassium and calcium-rich endolymph flow into the hair cells along an electrochemical gradient, causing depolarization of the hair cells.

In turn, depolarization of the hair cells triggers the opening of voltage-gated calcium channels, and further influx of calcium. This increase in calcium concentration results in exocytosis of vesicles containing neurotransmitters at the base of the hair cell, increase in firing of afferent neurons, and transmission of impulses to the brain via the cochlear nerve. However, movement of stereocilia in the opposite direction

closes the channels. This causes hyperpolarization of the cell and reduction of firing.

On the lateral wall of the endolymphatic (cochlear) duct is a specialized layered tissue called the stria vascularis. This produces the endolymphatic fluid, with its high potassium and low sodium concentration. The endolymph is also at a high positive potential (endocochlear potential). It is because of the electrochemical gradient between the endolymph and intracellular fluid that potassium flows into the hair cells when the channels at the top of the stereocilia are opened.

Central projections

Nerve impulses generated by sound are transmitted via the cochlear nerve with the vestibulocochlear (VIIIth) nerve to the cochlear nucleus, superior olive, inferior colliculus, medial geniculate body and up to the auditory cortex located in the temporal lobes.

The auditory system is organized tonotopically, i.e. according to frequency (pitch) of the sound. This means that high frequencies are detected at the base of the cochlea and low frequencies at its apex, and this 'tonotopicity' is retained in most of the higher levels of the auditory pathways. The higher centres integrate peripheral inputs for functions such as localization and language processing. The latter is performed by association areas (primarily Broca's and Wernicke's areas), with the left side (receiving input from the right ear) dominant in most individuals.

Balance and the vestibular system

The sensory receptors of the vestibular system are in the ampullae of the semicircular canals (SCCs) and the otoliths (saccule and utricle). Similar to the cochlea, they contain hair cells, but with some important differences. The stereocilia connect to an overlying gelatinous structure called the cupula (similar to the tectorial membrane of the organ of Corti). Endolymph movement generated by head rotation pushes against the cupula, bending the hair cell stereocilia and thereby modulating excitation of the vestibular afferent fibres. The SCCs work in pairs so that when receptors in one ampulla are excited, those in the opposite ear are inhibited. Therefore, the afferent nervous output of each canal determines the magnitude of the rotation.

Embryology

The inner ear

The inner ear begins to develop at about 3–4 weeks. In the caudal part of the hindbrain, there is a thickening of surface ectoderm to form the otic placode. The ectoderm then invaginates to form a cup and then the otic vesicle, or otocyst. The otic vesicle separates from the overlying ectoderm and starts to elongate to become the cochlear duct, with an appendage which is the endolymphatic duct and sac (Fig. 31.4). The

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Clinical relevance – disorders of hearing and vision

The protein components of the tip links and other links between stereocilia (shaft connectors, top connectors and ankle links) are crucial for hearing. These proteins interact to form a series of large molecular complexes, which tether the stereocilia to each other and anchor the connectors to the central actin core of each stereocilium, providing rigidity. Mutations in the genes encoding these proteins give rise to non-syndromic as well as syndromic forms of deafness. Type 1 Usher syndrome, for example, causes deafness and retinal dystrophy. As the affected proteins are expressed in cochlear and vestibular hair cells, both parts of the inner ear are affected. These proteins are not only important for stereocilia formation and function, but are also expressed in the photoreceptors of the eye, hence the dual sensory pathology. The clinical presentation is frequently one of congenital profound hearing loss, so the infants fail newborn hearing screening and have gross motor delay such as poor head control, late sitting and walking due to absent vestibular function. Later in childhood, the children develop retinal degeneration starting with the rod cells, resulting in night blindness, loss of peripheral vision and eventual blindness.

Clinical relevance – genetic causes of deafness

Genetic studies of children with congenital hearing impairment have shown that mutations in genes important for determining and maintaining the unique ionic composition of the endolymph are important causes of deafness in children. These include ion channels, transporters and gap junction proteins responsible for K+ recycling and maintenance of endocochlear potential. Mutations in the genes encoding these proteins may cause deafness in humans, with or without other clinical features. Genes include:

- *KCNQ1/KCNE1* (potassium channels) – causes deafness and long QT syndrome (Jervell and Lange-Nielsen syndrome)
- *SCL26A4* (a chloride/iodide transporter) which causes Pendred syndrome (deafness and goitre)
- *GJB2* (encoding the gap junction protein, connexin 26) – the commonest cause of genetic non-syndromic deafness in children

Fig. 31.4 Development of the inner ear. *(From Moore KL, Persaud TVN, Torchia MG. Before we are born, 8th edition. Saunders 2013, with permission.)*

cochlear duct continues to grow ventrally from the 4th–8th week and begins to coil. Within the cochlear duct, the organ of Corti begins to develop from cells in the wall of the duct. Mesenchyme surrounding the cochlear duct condenses and differentiates into the cartilaginous otic capsule. This later ossifies to form the bony labyrinth around week 23. Ganglion cells of the VIIIth nerve migrate into the cochlear duct and form the spiral ganglion, sending projections to the ends of the hair cells and the organ of Corti. The inner ear is fully developed by 20–22 weeks.

The external and middle ear

As the otic vesicle forms, the external and middle ear are also beginning their development just caudally. Development of the pinna of the external ear begins at about 5 weeks. It starts with the appearance of six mesenchymal swellings or hillocks, from the first and second branchial arches, surrounding the first branchial groove – from which develops the external auditory canal. Development begins in the upper part of the neck and as the mandible develops during the second month, the auricles move laterally and upwards level with the eyes. Migration of neural crest cells into the first and second branchial arches give rise to muscles and ligaments, and of importance here, the ossicles. The first arch neural crest cells give rise to the malleus and incus, and the second arch cartilage to the stapes.

> **Clinical relevance – external ear anomalies**
>
> Minor malformations of the external ear are not uncommon and may appear as isolated features or as part of a syndrome whose underlying mechanism is genetic. External ear anomalies range in severity from abnormal positioning, for example, low set or posteriorly rotated ears which reflect late developmental arrest of migration of the ears from their initial position in the neck, seen in Noonan's syndrome, to severe microtia or external auditory canal atresia seen in conditions such as Treacher Collins syndrome.

Genetic causes of hearing loss

Genetically determined hearing loss can either exist as an isolated feature (non-syndromic) or as a syndrome in which it is associated with other abnormal clinical features. It is said that around 70% of genetically determined childhood-onset hearing loss is non-syndromic. Well over 100 genes are known to underlie non-syndromic hearing loss (NSHL) alone, and over 600 syndromes in which hearing loss is a feature have been described to date in the London Medical Databases (Dysmorphology and Neurogenetics) (see Further reading).

Obviously, a paediatrician cannot be familiar with all of these syndromes, but some of the relatively common ones are listed in Table 31.1. It is helpful to be able to identify some of the more common syndromes involving hearing loss, to know how to approach investigation of a child with a suspected syndrome, and to be aware that some children who have apparent non-syndromic hearing loss may subsequently be determined as having a syndromic loss, as more clinical features become apparent with time. It is helpful to make these diagnoses in order to monitor for complications, and for the purposes of genetic counselling. For example, Pendred syndrome describes the association of congenital deafness and goitre, usually of teenage onset, which requires monitoring for subsequent hypothyroidism.

Clinical relevance – hearing loss at birth

In the absence of a proven environmental factor, most hearing loss present at birth is likely to be genetic. An isolated case of congenital hearing loss, especially if severe or profound, has a high risk of recurrence because it is most likely to be autosomal recessive. If, after the detailed history and examination, the clinician feels it is still most likely that a child has a non-syndromic cause of hearing loss, the next investigation should be genetic testing and further investigation, particularly analysis of the *GJB2* gene.

Table 31.1 Some of the syndromes in which hearing loss is a major feature

Syndrome	Features	Inheritance	Importance
Usher	Hearing loss and retinal dystrophy		Initially presents as NSHL. Child will have dual sensory impairment. Monitor for visual function.
Jervell and Lange-Nielsen	Congenital profound hearing loss with absent vestibular function; long QT interval with possible syncope	AR	Initially presents as NSHL. Assess QT interval; treat with beta blockers, or implantable defibrillator depending on cardiologist's advice. Mortality is high if untreated.
Pendred	Progressive high-frequency hearing loss; vestibular function may be normal or affected; thyroid dyshormonogenesis; enlarged vestibular aqueducts and incomplete partitioning of cochlea	AR	Initially presents as NSHL. Assess for goitre and dyshormonogenesis; monitor for subsequent hypothyroidism.
Treacher Collins	Bilateral, symmetrical facial features; abnormal external ears often with meatal atresia; cleft palate; malar, zygomatic and mandibular hypoplasia; coloboma of lower eyelids and sparse lower eyelashes; ossicular abnormalities; sensorineural hearing loss	AD	Can range from mild to severe features, which may include airway obstruction and require tracheostomy; risk of gonadal mosaicism in unaffected parent.
Waardenburg (WS)	Pigmentary anomalies of hair, skin or eyes and hearing loss	AD; also AR	
CHARGE	*C*oloboma, *H*eart defects, *A*tresia of choanae, *R*etarded growth and development, *G*enital hypoplasia, *E*ar anomalies (absent semicircular canals and VIIIth nerve hypoplasia)	AD	Clinical features highly variable; intellectual impairment may be mild to profound; development may initially appear to be severely delayed because of speech delay secondary to deafness and gross motor due to absent vestibular function.
Alport	High-frequency sensorineural hearing loss and nephritis	XL; also AR; AD	Intermittent haematuria (microscopic at first) leading to renal failure and characteristic findings on renal biopsy.

AD, autosomal dominant; AR, autosomal recessive; NSHL, non-syndromic hearing loss; XL, X-linked.

Non-syndromic hearing loss is very heterogeneous and may follow any mode of inheritance. Most genetic hearing loss is inherited in an autosomal recessive manner, accounting for about 80% of cases. The implication of this is that there may be no family history of deafness, but the risk of recurrence is high at 1 in 4. The remaining cases are either dominantly inherited (around 10–15%) or X-linked or mitochondrial (5% combined).

GJB2 is the commonest gene causing congenital deafness worldwide. It encodes the protein connexin 26. Connexins are components of gap junctions, present at the surface of epithelial cells to allow the passage of small molecules and ions between them. Gap junctions are thought to be essential for the recycling of potassium ions in the inner ear; potassium flows into hair cells from the endolymph when tip links cause the mechanotransduction channels at the top of the stereocilia to open in response to sound. This potassium has to be removed from the hair cells, and ultimately flows back to the stria vascularis, so that it can be transported into the endolymph again.

GJB2 accounts for almost 50% of autosomal recessive causes in many diverse populations, i.e. where there are siblings affected or where the parents are related. Even in singleton cases where there is no family history, around 10–20% of children with profound congenital hearing loss will be shown to have homozygous or compound heterozygous mutations in this gene and so it has become a first-line investigation in a child with non-syndromic hearing loss. Identification of mutations in *GJB2* helps to clarify genetic counselling for the parents (the chances of having another deaf child would be 1 in 4 with each

subsequent pregnancy) and may reassure them that their child has a non-syndromic form of hearing loss.

If the test for *GJB2* mutations is normal, a child may still have a genetic hearing loss caused by any one of an increasing number of genes, but there may be very few phenotypic clues as to which gene may be responsible. However, until recently the number of genes causing non-syndromic hearing loss and their large size precluded further genetic investigation due to cost and manpower limitations. The advent of 'next generation sequencing' (NGS) allows large numbers of genes to be sequenced simultaneously at relatively low cost. Therefore, a significant proportion of children with hitherto unknown causes of hearing loss are likely to receive a molecular diagnosis in the future.

Down's syndrome

Children with Down's syndrome are prone to a number of complications causing hearing impairment, including glue ear, and this is managed with hearing aids rather than grommets. Conductive hearing loss can occur in up to 80%. An underlying SNHL occurs in a small percentage. Both the external auditory canals and the Eustachian tubes are narrower, and low muscle tone may also result in dysfunction opening and closing the Eustachian tubes. These factors tend to exacerbate and predispose to conductive and middle ear problems which persist for longer during childhood than in other children. Furthermore, their facial anatomy appears to result in greater prevalence of rhinitis and sinusitis. The impact of even mild hearing loss is probably more significant than in other children due to their other difficulties. Educational, language and emotional development may all be affected. Hearing and inspection of the ears and upper airways should be monitored.

Widened/enlarged vestibular aqueducts

Enlarged vestibular aqueducts are one of the most common malformations seen on imaging of the inner ear in those with sensorineural hearing loss. It is an important finding for several reasons; hearing loss may fluctuate although there may be sudden progression without restoration, especially after infection or minimal head trauma; balance may also be affected and there may sometimes be accompanying vestibular symptoms such as vomiting, nystagmus and unsteadiness. It is a frequent feature in Pendred syndrome. This finding should therefore prompt genetic/endocrine investigation and counselling about sudden deterioration in hearing following minor head trauma.

Environmental causes

Intrauterine infections

There are a number of congenital infections that can cause congenital sensorineural hearing loss. Congenital cytomegalovirus (CMV) infection is the leading non-genetic cause of childhood SNHL, and is the commonest congenital infection worldwide (see Chapter 10, Perinatal medicine). The maternal infection is usually asymptomatic. There are abnormal clinical features in 10% of infected infants; the remaining 90% are asymptomatic at birth. SNHL affects approximately 50% of the survivors of the 'symptomatic' group, and 10–20% of the 'asymptomatic' group; these infants appear well, and are not routinely tested for CMV.

Congenital CMV is the only treatable cause of childhood SNHL and is important to detect as early as possible, as antiviral therapy commenced in the neonatal period has been shown in a randomized controlled trial to prevent hearing deterioration and improve neurocognitive outcomes. For neonates with SNHL and congenital CMV, urgent referral to paediatric infectious diseases to discuss treatment options is advised. Antiviral therapy is currently given orally if the infant is otherwise well, and recent evidence supports 6 months of treatment.

CMV-related hearing loss progressively worsens in half of cases. Bilateral profound deafness is the commonest audiological outcome, requiring referral for cochlear implantation. Congenital CMV also causes vestibular dysfunction and in a small proportion, visual problems. It is recommended that all children with SNHL of unknown aetiology should be offered tests for congenital CMV.

In the neonate, PCR is used to detect CMV DNA in urine or saliva swab samples; presence of CMV DNA in urine or saliva in the first 3 weeks of life confirms congenital CMV infection. Testing of the newborn blood spot (Guthrie card) for CMV DNA and MRI of the brain to look for signs of congenital CMV may be helpful. This is especially true where neonatal saliva or urine samples were not obtained. However, absence of clinical features cannot completely exclude CMV. In a child over 12 months of age, CMV IgG which is negative excludes CMV as a cause of deafness. Maternal CMV IgG is also useful and simple to test, which, when negative, excludes congenital CMV.

Congenital rubella still occurs in unimmunized populations and causes SNHL, as well as visual problems, congenital heart defects and cognitive impairment. Congenital toxoplasmosis and congenital syphilis are also causes of SNHL and these conditions are treatable with antibiotics. These infections may be tested serologically.

Question 31.1

Neonatal hearing impairment

A male infant is born at term, birth weight 3.5 kg. The pregnancy was uneventful and both he and his mother are clinically well. On his neonatal hearing screening test, he was noted to have bilateral sensorineural hearing loss (SNHL). His urine tested positive for CMV DNA.

Which of the following statements is correct? Select ONE answer only.

A. CMV DNA testing on saliva or urine can only confirm congenital CMV infection after 3 months of age.
B. Cochlear implants are contraindicated in congenital CMV-related hearing loss.
C. Congenital CMV SNHL is the commonest cause of failure to pass the neonatal hearing screening test.
D. Ganciclovir treatment of infants with neonatally detected CMV-related hearing loss reduces the long-term sequelae.
E. The hearing test should be repeated at 3 months as the hearing loss may have resolved spontaneously.

Answer 31.1

D. Ganciclovir treatment of infants with neonatally detected CMV-related hearing loss reduces the long-term sequelae.

CMV DNA testing is only accurate in the first 3 weeks of life to identify congenital CMV. Cochlear implants are a successful treatment. The commonest specifically identified causes of congenital SNHL are genetic in origin. SNHL does not resolve spontaneously.

Neonatal causes

In the neonatal period, many factors can lead to increased risk of hearing loss in infants. Babies who are admitted to the neonatal intensive care unit have a tenfold increased risk of sensorineural hearing loss. Risk factors in preterm infants include low birth weight, hypoxia, exposure to noise and ototoxic drugs.

Hyperbilirubinaemia is known to cause auditory nerve and cochlear damage, although deafness is transient in some cases. It is the toxic effects of circulating unconjugated bilirubin on developing neuronal pathways that can lead to bilirubin encephalopathy and kernicterus (see Chapter 11, Neonatal medicine). It is proposed that bilirubin disturbs the plasma, mitochondrial and endoplasmic reticulum membranes of neurons leading to the activation of cell death pathways. The severity of symptoms is dependent on the level of exposure and maturity of neural cells, and not just the peak total serum bilirubin measurement. Screening of hyperbilirubinaemic neonates using both ABR (automated brainstem responses) and OAEs (otoacoustic emissions) is recommended.

Prenatal exposure of the fetus to high levels of alcohol can result in fetal alcohol spectrum disorder (FASD), including restricted growth, damage to the central nervous system and characteristic craniofacial anomalies. Although hearing loss is not generally recognized as a major component of FASD, some studies have reported an association with hearing loss.

Drug ototoxicity

Aminoglycoside antibiotics e.g. gentamicin and streptomycin, as well as platinum-based chemotherapeutic agents such as cisplatin, can have irreversible effects on auditory function. Damage to the hair cells of the cochlea or to the stria vascularis is commonly associated with these therapeutic agents, and is thought to result from the production of free radicals that stimulate apoptosis in sensory cells and neurons causing permanent hearing loss. Some agents tend to be more vestibulotoxic if given in excess (e.g. gentamicin) and others more cochleotoxic (e.g. amikacin).

Loop diuretics (such as furosemide) can potentiate the ototoxic effects of aminoglycosides. Co-treatment with salicylate has some attenuating effects on the ototoxicity of aminoglycosides in animals and humans, but there are currently no recommendations for such use of aspirin to counter the effects of auditory ototoxicity. Other antioxidants have shown promise in ameliorating the effects of cisplatin treatment.

In some cases, mutations in the mitochondrial 12S ribosomal RNA specifically predispose vulnerable individuals to the side effects of aminoglycoside therapy even when drug levels are within normal therapeutic limits. The most common of these mutations is called m.1555A>G. This mutation increases the structural similarity of the mitochondrial ribosome to the bacterial ribosome and facilitates aminoglycoside binding. It occurs in 1 in 500 Caucasians and may be more common in other populations. However, the relationship of the mutation to aminoglycoside-induced ototoxicity is complex; some individuals appear to be exquisitely sensitive, and minimal doses precipitate irreversible deafness, yet others seem to be able to tolerate some aminoglycosides. This may be due to a

threshold below which deafness is not an inevitable sequel, or additional genetic modifiers which protect against ototoxicity. Further epidemiological studies are needed to determine the actual burden of this type of hearing loss to deafness, particularly in premature or sick neonates in whom aminoglycosides form part of first-line recommended antibiotic therapy.

Meningitis and other infections

SNHL occurs in 26% of survivors of pneumococcal meningitis and in about 11% following meningococcal meningitis. Bacterial invasion of the perilymphatic spaces in the cochlea can result in severe suppurative labyrinthitis, and it is thought that the subsequent production of reactive oxygen and nitrogen species leads to the damage and death of hair cells and spiral ganglion neurons. Within a few months of infection, new bone formation (ossification) occurs in the semicircular canal and extends to the scala tympani in the basal turn of the cochlea, which can complicate, but does not preclude, partial cochlear implant surgery. More extensive brain damage that can occur during meningitis infection may affect central auditory processing with subsequent consequences for outcome.

Mumps and measles are preventable causes of SNHL, but are less of a problem since the introduction of the MMR vaccine. Bacterial infection of the air spaces within the mastoid bone, 'mastoiditis', as a result of persistent middle ear infection may also cause hearing loss, although rapid treatment with antibiotics is effective and this is now uncommon in developed countries.

Case history

A 12-year-old girl who has bilateral moderate–severe hearing loss following meningococcal meningitis at the age of 8 years is referred regarding dizziness on head movement. Vestibular function testing confirmed bilateral vestibular hypofunction and she was referred for vestibular physiotherapy.

Autoimmune conditions

Autoimmune conditions can lead to acquired or late-onset hearing loss, which can be of sudden onset or progressive and is often associated with dizziness and sometimes tinnitus. It may also lead to cochlear ossification, and urgent scanning and cochlear implantation may be required in a rapidly progressing autoimmune-mediated hearing loss.

Malignancy

Tumours of the brain and ear and leukaemia can present with hearing loss, imbalance and may be associated with headache and raised intracranial pressure, abnormal eye movements and cranial nerve lesions.

Trauma

Traumatic hearing loss can be due to surgical trauma, head injury, or exposure to very loud noise.

Auditory neuropathy or auditory dyssynchrony

Sensorineural hearing loss caused by auditory neuropathy (AN) or auditory dyssynchrony (AD) represents 7–10% of hearing loss and is characterized by normal transient-evoked otoacoustic emissions (OAEs) or cochlear microphonics (CM) but abnormal automated auditory brainstem responses (AABRs). In 75% of affected children, the underlying pathophysiology is dysfunction of inner hair cells while outer hair cells remain active. In these cases, cochlear implantation generally works well when hearing aids have failed to improve auditory development.

Investigating the cause of infant and childhood auditory neuropathy (i.e. normal OAEs with abnormal ABR with cochlear microphonics) is essential, as it is increasingly reported that in some cases, particularly at-risk neonates, this condition may resolve over time. Regular testing after the age of 6 months and up to at least 12 months of age is recommended, and it is considered particularly important to obtain a behavioural measure of auditory response before proceeding with cochlear implantation surgery. If the cause of AD/AN SNHL is unknown, a viable approach may be to watch and wait; the hearing loss may be transient, and performing cochlear implantation may destroy any potential residual hearing.

Other causes of AN/AD include abnormalities of the afferent neural synapse, cochlear nerve, cochlear nucleus, auditory brainstem tracts and central auditory system, which are more difficult to overcome with cochlear devices. Further tests, including MRI and specialized physiological testing, can assist in the identification of individual pathologies.

Low-birth-weight infants are at increased risk of AN/AD, and onset correlates with exposure to ototoxic antibiotics, dexamethasone, hyperbilirubinaemia, hypoxia, ischaemia, immaturity of the central nervous system or mechanical ventilation. Other aetiological factors include intrauterine infections, complex syndromal disease, and non-syndromic forms of genetic hearing loss.

Investigation of hearing loss

In the case of a child with congenital or significant sensorineural hearing loss, the first diagnostic clues as to whether the cause is genetic or environmental, and if there is associated developmental delay, will come from history and clinical examination. Motor delay may suggest a vestibular problem if it is unaccompanied by delay in other domains. Immunization history is required with regard to MMR vaccination, as mumps, rubella and measles all cause hearing loss. Questions should also include family history of hearing loss and features of common syndromes (renal disease, eye diseases, pigmentary anomalies, thyroid disorders); consanguinity makes recessive inheritance more likely. Examination should include looking at the overall appearance of the child and then at specific features in detail: the shape, spacing, colour and orientation of the eyes and eyebrows; the shape and position of the ears, looking especially for pits and tags (suggestive of branchio-oto-renal syndrome (BOR) or Treacher Collins syndrome); the neck in terms of fistulae or marks (branchio-oto-renal syndrome), and shape (Noonan's syndrome); the skin in terms of texture, pigmentation, birth marks; the mouth, to look at the teeth in an older child and the shape of the palate, as well as the fingers and toes.
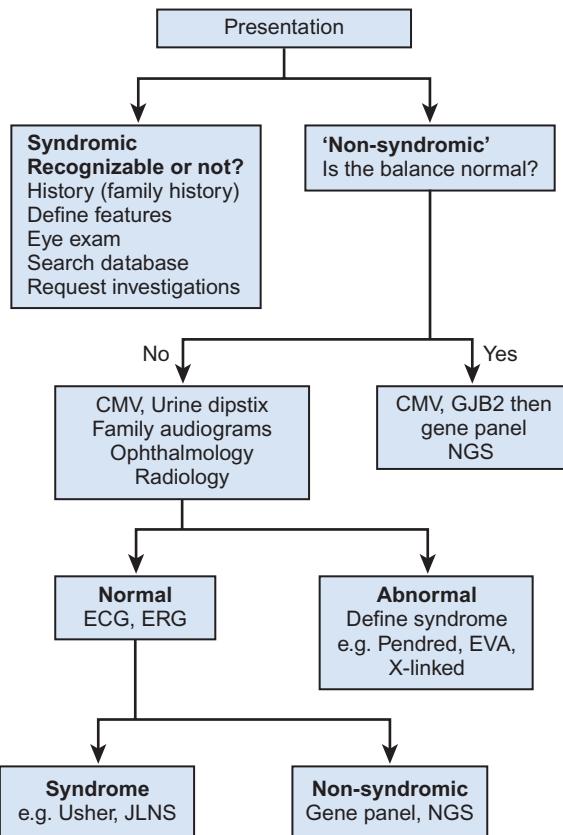
Fig. 31.5 Simple algorithm for investigation of congenital/childhood hearing loss. Radiological investigation should include MRI of the internal auditory meati (IAMs) and brain and renal ultrasound, especially if there are external ear anomalies. CT scanning should be carried out if there is a mixed hearing loss. EVA, enlarged vestibular aqueduct; NGS, next generation (massive parallel) sequencing.

If there is no obvious syndrome apparent, some basic investigations should be performed in all children with hearing loss of unknown cause (Fig. 31.5).

The consequences and measurement of hearing loss

Functional consequences of hearing loss

Hearing is important for awareness of many environmental sounds, but assessment usually focuses on the ability to hear speech as this has a major impact on language development and social functioning. If a child is unable to detect the spoken voice, there is no potential for acquisition of normal speech and language, with obvious far-reaching consequences. Lack of access to language, be it spoken or manual, such as sign language, will result in communication difficulties (depending on the severity of the hearing loss), with consequential educational and psycho-social

problems. Late-onset and progressive hearing loss in older children will similarly hamper further educational progress and life opportunities without appropriate audiological rehabilitation.

As outlined above, there is a wide range of aetiologies that produce hearing loss of varying degrees of severity. An important distinction in the assessment process is between permanent sensorineural losses (involving the cochlea) and conductive (middle ear) losses, which are usually temporary. Most types of hearing loss can be ameliorated by hearing aids or other devices to some degree (see below).

Assessment of hearing loss

The usual way to assess hearing function is to measure auditory thresholds, i.e. the quietest sounds which can be detected, as most hearing problems are associated with raised (poorer) thresholds.

The unit of measurement for sound levels is the dB (decibel), but the dB in isolation has no real meaning.

Rather, it is a ratio and is used to define a sound level as compared to a reference sound pressure. Two dB scales are used in hearing assessment:

- dB HL (hearing level) is the scale used for most threshold measurements. Audiometers and most other hearing measurement devices display levels in dB HL. With this scale, the reference pressure is that of normal hearing thresholds at each frequency (so that 'normal' thresholds are 0 dB HL). However, there is some variation, so that some individuals have slightly better thresholds (such as −5 dB HL) and thresholds up to 20 dB HL are usually considered to be in the normal range.
- dB A is an alternative scale, which is often used by sound level meters to measure sounds in the 'free field', especially when discrete frequencies are not being measured, such as speech sounds or background noise (Fig. 31.6).

Audiometry is the process of measuring hearing thresholds at a range of frequencies (pitches).
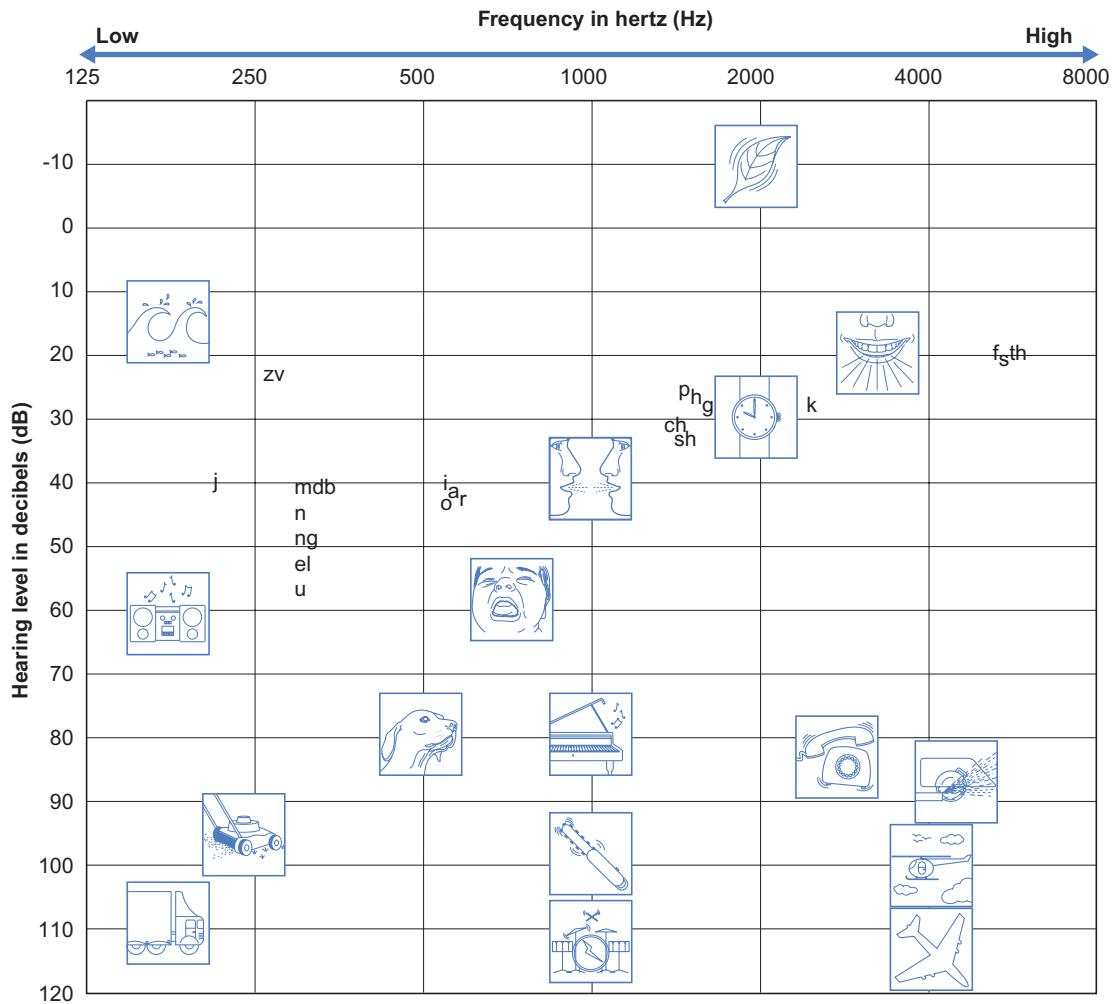
Fig. 31.6 Frequency and loudness of some everyday sounds. *(From Levene M. MRCPCH Mastercourse, 2007, Elsevier Churchill Livingstone, with permission.)*

Thresholds may be measured in various ways and are usually displayed on an audiogram, which shows the thresholds at each audiometric frequency. Figure 31.7 shows several audiograms. The horizontal axis shows the test frequencies. Octave intervals are tested from 250 to 8000 Hz (8 kHz). The vertical axis is the level of sound (dB HL) where the quietest levels are at the top. Thus, the 'normal range' is anything down to 20 dB HL and thresholds higher than 20 dB HL (lower on the audiogram) represent a clinically significant hearing loss. Thresholds for different degrees of hearing loss are as follows:

- Normal hearing: less than 25 dB in adults and 15 dB in children
- Mild hearing loss: 25–39 dB.
- Moderate hearing loss: 40–69 dB.
- Severe hearing loss: 70–94 dB.
- Profound hearing loss: 95+ dB

Functional hearing is represented by 'air conduction' (AC) thresholds (as shown in Figure 31.7), ideally measured using headphones, but often 'bone conduction' (BC) thresholds are also measured using a vibration generator placed on the mastoid bone.

The national Newborn Hearing Screening Programme

Currently, all children in the UK are screened shortly after birth under the national Newborn Hearing Screening Programme (NHSP). This is coordinated by regional audiological services and most babies are tested on maternity units within 48 hours of birth. Often, mothers are discharged prior to screening, in which case the tests are performed at home visits.

Otoacoustic emissions (OAEs) are sounds generated by the outer hair cells of the inner ear in response to an auditory stimulus. They are conducted through the middle ear and can be detected in the ear canal. Detection indicates a high degree of normality in the functioning of the middle ear and inner ear and is therefore a good screening test. However, it cannot detect all causes of hearing loss since the signals picked up by the cochlea also need to be transmitted higher up the auditory pathways.

All babies receive a test of OAEs shortly after birth. During testing, a soft probe is placed into the ear canal and the OAE or 'cochlear echo' is recorded in response to moderate level sound clicks delivered via the same probe. Presence of an OAE response (screen 'pass') confirms normal or near-normal hearing. Absence of a response indicates the possibility of a hearing loss and the need for follow-up testing, though is often due to temporary factors, such as excessive head movement or middle ear fluid.

The main follow-up test is auditory brainstem response (ABR) testing, which can detect retrocochlear pathology (Fig. 31.8). Disposable electrodes are attached to the baby's head and rapid clicks or tone pips are delivered to the ear by an insert probe. The electrodes detect field potentials generated by the lower auditory pathways (cochlea and brainstem), producing a characteristic waveform response. The intensity of the stimuli are reduced until the waves are no longer visible, providing a close approximation to behavioural hearing thresholds. Note is taken of the amplitude (reflecting the number of neurons firing), latency (the speed at which the waves are transmitted), interpeak latency and interaural latency (the difference between ears in terms of wave V latency). Babies demonstrating raised thresholds are monitored by audiological services and sometimes provided with hearing aids immediately if there is a large hearing loss.

Babies with certain risk factors (e.g. a graduate from the neonatal intensive care unit) are tested using both OAE and an automated version of the ABR test (AABR). One of the main aims of this combination is to identify auditory neuropathy spectrum disorder (ANSD), as this usually results in normal OAE but poor/absent AABR responses.

OAE is quick and easily administered, and is highly acceptable to parents to perform. About 15% of infants screened by OAE will be referred for further testing by ABR. Around 3% will subsequently be referred for formal audiology assessment. About 1 in 10 to 1 in 15 of infants referred on for detailed audiometry will be found to have a significant hearing problem. Overall, the NHS Newborn Hearing Screening Programme (see Box 2.12) identifies 1–2 per 1000 babies born in the UK as having hearing loss affecting one or both ears (1.1 per 1000 bilateral; 0.6 per 1000 unilateral).

Behavioural threshold testing in older children

Older children are usually assessed using behavioural tests of hearing, as these are considered to represent functional hearing more reliably than objective tests.

From around 6 months to 3 years of age, the usual method is visual reinforcement audiometry (VRA). The child sits in front of a low table and one of the testers keeps the child's attention to the front using simple toys. To one side is a loudspeaker and a visual reinforcer (a box containing an interesting toy). During the initial (conditioning) phase, moderately loud sounds are delivered for a few seconds and the reinforcer is illuminated and/or activated. The
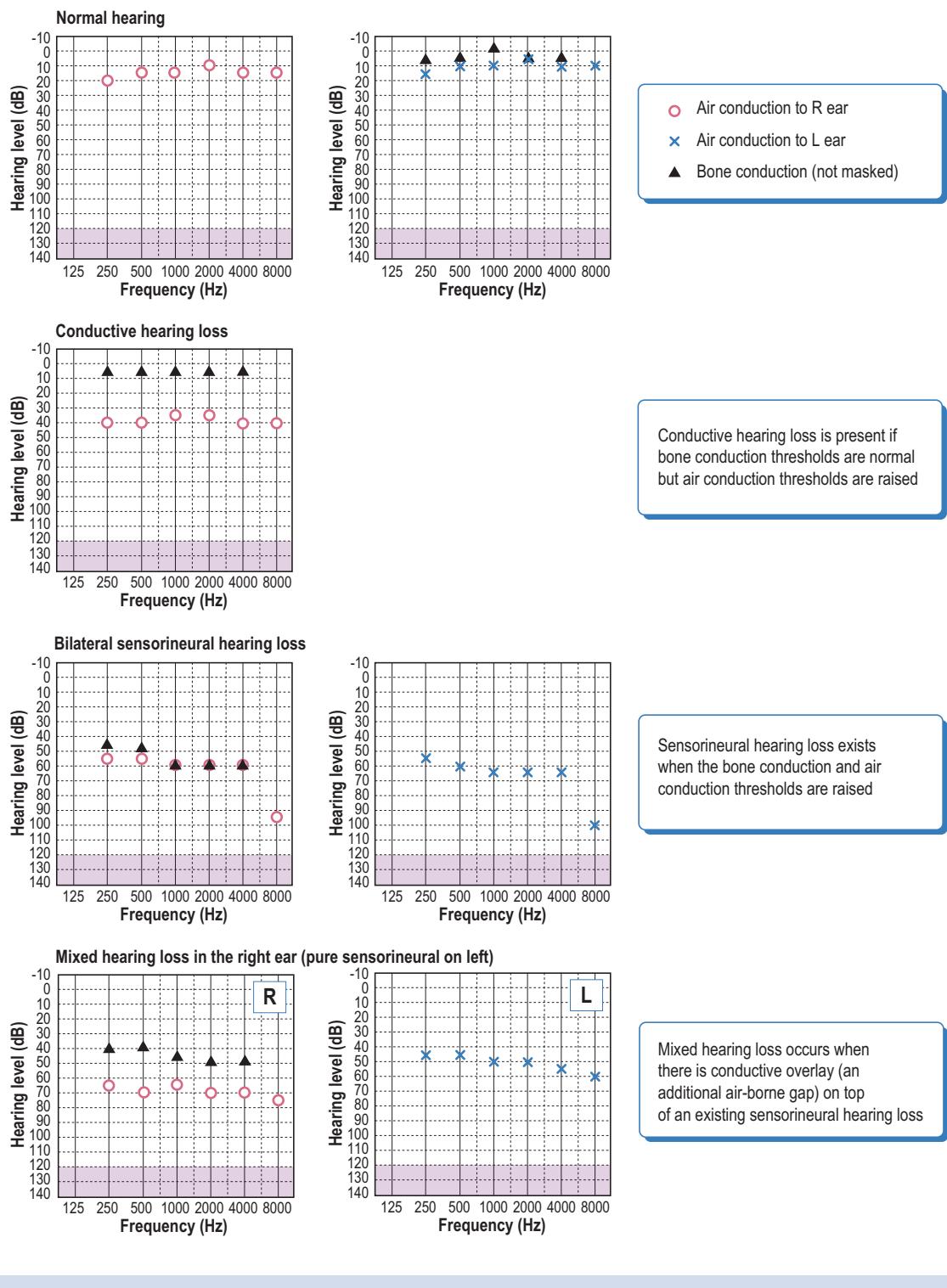
Fig. 31.7 Audiogram showing normal, conductive, sensorineural and mixed hearing loss. *(From Levene M. MRCPCH Mastercourse, 2007, Elsevier Churchill Livingstone, with permission.)*
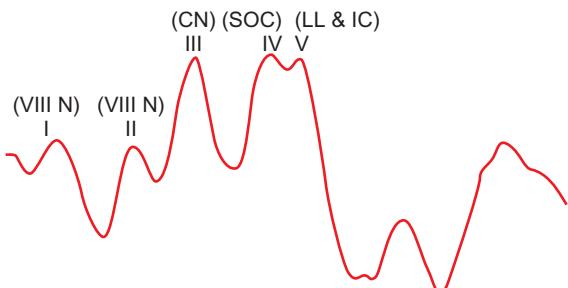
Fig. 31.8 Schematic representation of the auditory brainstem response (ABR). The output consists of five waves; waves I to III are generated by the auditory branch of the VIIIth nerve, the spiral ganglion and the cochlear nucleus (lower brainstem), and waves IV and V by the upper brainstem (superior olivary complex and inferior colliculus).

Fig. 31.9 Example tympanogram shapes (according to the so-called 'Jerger classification'). The peak of each curve indicates the amount of tympanic membrane (TM) movement, which normally occurs at around normal (0 daPa) middle ear pressure (as in A). The other curves are abnormal: A_s shows a flattened peak (reduced 'compliance') at normal pressure, indicative of early or resolving middle ear effusion; A_d shows abnormally high compliance typical of ossicular dislocation; B is a flat trace, seen with severe effusion or perforation; the C trace shows normal TM movement but negative middle ear pressure (i.e. TM retraction).

reinforcer is pointed out to the child so that he/she learns to associate the sound with the reinforcer activation (reward). During the test phase, the child's attention is kept forward and tones are occasionally delivered via the loudspeaker without reinforcer activation. If the child turns to look at the reinforcer, then it is activated (to maintain conditioning) and the response is taken to indicate positive hearing. The sound level is reduced until the child does not respond, so that the threshold for that frequency can be estimated. Several frequencies are usually tested, but the thresholds obtained relate to the 'better' ear, i.e. a child may not hear on one side but still be able to respond normally using the good ear. VRA is therefore sometimes performed with the sounds delivered by insert phones rather than a loudspeaker, in which case ear-specific thresholds can be measured.

Pure tone audiometry (PTA) is considered the ideal behavioural hearing test because it depends on active listening. Headphones are used to deliver short tones at individual frequencies. Older children are required to press a button each time the tone is heard, but the test may be modified in younger children ('play audiometry'), where the response will involve actions with toys. The level of each tone is adjusted to identify thresholds. Children as young as 2½ years can usually be tested using some form of PTA.

To differentiate between conductive and sensorineural hearing losses, visual reinforcement audiometry (VRA) and pure tone audiometry (PTA) can also be used to measure bone conduction (BC) thresholds using a bone vibrator in place of loudspeaker or headphones. The vibrator is held over the mastoid bone by a flexible band and by-passes the middle ear, indicating the status of the cochlea. The skull vibrations pass to both ears more or less equally, and so measured thresholds actually represent the better ear,

though it is often possible to measure ear-specific BC thresholds by 'masking' the opposite ear.

Auditory processing tests

Some children can have difficulties in understanding speech even though their auditory thresholds appear to be normal. Such cases may be due to auditory processing disorder (APD). Specialized tests are available to assess central processing, which include components such as auditory memory (digit span) and competing speech (where target words or phrases presented to one ear are repeated by the child while competing speech is presented to the opposite side). Results are compared to age-specific norms (typically for ages of around 7–12 years).

Tympanometry

Temporary middle ear congestion is common in young children and can produce a conductive hearing loss which increases thresholds by up to 30–40 dB. Tympanometry is therefore usually performed as part of a hearing assessment, which is a physical measurement not requiring any patient response. A probe is placed in the ear canal for a few seconds, which delivers a tone and changes the air pressure. The way in which the pressure changes affect the sound level developed in the ear canal provides information about the status of the middle ear (Fig. 31.9).

x

CHAPTER THIRTY-ONE

Treatment of hearing loss

Conductive hearing losses

Temporary conductive losses

Temporary conductive hearing loss due to middle ear congestion (otitis media with effusion; OME) is very common in children, particularly in the pre-school years and with certain conditions such as Down's syndrome. There may be tympanic membrane retraction, middle ear fluid and sometimes perforations if fluid has become infected. All of these produce some degree of conductive hearing loss. Typically, this will be in the order of 20–40 dB, and tends to be predominantly in the low frequencies. The hearing loss may be unilateral, but both ears are often affected at similar times.

Such hearing losses do not usually have a major functional impact, at least in the short term. Parental speech is usually audible as long as the parent is reasonably close. School-aged children tend to be affected more severely than younger children, as they often have to cope with high levels of classroom noise as well as more distant speakers.

As OME usually resolves within days or weeks, the first-line of treatment is to monitor the situation, with parental advice to keep the voice full and clear (but without shouting) and with awareness of the effects of speaker distance and background noise. Medical intervention would not usually be considered until the condition has persisted for several months with documented significant hearing loss. Although a formal hearing test would usually be performed at some point, particularly before intervention is considered, the disease status can often be satisfactorily monitored by tympanometry alone, typically performed every month or so.

If the condition is bilateral and persists for many months, then surgical intervention may be considered, though this strategy is not universal. The condition often recurs after initially successful intervention, so that some ENT clinicians feel that intervention is not always justified. Surgical intervention usually involves myringotomy (small incision in the tympanic membrane) under general anaesthetic, aspiration of middle ear fluid and insertion of a grommet, which maintains aeration of the middle ear. Grommets usually extrude naturally after several months, by which time the cause of the problem (usually inflammation of the Eustachian tube) has resolved, though specially designed ventilation tubes are available if longer term treatment is required.

Occasionally, hearing aids (covered in more detail below) may be prescribed if there is a longstanding hearing loss, though, again, this practice is not universal. Amplification of conductive hearing loss is usually very effective as the cochlea is usually normal, but there may be other practical difficulties. Parents need guidance in order to ensure that their child benefits from aiding, and practical difficulties may largely offset potential benefits. Another problem is that OME often produces hearing losses that fluctuate in severity over time, so that a child using hearing aids may be under- or over-amplified at different times.

Permanent conductive losses

Craniofacial abnormalities involving the outer and/or middle ear often produce permanent conductive hearing losses. There may be a deformed or absent pinna, absent external auditory meatus or ossicular or other middle ear abnormalities. The resultant hearing loss will be permanent, stable and may be severe (up to around 60 dB), particularly if there is an absent auditory meatus. The cochlea is usually (but not always) normal or near-normal.

Reconstructive surgery is rarely effective in addressing these hearing losses, but may be of significant benefit for cosmetic purposes, particularly if the pinna is severely affected.

Hearing loss is therefore usually managed using various types of hearing aids. Conventional 'air conduction' aids may be used in some cases, but more often bone conduction aids are required in order to by-pass the conductive loss. These may be body-worn or ear level, but with a bone vibrator placed on the mastoid bone instead of sound output to the ear canal. The acoustic signal provided by these aids is generally good, but there are significant practical difficulties in keeping the vibrator in place, especially in a young child, and the headbands can be uncomfortable.

In recent years, there has been a large increase in the use of bone-anchored hearing aids (BAHAs). These use a titanium fixture surgically-implanted into the mastoid bone. An external processor (similar to a hearing aid) picks up external sounds and vibrates the implanted fixture. The vibrations pass through the skull very effectively to stimulate the cochlea (on both sides) in a similar manner to measurements of bone conduction thresholds in audiometry.

There are several types of commercially available BAHA, of two fundamental designs. Some use a 'percutaneous' abutment, which protrudes a few millimetres through the skin. The external processor is directly connected to the abutment and can be coupled or removed as required. The alternative design is 'transcutaneous', in which the external processor produces vibration of an implanted magnet by electromagnetic induction across the intact skin (Fig. 31.10). Transcutaneous systems are often favoured for cosmetic and infection control reasons, but they cannot address sensorineural elements of a hearing loss as effectively as
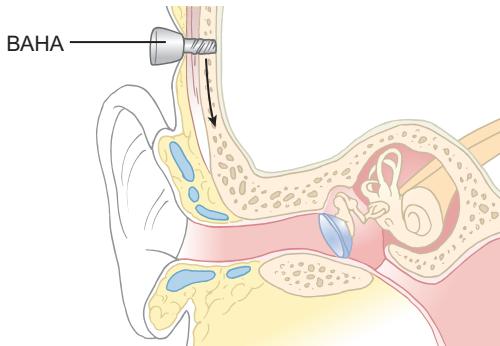
Fig. 31.10 Bone-anchored hearing aids showing the mode of action of a percutaneous device. The external processor vibrates the implanted fixture by direct coupling via the abutment and vibrations pass to the cochlea through the bone.

Fig. 31.11 Diagram of a cochlear implant.

percutaneous systems. In general, BAHAs are more acceptable than headband BC devices and provide a superior sound quality. They are also often used in cases of chronically discharging middle ears, as these may be exacerbated by the use of air conduction aids, which occlude the ear canal.

Sensorineural hearing loss

Sensorineural hearing losses may be of any severity or audiometric configuration, though severe and profound losses tend to be more pronounced in the high frequencies. They are almost always permanent but sometimes deteriorate further over time. In children, the majority of sensorineural losses are congenital or linked to neonatal factors, and nowadays most are identified through the Newborn Hearing Screening Programme. Any pre-lingual bilateral hearing loss of moderate degree or greater will potentially affect language acquisition in the early years, so that early intervention is of vital importance.

Apart from various types of short-term medication for certain specific conditions, such as antiviral therapy for congenital CMV, there are currently no medical or surgical treatments that can reverse sensorineural hearing loss, so the primary treatment is provision of hearing aids.

Hearing aid provision is managed by hospital audiology departments, who review children on a regular basis and usually provide open access for repairs and production of new ear moulds. Modern digital aids are computer-programmed in order to adjust their output to match the type and severity of the hearing loss. Some also have advanced sound processing features, such as directional microphones and noise reduction algorithms, and they may be compatible with external devices such as FM systems (see below).

All school-aged and most pre-school children also receive support from a multi-disciplinary team, which usually includes audiovestibular physicians, teachers of the deaf, speech and language therapists, ENT, and sometimes educational psychologists.
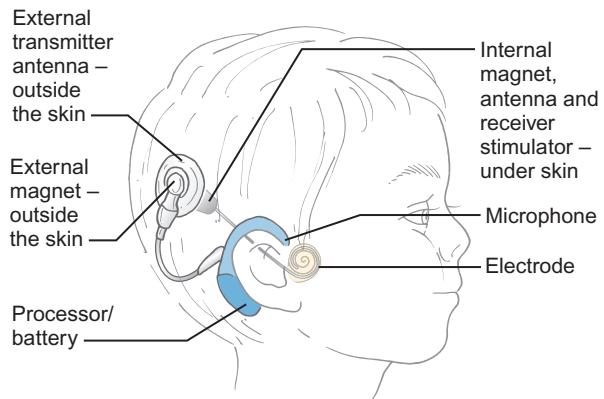
Cochlear implants

Sometimes a hearing loss is very severe or profound and conventional hearing aids are not able to provide sufficient amplification for speech understanding. In this situation, a cochlear implant (CI) may be considered, which effectively substitutes for the defective transduction of sound into neural signals that is normally achieved by the cochlear hair cells. If there is extensive inner hair cell damage, then an acoustic signal is unable to provide a satisfactory auditory percept, no matter how much amplification is provided.

The fundamental role of the CI is therefore to stimulate the peripheral neural elements electrically. Following inner hair cell loss, the primary afferent axons often degenerate, but many of the spiral ganglion cell bodies (together with their central projections) survive and these provide the main target neural elements for electrical stimulation.

There are several commercially available CIs, but they all have a basic layout, as illustrated in Figure 31.11. An external ear-level processor (inset) picks up sounds from the environment, processes them and passes the signal to an external transmitter coil. The transmitter sends a coded signal, together with electromagnetic power, through intact skin, to a surgically implanted receiver embedded in the mastoid bone. The receiver decodes the signal to produce a sequence of rapid electrical pulses, which are delivered to a row (array) of electrodes inserted into the scala tympani of the cochlea via the round window.

The incoming sound signal is divided into frequency bands, with low-frequency signals ultimately delivered to the most apical (deepest) of the implanted electrodes and high frequencies to the basal end of the

cochlea, thereby maintaining its normal tonotopicity. The amplitude of the rapid stimulating current pulses is modulated in order to represent loudness changes over time within each frequency 'channel'. Auditory thresholds using a CI are typically around 20–25 dB HL, so that all but the quietest speech sounds are audible.

A CI does not restore normal hearing; most adults describe the percept as 'robotic', but many recipients are able to follow speech without lip-reading except in very noisy conditions. Children with profound congenital hearing losses who receive CIs at an early age (typically between 12 and 24 months) usually develop near-normal speech and language and are able to attend mainstream schools.

Provision of CIs in children is through about 20 dedicated centres in the UK, which receive most referrals through tertiary ENT and audiological services. Referral criteria are based on NICE guidelines.

Auditory brainstem implants

In very rare instances, there is gross abnormality of cochlea, absent cochlea, or absent cochlear nerve. Auditory brainstem implant can be considered but is not widely available.

Assistive listening devices

In addition to hearing aids or CIs, many children with significant hearing loss are often provided with assistive listening devices (ALDs), which may be supplied by social and/or educational services. There are a variety of devices, such as doorbell and telephone amplifiers, and devices providing an interface between phones, televisions, etc., and hearing aids (via direct input). The most important ALDs in educational settings are personal FM (frequency modulation) systems, consisting of a transmitter worn by the teacher and a receiver worn by the child, which uses the direct input option of the hearing aid or CI processor. FM systems are very effective in reducing the deleterious effects of classroom noise.

Summary

There are about 45,000 hearing-impaired children in the UK. Hearing loss in children may be due to genetic or environmental factors. Aetiological investigation is important for both management and counselling parents. Prompt evaluation and rehabilitation is vital in order to minimize the effect on the child's language and social development.

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Nwanneka N Sargant, Lee Hudson, Janet McDonagh

Adolescent medicine

Adolescent healthcare has come a long way since Amelia E Gates, a San Francisco physician, established the first dedicated adolescent clinic at Stanford in 1918. However, a century later, the healthcare provision for young people is still in major need of improvement (see Chief Medical Officer's report, 2012). Although it has been included as a separate chapter, there are important strands of adolescent medicine woven through many of the other chapters.

What is adolescence?

Adolescence is the transition from childhood to adulthood. It is a complex sequence of profound biological, psychological and sociological changes, which can have a significant impact on a young person's health and behaviour. Perhaps because of their proximity to adulthood, it is frequently forgotten that young people are at a genuine developmental stage with specific needs just like children at other ages. They are not yet adults, but neither are they children. This needs to be considered when trying to understand their behaviours and specific health requirements. It is facilitated by adopting a life-course approach to healthcare where adolescence is seen as integral in the continuum between childhood and adulthood.

Defining adolescence according to specific ages is problematic because, as in other aspects of child development, there is much variation in both timing and tempo between individuals (Box 32.1). Throughout this chapter, the WHO definition of adolescence of 10–19 years will be used. The start of adolescence reflects the onset of puberty and begins earlier in girls with breast budding, normally at 10–11 years. Defining an end to adolescence is more complex, although the provision in law of minimum age limits is implicit of society's expectation that sufficient neurodevelopmental competencies for important adult responsibilities (e.g. voting) will have been acquired by 18 years of age. In legal terms, young people under the age of 18 in the UK are still provided for under the Children Act of 2004, with parental responsibility taking prominence. However, concepts of competence have changed in recent years to allow young people under the age of 18 years to be able to give consent for their own treatment (see Chapter 35, Ethics) and neuroscience research suggests that adolescent brain development continues well into the third decade.

Cultural aspects of a young person's life are also important in defining a transition from childhood to adulthood. Commencement of adult social roles, such as employment and childbirth, can occur during adolescence. In high-income countries, it is interesting to reflect on the widening gap which exists between childhood and key early adult life events, which have traditionally represented autonomy and independence (such as marriage, first child and leaving the family home). This has mostly been driven by

WHO definitions:
Adolescent: 10–19 years
Young people: 10–24 years
Youth: 15–24 years
Other:
Teenage: 13–19 years
Young adult: 16–25 years
Adolescent developmental stages:
10–13 years: Early adolescence
14–16 years: Mid adolescence
17–19 years: Late adolescence
19+ years: Emerging adulthood

socio-economic changes, and in the past 30 years, a significant popular cultural movement has also developed specific to adolescence, with commercial recognition of the influence the adolescent age group has. The rise of this cultural movement has been associated with both positive and negative effects on adolescents.

Epidemiology

There have never been as many young people in the world as there are now, with a quarter of the global population represented by 10–24-year-olds. In the UK, young people represent 12.5% of the population, a similar proportion to the over 70-year-olds and the 0–9-year-olds. A fifth of adolescents in the UK are from ethnic minorities.

Lifelong health behaviours develop during adolescence and therefore it is important to promote healthy lifestyles during this life stage in order to influence long-term health outcomes. Health promotion is discussed in detail later in this chapter. A significant proportion of the 11–18 year age group are overweight or obese (31% of boys and 37% of girls), whilst much smaller proportions of young people meet recommended levels of physical activity, with girls being worse than boys. It is recognized that half of all lifetime cases of psychiatric disorders manifest by age 14 and three quarters by age 24. Studies have shown that approximately 13% of boys and 10% of girls aged 11–15 years have mental health problems, with conduct disorders being most common in boys and emotional difficulties in girls. Mental health is covered in Chapter 24, Child and adolescent mental health, and substance use and sexual activity will be discussed later in this chapter.

Long-term conditions or disabilities affect a significant minority of adolescents. One study in England found that one in seven young people aged 11–15

reported having been diagnosed with a long-term medical illness or disability. Furthermore, two thirds of those with a long-term condition were taking medication and one third reported that their condition affected their engagement with school. Long-term pain and chronic health conditions were the most common forms of impairment experienced by older adolescents and young adults. Advances in medical care have resulted in increasing numbers of these young people with chronic illnesses (such as cystic fibrosis, congenital heart disease, inherited metabolic disease, cancer and cerebral palsy) surviving into adulthood, whereas previously they died in childhood. These survival rates have major implications for the development of transitional care provision as young people move from child- to adult-centered health services.

A number of long-term conditions are characterized by a peak age of onset in adolescence and young adulthood. These include type 1 diabetes, inflammatory bowel disease, juvenile systemic lupus erythematosus, eating disorders and other mental health disorders. The number of hospital admissions in England among 10–19 year olds for diabetes, epilepsy and asthma has been increasing over the last decade. These increased admission rates raise questions about the standards of care for young people with long-term conditions, particularly around the transfer from paediatric to adult care.

Determinants of adolescent health

Health is affected by a wide range of social, economic and environmental factors irrespective of the age of the individual. In the UK in 2010–2011, more than a fifth (22%) of young people aged 11–15 years were living in families with the lowest levels of income and at increased risk of ill-health. Adolescence is a key period for establishing both health promoting as well as health risk behaviours, which in turn are influenced by family, peers, local community and education. Since such behaviours track into adulthood, social determinants of adolescent health are crucial to the health and economic development of the society they live in.

The strongest determinants of the health of adolescents worldwide are national wealth, income inequality and access to education, closely followed by family, schools and peers. Improving adolescent health will therefore need to consider these issues in addition to improvements in access to education and employment for young people and the reduction of risk of road traffic accidents. In the UK, although participation in further and higher education has increased in

recent years, youth unemployment has also risen and was 14% in 2015, almost three times the overall rate. The health of these adolescents and young adults who are not in employment, education or training is of increasing concern.

Mortality in adolescence

Adolescence is often considered a healthy stage of life, but there are deaths among 10–24 year olds which are often preventable. The main causes of death in this age group are external, namely traffic accidents, violence-related or self-harm, followed by neoplasms, diseases of the nervous system (e.g. muscular dystrophy) and congenital and chromosomal abnormalities.

Table 32.1 Infant and childhood mortality rates by age and sex, UK, 2012

Age (years)	Male	Female	Overall	Number of deaths
Infant deaths per 1000 live births				
	4.4	3.5	4.0	3219
Deaths per 100,000 population in age group				
1–4	18	15	16	523
5–9	9	8	9	325
10–14	11	8	10	340
15–19	33	15	24	959

Source: Office for National Statistics. (From: Why children die: death in infants, children, and young people in the UK Part A. © Royal College of Paediatrics and Child Health and National Children's Bureau 2014.)

Although overall trends have been decreasing since 2003, death in the 15–19 and 20–24-year-old age groups is more common than in younger children if infants are excluded. In particular disease groups, the reduction in mortality seen in other age groups has not occurred. For example, adolescent-onset cancer mortality is unchanged compared to the improved rates in child and adult-onset disease. Rejection-related death following cardiac transplant is highest in the adolescent and young adult age groups. The explanation for these differences is not yet known, but intrinsic factors, such as the impact of aspects of adolescent development including puberty and brain development, as well as extrinsic factors, such as health service provision, are likely to be contributing factors.

Resilience

The other core principle underpinning adolescent medicine is that of resilience. Resilience refers to the ability to rebound from adversity and be flexible and adaptable, with resilient individuals even managing to thrive against what appears to be overwhelming odds. When taking a history from a young person, it is important to consider resilience as well as risk. What talents, resources and skills does this individual young person possess which will protect his health and emotional well-being? The HEADSSS psychosocial screening tool is useful in this regard (Table 32.2).

Table 32.2 HEADSSS acronym for psychosocial history in adolescents

H	**Home life**	Relationships, social support, household chores
E	**Education**	School, exams, work experience, career, university, financial issues
A	**Activities**	Exercise, sport, other leisure activities Social relationships, friends, peers, who can they rely on?
D	**Driving**	Aged 16 if has high-rate mobility component of the Disability Living Allowance (DLA)
	Drugs	Drug use, cigarettes, alcohol. How much? How often?
	Diet	Weight, caffeine (diet drinks), binges/vomits
S	**Sex**	Concerns, periods, contraception (and in relation to medication)
	Sleep	How much? Hard to get to sleep? Wake often?
	Suicide/affect	Early waking? Depression, self-harm, body image

(From: Tom Lissauer, Graham Clayden. Illustrated Textbook of Paediatrics, 4th edn. Edinburgh: Mosby Elsevier, 2012.)

Adolescent medicine

Which of the following statements are true (T) and which are false (F)?

A. Back pain is a common, usually benign symptom in late adolescence (17–19 years).

B. During adolescence, most boys have an increase in percentage body fat.

C. The risk of limb length abnormality in children with juvenile idiopathic arthritis (JIA) is greatest during puberty.

D. The risk of permanent reduction in adult height is greater in girls with an eating disorder than in boys.

E. Vitamin D levels are usually higher in adolescence than in younger, school-aged children.

Answer 32.2

A. True; B. False; C. True; D. False; E. False.
See below for discussion.

Specifics of adolescent development

Physical development

The physical hallmark of development in adolescence is puberty. This has been discussed in detail in Chapter 12, Growth and puberty. In girls, the growth spurt occurs before the onset of menses, whereas in boys, the growth spurt occurs later. In certain conditions, this has significant consequences. The peak onset of eating disorders in males tends to occur before or during the growth spurt, whereas, in females, onset is typically after the growth spurt. Risk of growth stunting following eating disorders is therefore higher in males.

Rapid growth seems to increase the risk of some symptoms. Adolescent back pain is more common in those with increased truncal length. Back pain occurs commonly in adolescents, affecting up to 50% of children by age 18–20 years. Whilst an underlying cause is not identified in most children, it is important to consider spondylolysis and spondylolisthesis, particularly in active and rapidly growing adolescents.

Spondylolysis is a fracture of the pars interarticularis or pedicle. This is most likely to affect the lower lumbar vertebrae and be caused by an injury or repetitive activity. The activities that most likely cause spondylolysis include extension (bending backwards) and rotation. Spondylolysis can also cause back pain in children, especially those that are active in sports. It may happen in 4–5% of children by the age of six, and up to 6% of adults. Spondylolysis is three times more common in boys than girls. Growth spurts and involvement in contact sports may explain this observed sex difference. Spondylolysis may cause pain in a particular spot in the low back and spasm of the muscles along the spine. Often it will cause pain into the buttocks or thighs.

Initially, plain spine X-rays may not show a fracture and MRI scanning of the spine may be required to confirm the diagnosis. It is likely to heal with a change in activity, rest, and avoiding hyperextension and rotation. Bracing may be helpful if symptoms do not improve. If symptoms do not improve, spondylolisthesis, the forward displacement of one vertebra on another, may be responsible.

Likewise, premature fusion of epiphyses, which may also occur as a consequence of inflammatory arthritis leading to asymmetrical growth, should be considered during examination of affected young people. Distribution of drugs can be affected by the changes in body size and composition characteristic of puberty. The increase in lean body mass during adolescence is usually greater in boys than girls, resulting in girls having relatively more body fat than boys in late puberty; this has implications for the volume of distribution of some drugs.

Pubertal assessment (including the identification of abnormal pubertal timing) is important in all clinical interactions with young people, particularly with respect to the impact of puberty on psychosocial development. The use of pubertal self-assessment tools are useful in the clinical consultation and provide a means of facilitating discussions in this area with individual young people.

Other aspects of adolescent physical growth include bone mass development, with 40% of adult bone mass being accrued during this period. This is coupled with a reduction in observed vitamin D levels, which can result in suboptimal bone mineralization, an increased fracture risk and more commonly bone pain.

The proportion of children with vitamin D insufficiency increases with age. In the UK, 11–16% of adolescents (aged 11–18 years) have vitamin D deficiency compared to less than 7% of children aged between 1.5 and 10 years of age. This has led to some countries, like the USA, to recommend routine vitamin D supplementation for all adolescents.

Psychological development

Development of a perception of one's own body, such as how it looks, feels and moves (body image), is

associated with the rapid changes in the physical body that come with puberty. Body image is shaped by perception, emotions, and physical sensations and can vary in response to mood, physical experience and environment. There are intrinsic influences of body image (self-esteem and self-evaluation) as well as extrinsic influences (evaluation by others, cultural messages and societal standards). Addressing body image, particularly in the peri-pubertal phase, is important.

The other key features of psychological development in adolescence were first described in 1929 by Piaget and later by Erikson in 1950. Piaget identified that during adolescence there is a shift in cognitive style from the concrete processes of childhood to more abstract ways of thinking, allowing problem-solving using hypotheses and propositions. Erikson then identified search and acquisition of identity as being characteristic of development in adolescence. Both abstract thought and independent identity are important skills to acquire for successful function as an adult. These are important concepts for doctors working with young people, as a better understanding of the cognitive level of individual young people will inform the consultation and help to understand the impact of current interventions and exposures upon future health outcomes. For example, the use of immediate motivators are preferable with concrete thinkers whereas future motivators are fine to use with abstract thinkers. The different perceptions of young people undergoing similar problems is important to consider in consultation and is exemplified in the case history below. Finally, one must recognize that there may be delay in the development of abstract thought in adolescents with chronic conditions or regression to concrete thought during times of stress.

Case history

Adherence to drugs

A 13-year-old boy with juvenile idiopathic arthritis has come to see you in clinic. His mother tells you that he has not been taking his methotrexate as regularly as you had prescribed. The boy says that he is feeling fine at the moment.

Question: What do you think a young person who has developed concrete thinking skills will believe about the need for methotrexate, prescribed as a long-acting, disease-modifying antirheumatic medication?

Answer: The doctors told me that if I miss my methotrexate then my arthritis will get worse, but I have forgotten it a couple of times and haven't got worse so I don't think I need it any more.

Question: What do you think a young person who has developed abstract thinking skills will believe about the need for methotrexate?

Answer: I missed my methotrexate because I was busy and forgot to take it. However, I realize it is a long-acting sort of drug and I still need to take it in order to stop the arthritis coming back and doing long-term damage to my joints, so I've put an alarm on my phone which will hopefully remind me to take it in future.

Social development

The key social developmental milestones during adolescence are detailed in Box 32.2. Assessment of social development should be routine during all adolescent consultations in view of the implications for the rest of development (i.e. physical, cognitive and psychological). The role of peers and close friends is important during adolescence, particularly with regard to sources of support and influence on adherence and health promoting and health risk behaviours.

Vocational development is another key series of adolescent milestones to consider and not simply one of assessment of educational achievement. Vocational readiness also encompasses prior work experience, communication skills (including those of disclosure), expectations of the young person, family, psychological state (such as self-esteem), knowledge and resources. Impact of a health condition on such development is integral to adolescent health practice.

Social development may be difficult for parents and carers, who may struggle when a young person starts to question previously concretely held views, especially around healthcare. Young people may also find an increased confidence and interest in peer opinions, which may differ from that of their parents! It should be remembered that abstract thought and identity

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Box 32.2 Social developmental milestones during adolescence

Early adolescence
- Realization of differences from parents
- Beginning of strong peer identification
- Early exploratory behaviours

Mid adolescence
- Emotional separation from parents
- Strong peer group identification
- Exploratory/risk behaviours
- Early notions of vocational future

Late adolescence
- Development of social autonomy
- Development of intimate relationships
- Development of vocational capability

development might come into conflict during decision-making in a young person's health behaviour – for example, a young person with diabetes might understand that withholding their insulin and eating a high-sugar snack will make their blood sugar rise and make them feel unwell; but also might feel conflicted with the possibility of appearing different whilst out for a meal with their peers.

Question 32.3

Adolescent brain development

Regarding the development of the adolescent brain, which of the following statements is most correct? Select ONE answer only.

A. Behavioural and MRI studies have shown that there is no development of executive functions.

B. Changes in the frontal and parietal regions are particularly pronounced.

C. Grey-matter development is linear.

D. There is a marked decrease in the proportional content of the central dopaminergic regions of the brain.

E. There is no remodelling as neural plasticity ceases by the age of 10.

Answer 32.3

B. Changes in the frontal and parietal regions are particularly pronounced.

MRI studies confirm non-linear grey-matter development in the frontal and parietal regions of the adolescent brain.

Integrating psychological and physical development through neuroscience

Recent advances in the field of magnetic resonance brain imaging have allowed a better understanding of brain development during adolescence. Whilst most brain size has been acquired by late childhood, rates of neuronal pruning are at their greatest level since the neonatal period. Adolescent brain development initially sees a significant increase in the proportional content of the central, dopaminergic regions of the brain – areas associated with sensation-seeking and important for learning new skills. At a later stage of adolescent development, there is more pronounced development of the prefrontal cortex, which is responsible for executive function, and can be thought of conceptually as the domain of abstract thought and forward planning. This process continues well into the
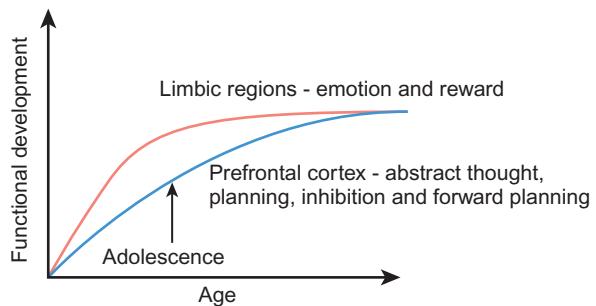
Fig. 32.1 Brain development and the adolescent mismatch. *(From Casey BJ, et al. The adolescent brain. Ann N Y Acad Sci 2008;1124:111–26, with permission.)*

Table 32.3 Pubertal timing and adolescent development

Early puberty	Late puberty
↑ risk of substance use	↓ self-esteem in boys
↑ risk of early sexual behaviour	↑ risk of osteopenia in girls
Self-esteem – ↓ girls, ↑ in boys	↑ frequency of disturbed body image in boys
↑ risk of depression and other psychological problems in girls	
↑ frequency of disturbed body image in girls	
↑ engagement in exploratory & delinquent behaviour	

third decade. The time lag between growth in the central areas of the brain and the prefrontal cortex effectively leads to a period of developmental mismatch between activity and control (Fig. 32.1) – a period of time associated with greatest risk and of key importance in health behaviours in young people.

These processes appear to start earlier in females and finish later in males. Although it is attractive to link these events with the physical events observed in puberty, studies have yet to capture such an association effectively. The amount of brain development which occurs in adolescence has significance for exposure to drugs and alcohol during this period. Pubertal timing in itself has implications for aspects of both social and psychological development (Table 32.3) and it is therefore important to acknowledge that chronological age is not always a good correlate of adolescent developmental status.

Engaging young people

Communication

Communication with young people needs to reflect the cognitive, emotional, social and behavioural changes in development throughout adolescence, mentioned already in this chapter.

Young people value adults who are approachable, open, trustworthy, honest, who listen, explain things in ways they understand, take the time to learn how

they prefer to communicate and are not patronising. Paediatricians need to adopt all of these skills for effective consultation whilst being aware of the dynamic shifts in parental roles, which occur during adolescence. The right of children and young people to participate in matters affecting them, including healthcare, is laid out in both Article 12 of the United Nations Convention on the Rights of the Child (UNCRC) and *Working together to safeguard children*, encouraging professionals to hear 'the voice' of children and young people. The Department of Health's *You're welcome* document focuses on including, involving and supporting the participation of young people in healthcare, promoting the idea that hearing and responding to the voice of young people is central to the delivery of good healthcare.

Two fundamental aspects of adolescent healthcare are, firstly, the opportunity for young people to be seen independently of their parents/caregivers and, secondly, that they understand their rights with respect to confidentiality. Data would suggest that such practices are not yet universal. Autonomy during clinic visits has also been reported to be a major determinant of transition readiness for young people with long-term conditions. A core component of the consultation is the assessment of the young person's understanding of what confidentiality means and the conditions when confidentiality has to be broken. Research suggests that such confidential care is of particular importance to young people, who will forgo healthcare if confidentiality is not assured (in particular, those who are not getting on with their parents, who exhibit health risk behaviours and/or have mental health issues).

Motivational interviewing techniques (the idea that motivation to change is elicited from the young person, and not imposed from outside forces) are ideal for use with adolescents, as they address resistance or ambivalence as well as emphasizing self-responsibility in changing or modifying one's behavior. For example, asking the young person questions such as 'How might you like things to be different?' or 'How does _____ interfere with things that you would like to do?' encourages them to suggest behavioural changes themselves and thus set realistic goals.

Adolescents are reported to be worse at reading facial expressions and body language than either children or adults. The young person may think that the health professional is angry when they are simply concentrating on a physical exam, or thinking about which drug dose to use.

The wording of questions should bear in mind the stage of adolescence. Questions such as 'How are you doing at school?' during early adolescence are guaranteed to get a single word response such as 'OK' or 'fine'.

Better wording such as 'Which school do you go to?' or 'Which subjects do you enjoy?' open up discussion and are more developmentally appropriate.

A proactive, anticipatory approach to adolescents is advocated by using tools such as HEADSSS and supported by evidence that suggests young people are more likely to have positive perceptions of the health professional and are more likely to take an active role in treatment when there has been discussion of a sensitive health topic. Opportunistic use of the HEADSSS tool has been shown to result in the identification of issues requiring intervention in almost a third of adolescents.

Question 32.4

Consent and the UK law

Which of the following statements concerning current UK law are true (T) and which are false (F)?

A. A social worker, nurse or teacher who has consensual sex with a 17-year-old is committing a sexual offence.

B. Consensual sex between two 14-year-olds is lawful where both parties are 'Fraser competent'.

C. Sex between a 12-year-old girl and a 14-year-old boy would not be classified as 'rape' if she fully consented and was deemed to be 'Fraser competent'.

D. The age of consent is 16 years for heterosexual activity and 18 years for homosexual activity.

E. The duty of confidentiality owed to an 18-year-old girl seeking contraception is absolute.

Answer 32.4

A. True; B. False; C. False; D. False; E. False.

The Sexual Offences Act provides a tier of protection for 'older' children (16–17-year-olds) from adults in a 'position of trust' where the adult has a professional relationship with the young person – consent of the young person is NOT relevant. Although prosecution for consensual sex between individuals under 16 is uncommon it is unlawful. Penetrative sex with an individual under 13 years is classified as rape. The age of consent for heterosexual or homosexual sex in the UK is 16 years. There are many possible reasons for breaking confidentiality and it is not an absolute duty. See www.gmc-uk.org/guidance/ethical_guidance/confidentiality.asp for further details.

Consent and the UK law

All people aged 16 and over are presumed in UK law to have the capacity to consent to medical treatment unless there is evidence to the contrary. Children under 16 may also be legally competent if they have sufficient understanding. Encouraging adolescents in decision-making may aid the 'non-competent' adolescent in the development of competency over time, by presenting them with information appropriate to their age and level of education. By exploring adolescents' wishes and feelings about their health issues and discussing management options with them whilst they still have the support of their parents, healthcare professionals can empower young people to make their own decisions and prepare them for adulthood. Chapter 35, Ethics, discusses issues of consent and competency in greater detail.

Chronic pain syndromes

Pain is a common presentation during adolescence, with a prevalence of up to 25% of young people presenting with pain. When this pain becomes chronic (longer than 3 months), young people may experience adverse effects on their psychosocial or vocational development. This in turn leads to significant cost to UK society. Furthermore, chronic pain in childhood and early adolescence has been linked with chronic pain in early adulthood. Effective pain management during adolescence is therefore of prime importance.

The mean onset of chronic pain syndromes is early adolescence, with greater female predominance. Frequency of pain is reported to increase with age and the commonest sites of pain in the absence of an underlying condition are headache, abdomen, limbs and back. Pain is also increasingly recognized as a significant morbidity in association with other long-term conditions including cystic fibrosis, cerebral palsy and juvenile idiopathic arthritis. In young people with cerebral palsy, pain is a major determinant of health-related quality of life.

Fatigue and sleep disturbance are frequent associated symptoms of chronic pain and asking about them is integral to the assessment of affected young people. Chronic pain may also result in school absence, impaired leisure and peer activities, as well as psychological problems.

The purpose of pain is to act as a motivational driver for protection. Pain is closely associated with fear and stress responses as part of a protective mechanism. Even when the threat is not real, the brain may misinterpret signals (e.g. stress) as a 'threat', leading to a pain response.

There is growing evidence that the brains of people with chronic pain are different at a functional, structural and molecular level. These changes are reversible, but it is not known whether these changes represent cause or effect.

The pain neuro-matrix is the combination of cortical mechanisms which produce pain when activated. This matrix encompasses both nociceptive and non-nociceptive (cognitive, beliefs and attitudes) mechanisms, all of which need to be considered when assessing an adolescent with chronic pain. Once activated, there is increasing conviction of the central nervous system that body tissue is in danger and under threat. Whilst the threat remains, so will the pain. Hence, any pain management programme needs to both identify and reduce the threat.

The mainstay of pain management in adolescents is a multidisciplinary approach. These frequently include several of the following components: education, goal-setting, a graded activity programme with pacing, anxiety management and relaxation, sleep hygiene, coping strategies, desensitization, relapse prevention and school reintegration. Cognitive behaviour therapeutic techniques are particularly useful with modification of negative and unhelpful thinking and relapse prevention. Outcomes have been reported to be much better than in adults, with the majority experiencing complete recovery.

Exploratory and risk behaviours

Exploratory behaviours are part of normal adolescent social development and only when they become unsafe or risky do they become health risk behaviours. Smoking, drug and alcohol use, dangerous driving, violence, shoplifting and unprotected sexual activity all occur in young people at increasingly younger ages. Most adolescents emerge from this transitional stage well, but genetics and childhood experience all affect behaviour. In addition, we are starting to understand how these factors act in the context of a brain that is changing, with its own impact on behaviour. As cognitive control over high-risk behaviours and the ability to moderate behaviour in social situations is still maturing, they are more likely to engage in risky behaviours. Evidence suggests that health risk behaviours started in adolescence tend to persist into adult life.

Substance use

The main substances used by adolescents in the UK today are alcohol, tobacco, and cannabis. Alcohol is currently the substance of greatest concern in the UK.

A fifth of young people aged 16–24 are exceeding the recommended limit of 21 units of alcohol per week for men, and 14 units for women. The proportion of school-aged children drinking has decreased slightly in recent years. However, the mean weekly consumption by school children has increased. About 40% of young people report binge drinking. The UK has one of the highest rates of admission to the emergency department or hospital due to alcohol use in 15–16-year-olds in Europe.

Current trends suggest that the number of adolescent smokers is decreasing in the UK. There are, however, more female smokers than male. One hypothesis is that this discrepancy is related to the greater use of tobacco for weight control in females. Smoking in young people remains a significant concern due to long-term consequences, such as addiction, carcinogenic effects and the reduction of the oxygen-carrying capacity of the blood by carbon monoxide, but also short-term effects, such as respiratory illness and decreased physical fitness. Smokers are more likely to use alcohol, smoke cannabis and use other illegal drugs, in addition to participating in risky behaviours. Two thirds of new smokers start before the age of 18. The impact of electronic cigarettes in this age group is as yet unknown.

Since 2001, there has been a downward trend in the school-aged population who report using illegal substances at any point in the last year. In 2011, 26% of 13–15-year-old males and 21% of females reported some experimentation. The substance most commonly used is cannabis. Use of class A drugs, volatile substances (glue sniffing, etc.) and other drugs is much rarer.

There has been concern about a growth in the availability of synthetic or new drugs that have not yet been made illegal and are available on the internet ('legal highs'). The most popular are synthetic cannabinoids, and speed or ecstasy-type substitutes. There has also been an increase in the popularity of energy drinks amongst young people. The main psychoactive ingredient tends to be caffeine, but they also contain varying quantities of other potentially harmful substances. Robust research on prevalence and use is not yet available for the UK.

When screening for smoking practices, it is important to clarify exactly what young people smoke, i.e. tobacco alone or with cannabis. Young people who co-use cannabis and tobacco are reported to have greater dependency, more psychosocial problems and poorer cessation outcomes.

Case history

Substance misuse

Joseph, a 14-year-old boy is admitted to the emergency department with a history of being hyperactive, restless and 'not himself'. His pupils are dilated. He admits to smoking cannabis and taking 'a pill' at a party, but is not sure what it was.

What advice would you give him about the consequences of cannabis use?

The use of cannabis in adolescence has been linked to a range of developmental and social problems. Research suggests that persistent use is associated with significant neuropsychological disturbance, including cognitive and memory problems and declining IQ. Significantly, studies indicate that cessation of marijuana use does not fully restore neuropsychological functioning among adolescent users. In addition to memory, attention and learning, cannabis use is linked with poor school performance, increased risk-taking behaviour and an increased risk of mental health issues.

What are the physiological effects of recreational drugs?

These are summarized in Table 32.4.

What are the different types of approach to health promotion that could be adopted?

Health promotion is important, as unhealthy adolescent behaviours can become long-term risk factors for chronic health conditions in adulthood. Health promotion can be approached to target:

- Individuals – Health professionals can use consultations for opportunistic health promotion and use techniques such as motivational interviewing and brief intervention to encourage change.
- Training – Programs that involve adolescents in activities enhancing competence and capacity and help them avoid negative choices and outcomes.
- Families/schools and communities – Health promotion in the environment most familiar to the young person, aiming to decrease risk factors and increase protective factors within peer groups of adolescents.
- Society as a whole – Global health promotion using social media/television and advertising can be very effective.

Table 32.4 Physiological effects of recreational drugs during adolescence

	Recreational drug	**Clinical effects**	**Extreme use**
Central nervous system stimulants	Cocaine (incl crack) MDMA (Ecstasy) Alkyl nitrites Amphetamines	Dilated pupils Tachycardia, hypertension Increased energy Euphoria Feelings of enhanced sociability, sexuality and confidence	Paranoid psychosis Depression Seizures Extreme anxiety states Myocardial infarction/cerebrovascular accidents Hallucinations
Central nervous system depressants	Gases Glues and aerosols Alcohol Barbiturates Benzodiazepines	Slurred speech Relaxation/decreased inhibition Impaired memory/ thinking Decreased motor skills	Respiratory depression Seizures Liver disease Heart disease
Hallucinogens	Cannabis LSD Magic mushrooms Ketamine	Hallucinations Dizziness, nausea and vomiting Feelings of enhanced mental capacity	Psychosis Poor judgement leading to serious injury/death Anxiety/depression
Analgesics	Heroin Morphine Codeine	Pinpoint pupils Analgesia Intoxication followed by euphoria Constipation Drowsiness	Respiratory depression Blood-borne infections (from sharing needles) Myocardial infarction/cerebrovascular accidents

Question 32.5

Sexually transmissible diseases

Following (A–J) is a list of diagnoses:

A. Bacterial vaginosis
B. *Chlamydia trachomatis*
C. Genital warts
D. Herpes simplex
E. HIV
F. *Neisseria gonorrhoeae*
G. Non-gonococcal urethritis
H. Scabies
I. Syphilis
J. *Trichomonas vaginalis*

Choose the most likely diagnosis for each of the following. Select ONE answer only for each question.

1. A 16-year-old student presents for the 'emergency contraceptive pill' after an unprotected sexual episode the previous night. She has had five sexual partners in the past 6 months and does not use condoms or any other contraceptives. Her periods have been regular, but she has recently noted some spotting between periods. Last menstrual period was 4 weeks ago. The genital exam reveals normal vulva and vagina. Her cervix appears inflamed, bleeds easily, with a purulent discharge coming from the cervical os. The bimanual exam is normal without cervical motion pain, uterine or adnexal tenderness. NAAT test is positive.

2. A 16-year-old male presents to the STD clinic with a sore on his penis for one week. He had an unprotected sexual episode 3 weeks earlier without a condom. Physical exam shows no oral, perianal, or extra-genital lesions. Genital exam shows a red, indurated, clean-based, and non-tender lesion on the ventral side of the penis near the frenulum. He has two enlarged tender right inguinal nodes and no urethral discharge.

3. A 15-year-old girl presents with a widespread pruritic rash present for one week. She lives in a children's home and has been sexually active for 6 months, only using condoms 'occasionally'. Physical exam shows a widespread erythematous papular rash pronounced on her buttocks, abdomen, hands, elbows and axilla.

Sexual health in adolescence

In addition to puberty, adolescents also develop an understanding of their gender identity and sexual orientation. Gender identity refers to whether they consider themselves masculine, feminine or both (transgendered), whilst sexual orientation refers to patterns of attraction to others and includes physical, emotional, sexual, and romantic attraction.

The average age for first heterosexual intercourse in the UK is 16 years and whilst two thirds of 16–19-year-olds have a sexual partner, one in ten of those do not use contraception. Risk-taking sexual behaviour may result in sexually transmitted infections (STIs) and/or unplanned pregnancy. Taking a sexual history is therefore an important part of health screening and an opportunity for health promotion. When taking a sexual history, it is important to be non-judgmental and supportive, use gender-neutral language and avoid assumptions about the patient's sexual orientation, sexual behaviours, or number of partners. Paediatricians must be aware of the significant psychological, social and medical issues faced by adolescents who are gay, lesbian or bisexual, all of which can have an impact on self-esteem and identity formation.

Starting discussions around pubertal development can be a useful strategy to introduce these potentially sensitive topics as well as building on what they are learning at school in sex and relationship education. The latter is particularly useful in addressing parental concerns.

Sexual health is an important consideration for all young people, including young people with long-term health conditions. Such young people often have

> **Box 32.3 Implications of long-term conditions (including therapy) to sexual and future reproductive health**
>
> Physical aspects
> - Oral (e.g. kissing with peanut allergy!)
> - Musculoskeletal and/or neurological abnormalities, e.g. limited hand function re condom use, masturbation
> - Fatigue
>
> Reproductive
> - Heredity issues
> - Fertility issues
>
> Drug-related
> - Contraception on teratogenic drugs
> - Egg/sperm storage on cytotoxic therapy
> - Drug side effects on e.g. function, desire, menstrual cycle
>
> Infection risk on immunosuppression
> Psychological
> - Sexual identity
> - Disclosure
> - Body image
> - Self-confidence/esteem/efficacy
>
> Cultural
> Opportunity

additional issues due to the implications of their condition and/or its therapy for their sexual and reproductive health (Box 32.3).

Sexually transmitted infections in the UK

> **Case history**
>
> 16-year-old Rose presents with a history of vaginal discharge and pain during sexual intercourse. She and her boyfriend are not using condoms 'as she is on the pill'. She did do one of those STI 'self-test kits' at school 6 months previously but doesn't know what it was testing for.
>
> **What are the common STIs of adolescence?**
>
> *Chlamydia* is the commonest STI diagnosis amongst adolescents in the UK, with those under 25 years accounting for 64% of all new chlamydia cases. It is often asymptomatic but may present with unusual discharge, post-coital/inter-menstrual bleeding, lower abdominal pain, sterile pyuria or dysuria. Long-term complications include pelvic inflammatory disease, ectopic pregnancy and

infertility. Treatment is with a single dose of azithromycin or a longer course of doxycycline.

Gonorrhoea is the second most common STI diagnosis in adolescence in the UK. It too can be asymptomatic or can present with urethral discharge, dysuria or inter-menstrual bleeding. Complications are similar to those of chlamydia. Treatment is with a single dose of a cephalosporin.

Genital warts are caused by the human papillomavirus (HPV), typically by two strains of the virus, type 6 and 11. Other strains of HPV can cause cervical cancer. The HPV vaccine routinely offered to 12–13-year-old girls as part of the childhood vaccination programme protects against genital warts in addition to cervical cancer. Warts are found on the penis, anus and vagina and often resolve spontaneously but can be treated with creams and/or cryotherapy.

Genital herpes is caused by the herpes simplex virus (HSV), resulting in painful blisters on the genitals and surrounding area. There is no cure for genital herpes but symptoms can be controlled using antiviral medicines.

Although not usually thought of as an STI, *Candida* can be passed on to sexual partners during intercourse. Symptoms typically include itching, soreness, redness and an odourless 'cottage cheese'-like discharge. *Candida* often occurs during treatment with steroid therapy.

What can you tell Rose about the National Chlamydia Screening Programme?

In 2003, the National Chlamydia Screening Programme was established in England to control chlamydia through early detection and treatment of asymptomatic infection, thereby also reducing onward transmission and the consequences of untreated infection. The programme has resulted in a decrease in the prevalence of chlamydia among sexually active under-25-year-olds. It offers free and confidential self-test kits for under-25-year-olds, eliminating the need for an examination.

In addition, the '3Cs & HIV' programme has been set up in England to support primary care physicians and sexual health centres to:

- Provide the '3Cs', offering of a chlamydia screen, signposting or provision of contraceptive advice and free condoms, during routine consultations with 15–24-year-olds
- Deliver HIV testing in young people over 16 years.

Contraception

The UK Government's new sexual health strategy aims to increase knowledge and awareness of all methods of contraception for all ages. Research suggests that the majority of young people do use contraception during

sexual intercourse, although lowest levels of use remain within the 16–19-year-old age group. In addition, use of contraception may be irregular or incorrect. Awareness of resources is also variable, with only 47% of 15-year-olds knowing where the local service for contraceptive advice is.

Transitional care

Due to the advances in paediatrics, an increasing number of children are surviving into adolescence and adulthood. Transitional care is a key element of adolescent healthcare irrespective of the presence or absence of chronic illness or disability. All young people will hopefully make the transition from childhood to adulthood and, in doing so, move from the family home to live independently, from school to further education, training or work. This process is mirrored in healthcare with the transition of young people from paediatric to adult services. Many young people make these transitions successfully but some experience great difficulty.

Transition has been defined as 'a multi-faceted, active process that attends to the medical, psychosocial and educational/vocational needs of adolescents as they move from child- to adult-centred care'. Transfer is but a single event within a much longer process of transition, although these two terms are often erroneously used interchangeably. Research supports current guidance that transitional care should start in early adolescence with transfer generally occurring in late adolescence in a planned and coordinated manner. Conditions for successful transition include planning, patient education, skills training and a willingness to address the concerns of both the young person and their parents. Dedicated transition clinics help create an appropriate environment for this process to be facilitated in a patient-centred and coordinated fashion.

As transitional care is multidimensional, it can involve primary care, education, social care and vocational services as well as the paediatric and adult secondary care services. Effective communication, continuity, appropriate staff competencies and consistency within and between these various systems are vital to ensure successful transitional care for young people with long-term conditions.

Youth-friendly health services

There is increasing interest, both nationally and internationally, as to what determines a youth-friendly health service (Box 32.4). Developmentally appropriate healthcare for age is every child and adolescent's right and is thought likely to improve their health

> **Box 32.4 Core indicators of youth-friendly healthcare**
>
> - Accessibility of healthcare
> - Staff attitude
> - Communication
> - Medical competency
> - Guideline-driven care
> - Age-appropriate environments
> - Youth involvement in healthcare
> - Health outcomes

outcomes. It will also improve the experience of young people, enhance their well-being and strengthen their self-determination.

It is hypothesized that youth-friendly services will increase engagement, thereby reducing healthcare costs and healthcare utilization in the long term. This is particularly pertinent to those young people who tend to be under-represented in research, such as those from minority ethnic communities, looked-after young people, care leavers, asylum seekers and teenage parents.

Several important features of developmentally appropriate healthcare for adolescents have already been discussed, including routine psychosocial screening, opportunity to be seen independently of parents and confidential service provision.

The UK *You're welcome* quality criteria for youth-friendly health services reflect this and have been validated with respect to young people's satisfaction.

Every clinical encounter with a young person represents a potential opportunity to raise awareness of their developing strengths and the role they can play in their own health and well-being. Paediatricians can motivate and assist adolescents in taking on responsibility for their own health, actively promote their strengths and in so doing convey belief in young people.

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Dan Magnus, Anu Goenka, Bhanu Williams

Global child health

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Know about the major causes of child mortality globally
- Know about the most common illnesses in low resource countries: pneumonia, gastroenteritis, malaria, HIV infection, tuberculosis, measles
- Know about intervention programmes to improve health: immunization, paediatric life support courses, integrated management of childhood illness (IMCI)
- Know about the identification, pathophysiology, clinical features and management of malnutrition
- Know about the major causes of neonatal morbidity and death
- Be aware of neglected issues in global child health: adolescent health, mental health, neglected tropical diseases
- Be aware of vulnerable children: child labour, street children, armed conflict

Epidemiology and child survival

Case history

Chances of survival

A baby girl, Aminatta, is born to subsistence farmers in rural Senegal. What is Aminatta's chance of surviving to her 5th birthday?

Senegal's under-5 mortality rate in 2013 was 55 per 1000 live births, compared to UK figures of 5 per 1000 live births and Sierra Leone's 161 per 1000 live births. Millennium Development Goal (MDG) 4 aimed to reduce the under-5 mortality rate by two thirds between 1990 and 2015. In 2013 there were 6.3 million child deaths worldwide, compared to 12 million in 1990. The global under-5 mortality rate (defined as deaths in children under the age of 5 years per 1000 live births) has fallen from 90/1000 in 1990 to 48/1000 in 2012. In sub-Saharan Africa, 1 in 11 children die before their 5th birthday.

In which countries do most child deaths occur?

Large population size combined with high mortality rates mean almost half (49%) of child deaths occur in just five countries: India, Nigeria, Democratic Republic of Congo, Pakistan, and China.

What are the major causes of child mortality worldwide?

Data capture and ascertainment of causes of death are fraught with difficulty in countries without proper systems in place for birth and death registration. Of the 12 million deaths in 1990 only 2.7% were medically certified. Many countries use techniques such as verbal autopsy, which involves questioning family members regarding the child's symptoms immediately prior to death in order to retrospectively assign a diagnosis. Data suggest that the major causes of under-5 mortality are pneumonia (13%), preterm birth complications (15%), complications during birth (11%), diarrhoea (9%) and malaria (7%) (Fig. 33.1). Malnutrition is a major underlying cause of death and undernutrition is thought to contribute to 45% of under-5 deaths.

There are important inter-country and interregional differences that need to be considered before planning specific public health interventions. For example, malaria is a more significant threat in Africa, where it is responsible for 15% of deaths in children
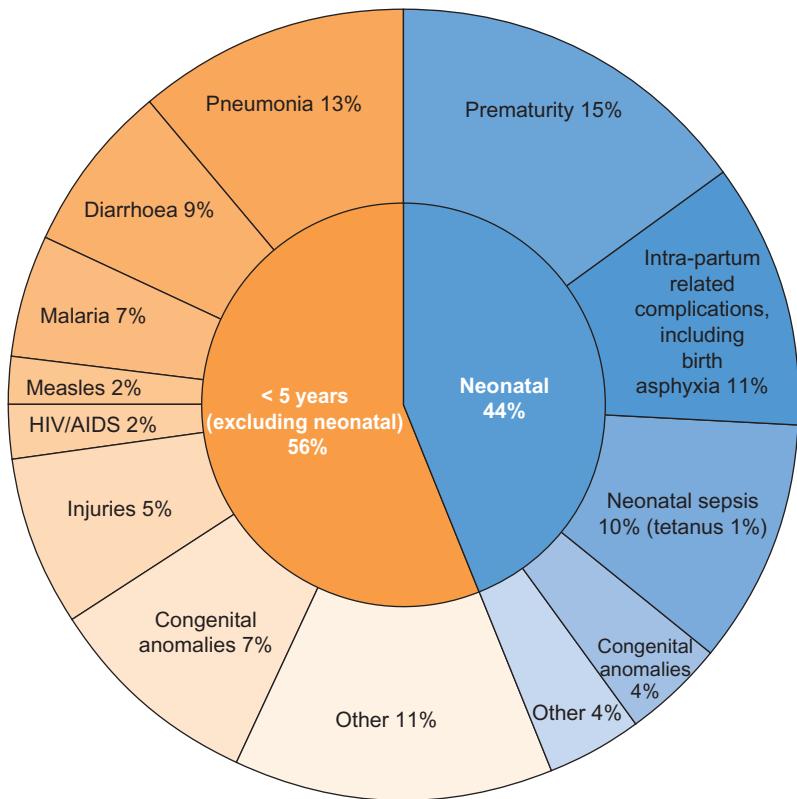
Fig. 33.1 **Major causes of child deaths in 2012.** *(From Committing to Child Survival: A Promise Renewed (UNICEF, 2013) with permission.)*

under 5, compared with south-east Asia, where it contributes just 1% to under-5 mortality. Though neonatal causes still account for a substantial proportion of under-5 deaths in most low-resource settings, their contribution varies, e.g. 52% of under-5 deaths in south-east Asia, compared with 30% in Africa. In the post-neonatal period in South and Central America, it is injuries that are the single largest threat to under-5 survival, causing 16% of mortality.

What indicators can be used to measure child health and inequalities of child health?

There are marked inter- and intra-country inequalities in child health. In 2012 the under-5 mortality rate was 147/1000 live births in Somalia, 56/1000 in India and 5/1000 in the United Kingdom. Marked inequalities in health also occur within countries. The poorer the child, the more likely they are to be exposed to risk factors for ill health. Unclean water and poor sanitation lead to diarrhoeal disease, while inadequate housing, air pollution and overcrowding promote the spread of respiratory pathogens. Poorer children are

more likely to experience worse clinical outcomes for most illnesses compared with children from more wealthy backgrounds. This is partly because children living in poverty are more likely to be underweight and micronutrient deficient, have less resistance to disease, are less likely to be able to reach a health facility and less likely to receive adequate care. As well as poverty, mortality is higher in rural rather than urban areas and to a mother with little or no education. In addition, preventive public health measures such as vaccination, vitamin A supplementation and insecticide-treated net distribution tend to have the worst coverage amongst the poorest populations with the greatest need.

Child health can be measured using a variety of numerical indicators. The most common, showing the rates for sub-Saharan Africa, are displayed in Table 33.1.

Most child deaths are preventable through the scaling up of evidence-based child health interventions, adapted according to country-specific local disease epidemiology, with an emphasis on targeting the most vulnerable children. Educating girls is likely to have a positive impact on reducing child mortality

Table 33.1 Child health indicators

Indicator	Definition	UK rate	Sub-Saharan Africa rate
Under-5 mortality rate	Under 5 years of age: deaths per 1000 live births	5	98
Infant mortality rate	Under 1 year of age: deaths per 1000 live births	4	64
Neonatal mortality rate	Deaths before 28 days of age per 1000 live births	3	32
Perinatal mortality rate	Stillbirths and early neonatal deaths (deaths before 1 week of age) per 1000 live and stillbirths	7.6	Unknown
Stillbirth rate	Stillbirths (WHO definition – infants born with no signs of life ≥ 28 weeks' gestation; in UK ≥ 24 weeks' gestation) per 1000 live and stillbirths	4.9	Unknown

and studies have demonstrated a strong correlation between maternal education and child mortality. However, it has been argued that maternal education may be a proxy measure of socio-economic status; once paternal education and access to piped water and sanitation is taken into consideration, the impact of maternal education has been shown to be less marked, although still significant.

Why have child deaths fallen?

As well as rising wealth in many countries, the reduction in child deaths may be attributed to the implementation of child survival initiatives. Despite impressive reductions in child mortality in some countries, such as Rwanda and Bangladesh, the slowest improvements have been in West and Central Africa and it is unlikely that the MDG4 target will be met globally. The greatest gains in reducing post-neonatal under-5 mortality have occurred with the scaling up and improved coverage of preventative interventions, such as vaccinations and insecticide-treated nets for prevention of malaria. In stark contrast to the progress achieved in reducing post-neonatal under-5 mortality, efforts to reduce neonatal mortality have been hampered by a lack of a continuum between maternal and child care, which is discussed further below.

International child health programmes

The role of international organizations in delivering programmes for improving global child health

Individual governments fund and facilitate important global health programmes, often through government organizations, e.g. USAID (United States Agency for International Development) and DFID (UK Department for International Development). However, it is intergovernmental organizations such as the United Nations or the International Labour Organization that often exert the greatest influence through cross-country collaborations and large, well-funded global partnerships. It is under the auspices of the United Nations that the World Health Organization, the World Bank and UNICEF are able to function and to deliver some of the most influential child health initiatives. The field-level implementation of such child health improvement initiatives is often achieved in collaboration with non-governmental organizations (NGOs), who rely on public and donor funding, e.g. Oxfam, and the Malaria Consortium. NGOs may operate internationally (e.g. Médecins Sans Frontières), nationally or regionally. Effective co-ordination between NGOs as well as government programmes are critical factors in determining the success of child health improvement initiatives.

Governmental, intergovernmental and NGO partnerships only form part of the global picture on efforts to improve child health. Public–private partnerships also play an important role in financing and rolling out global health initiatives; GAVI (Global Alliance for Vaccines and Immunization) is a good example of this. Private foundations, such as the Bill and Melinda Gates Foundation, also provide significant investment and funding into global health programmes and research.

Major threats to child survival

Case history

Acute febrile illness

Tomoka is a 2-year-old girl living in rural Malawi who has a short history of fever, cough, coryza, rash and diarrhoea. She is taken to a primary healthcare clinic by her aunt. Her mother died

recently after an illness characterized by chronic cough and wasting. Tomoka's health card has been lost, which contained details of her past medical history, vaccination status and growth charts.

What are the major threats to her survival? Which intervention programmes would be of greatest benefit for Tomoka's health? These are listed below.

Pneumonia and diarrhoea

Tomoka's clinical presentation encompasses diarrhoeal disease and possibly pneumonia. They account for the majority of child deaths outside the neonatal period and the global burden is highest in Africa and south-east Asia. Pneumonia and diarrhoea are often considered together as they share common risk factors and programmatic solutions, including tackling poverty, undernutrition, poor hygiene, suboptimal breastfeeding, zinc deficiency as well as improving access to vitamin A and vaccination.

The World Health Organization (WHO) has streamlined its case definitions to stratify the clinical severity of pneumonia and diarrhoeal disease. Pneumonia is now simply classified as 'pneumonia' and 'severe pneumonia' and diarrhoea is divided into syndromes (acute, persistent, bloody, etc.) with assessment of level of dehydration (none, some and severe). These classifications rely on objective clinical symptoms and signs that can be easily elicited by community health workers and staff working in primary care, facilitating the early referral of appropriate cases to secondary care. Oral rehydration solution (ORS) remains the cornerstone of management of diarrhea, coupled with continued feeding. Effective management of pneumonia relies largely on access to antibiotics. The treatment of hypoxaemia with oxygen has also been shown to reduce pneumonia deaths.

Approximately one third of severe episodes of diarrhoea and pneumonia are preventable by vaccination. Despite increased vaccination coverage, the majority of pneumonia deaths are attributable to vaccine-preventable organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Roll-out of pneumococcal conjugate vaccine (PCV) lags behind Hib vaccine, despite the benefits of PCV even extending to children with viral pneumonia. Rotavirus vaccine continues to be introduced into the immunization schedules of many countries and effective coverage reduces mortality attributable to diarrhoea.

Malaria

Tomoka's clinical presentation does not immediately suggest malaria but it is important to assess all febrile children who live in endemic areas for malaria. Most deaths from malaria occur in children under 5 and pregnant women. There has been some progress in reducing morbidity and mortality attributable to severe malaria, which is usually caused by *Plasmodium falciparum*. *Plasmodium vivax* and *ovale* cause less severe disease but have a liver hypnozoite stage that requires specific treatment to effect eradication. While *Plasmodium malariae* is seldom associated with severe disease, it can be associated with nephrotic syndrome. The WHO 2013 malaria report stated there were 627,000 deaths from malaria in 2010, 77% of which were in children under 5. The Roll Back Malaria Partnership has been coordinating international efforts since 1998 to scale up preventative diagnostic and therapeutic interventions with the overarching vision of freeing the world of the burden of malaria. Central to prevention of malaria is the use of long-lasting insecticide-treated bed nets (ITNs), which reduce the vector population of *Anopheles* mosquitoes. Currently, approximately 40% of children in sub-Saharan Africa sleep under an ITN. Households can be further protected from mosquitoes by indoor residual spraying (IRS) with insecticides. Various candidate malaria vaccines are in development, which, even if partially efficacious, could substantially reduce mortality and morbidity.

The clinical presentation of malaria involves non-specific symptoms such as fever and headache. Clinical assessment alone carries the risks of both over-treatment and under-treatment. It is therefore essential to confirm the diagnosis before initiating treatment. The diagnosis of malaria in low-resource settings has been facilitated by the use of rapid diagnostic tests (RDTs), which are cost effective, require minimal training and can be used by community health workers. The management of acute severe malaria depends not only on prompt access to appropriate antimalarial drugs, but also effective treatment of hypoglycaemia, anaemia and convulsions.

The superiority of artemisinin-based antimalarial treatment over quinine was demonstrated in two large multicentre trials involving more than 6500 children: the SEAQUAMAT study in south-east Asia and the AQUAMAT study in sub-Saharan Africa. The latter trial, a multicentre randomized controlled trial of children with severe malaria, showed significantly reduced mortality (relative risk reduction 22.5%, 95% Confidence Interval (CI) 8.1–36.9; odds ratio for death 0.75, 95% CI 0.63–0.9) and reduced coma and seizures with artemisinin compared with quinine. Since the publication of these landmark studies, the WHO recommends artemisinin combination treatment (ACT) as first line in severe malaria. Artemisinin is combined with partner drugs to delay the development of drug resistance. Nonetheless, artemisinin resistance has emerged in south-east Asia.

HIV

Question 33.1

HIV transmission

Which of the following has been shown to reduce the risk of mother-to-child HIV transmission in low-resource settings? The answer to each may be true (T) or false (F).

A. Breast and artificial feeding rather than exclusive breastfeeding

B. Co-existent sexually transmitted diseases in the mother

C. Delivery by caesarean section

D. Exclusive formula feeding

E. Giving all women antiretroviral therapy irrespective of CD4 T-cell count or clinical staging

Answer 33.1

A. False; B. False; C. True; D. True; E. True.

Exclusive formula feeding reduces the risk of HIV infection, although risk of death from gastroenteritis and other causes may be increased. Delivery by caesarean section reduces the risk but may not be indicated if the mother's viral load is suppressed. Giving all women antiretroviral therapy irrespective of CD4 T-cell count or clinical staging is now WHO recommended policy.

Tomoka's mother died recently after a wasting illness. In a setting with high rates of HIV transmission, suspicion should be raised that Tomoka may have been vertically infected with HIV. Approximately 2 million children globally are currently living with HIV, most of whom acquired the infection perinatally. The rate of new paediatric infections has significantly declined, primarily due to the success of prevention of mother-to-child transmission (PMTCT) interventions. Maternal-to-child transmission of HIV without any of the preventative interventions listed in Box 33.1 can be between 30% and 40%; with intervention, this can be reduced to <1%.

Tomoka's HIV status should be ascertained as soon as possible. As Tomoka is 2 years old, a positive antibody test would indicate she is HIV-infected. HIV antibody is placentally transferred, and therefore a positive antibody test before the age of 18 months may indicate maternal HIV infection only. HIV proviral polymerase chain reaction (PCR) is the diagnostic test of choice in infants. At birth, HIV PCR has a low sensitivity (due to low viral load) and does not rule out infection. By 3 months, sensitivity is almost 100%.

Box 33.1 Prevention of mother-to-child transmission (PMTCT) interventions

- Primary HIV prevention in women of child-bearing age through education, self-determination and condom use.
- Universal lifelong antiretroviral therapy for all pregnant women, aiming to suppress viral load before delivery (WHO plan B+).
- Treatment of coexistent sexually transmitted infections in the mother.
- Caesarian section, although vaginal delivery can be considered if viral load suppressed and mother well. Avoid prolonged rupture of membranes.
- A minimum of 6 weeks of postnatal antiretroviral prophylaxis for the newborn.
- Exclusive breastfeeding for the first 6 months of life in low-resource settings, where the use of artificial (formula) feeding is associated with greater risks of mortality from gastroenteritis and pneumonia. Thereafter, introduction of complementary foods at 6 months of age with concomitant continuation of breastfeeding until 12 months.
- Breast milk pasteurization or 'flash heating' has been associated with reduced transmission.
- Mixed breast and artificial feeding is the least desirable option, due to the increased mortality associated primarily with gastroenteritis and pneumonia, as well as increased HIV transmission (artificial feeding is associated with increased mucosal inflammation, which can act as a 'portal of entry' for the HIV virion in infants co-fed with breast milk).
- Support for mothers who choose exclusive artificial feeding, providing this is acceptable, feasible, affordable, sustainable and safe (AFASS criteria)

HIV infection is very unlikely if the child has two negative PCRs (one after 3 months) or two negative antibody tests if <12 months or one negative antibody test after 18 months.

Tomoka needs to be assessed for the clinical features and complications of HIV infection. HIV infects CD4+ T cells, macrophages and neuronal cells, amongst others. Primary HIV infection is a mostly mild, mononucleosis-like illness, which resolves spontaneously, with the virus entering a phase of clinical latency. As infection progresses, the CD4+ cell count drops, determining the further clinical course of manifestation of opportunistic infections and malignancies. HIV can cause a chronic encephalopathy with developmental delay and faltering growth. The advance to acquired immune deficiency syndrome

(AIDS)-defining diseases in children is highly variable; however, untreated infants and children have a high risk of progression to severe infections and death. In contrast, some vertically infected children may be asymptomatic into their teenage years. The CD4+ cell count and the HIV viral load are therefore the most important laboratory parameters to monitor in HIV-infected children.

A randomized controlled trial (CHER trial) involved 377 HIV-positive infants assigned to receive early antiretroviral therapy (ART) at diagnosis in early infancy, or delayed ART until such time that immunological (CD4+ count) and clinical (WHO Clinical Stage) criteria were met. The study demonstrated a 75% reduction in mortality and disease progression with early antiretroviral therapy (ART) at diagnosis compared with delayed treatment. WHO guidelines now recommend the commencement of lifelong ART for all HIV-infected children and adolescents irrespective of CD4 count. Some countries have not yet incorporated this guidance owing to the cost. However, even prior to this revised WHO guidance, a significant number of HIV-infected children in low-resource settings found themselves within the 'treatment gap': in 2011, only 23% of eligible HIV-infected children were receiving ART compared with 51% of adults.

The integration of HIV into the host genome (CD4+ lymphocytes) and subsequent virion replication is reliant on the error-prone reverse transcriptase enzyme. This process provides many opportunities for the virus to develop resistant mutants to ART. To minimize this, highly active antiretroviral therapy (HAART), a combination of a minimum of 3 drugs, is used. First-line antiretroviral therapy involves 2 nucleoside reverse transcriptase inhibitors (usually abacavir and lamivudine) and either a non-nucleoside reverse transcriptase inhibitor (usually efavirenz in children over 3 years of age) or a protease inhibitor (usually lopinavir/ritonavir). Recent data from the ARROW study has shown it is possible to keep children well and virally suppressed in low-resource settings without regular laboratory testing for efficacy (CD4+ cell counts) and toxicity (haematology and biochemistry). The results of this study suggest that ART roll-out and adherence support services should take priority in low-resource settings where there is no comprehensive HIV care programme.

Tuberculosis

Tomoka's mother had a chronic cough, which may indicate that Tomoka has been infected with tuberculosis (TB). Initial pulmonary tuberculosis is characterized by the primary complex (Ghon focus with local adenitis), which usually resolves with calcification or scarring. Children under 5 years are at high risk of

developing primary progressive disease, which can involve dissemination to any organ in the body.

The number of new case notifications of TB in children is rising, despite the overall global fall in TB incidence and prevalence since 2000. In 2012, there were an estimated 530,000 new cases of childhood TB and 74,000 deaths. This increase may represent improved surveillance methods in children rather than a true increase in disease incidence. Despite this, the overall case burden of childhood TB is still likely to be underestimated; case detection of TB in children is difficult due to its non-specific clinical presentation, paucibacillary nature and absence of available diagnostic tests which are both sensitive and specific.

The diagnosis is usually made from a composite of clinical features, radiology, tuberculin skin testing (TST), microscopy and culture of respiratory specimens along with newer PCR methods such as the Xpert MTB/RIF assay, an automated assay to identify *Mycobacterium tuberculosis* (MTB) DNA and resistance to rifampicin (RIF). The TST relies on the development of a delayed-type hypersensitivity reaction to tuberculin purified protein derivative, which is a combination of proteins from *M. tuberculosis*, some of which are also present in BCG vaccine. Therefore, children who have received BCG may have a false positive TST, and a different cut-off is used in the UK to allow for this. Interferon-gamma release assays (IGRAs) were developed to circumvent this problem and measure T-cell interferon-gamma production to proteins that are unique to *M. tuberculosis* and not present in BCG (ESAT-6, CFP-10 and TB7.7). Sensitivity and specificity is less than in adults. Neither the TST nor IGRAs can be reliably used to distinguish between latent and active disease, as they indicate infection by the organism. However, one or both can be used during contact tracing to identify which individuals have been infected. The microbiological confirmation of TB requires culture or PCR. Liquid culture is the most sensitive method of bacteriological confirmation. Almost half of low- and middle-income countries have adopted the WHO guidance recommending the use of Xpert MTB/RIF assay, which is more sensitive than microscopy and can be performed within 100 minutes.

The management of childhood TB is hampered by the lack of paediatric drug preparations, in particular fixed dose combinations. This is especially true for multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB), where there is an urgent need for child-friendly preparations. There are few signs that this will be met in the near future.

Treatment of latent TB is effective at preventing development to active TB disease. Primary chemoprophylaxis is the practice of giving preventative therapy, usually isoniazid, to immunocompetent children who have been exposed to an individual with

sputum smear-positive TB for more than 8 hours to prevent development of progressive TB disease, even if there is no initial evidence of TB infection. HIV-infected children are at significantly increased risk of developing TB, although ART markedly reduces this risk. Some authorities recommend offering TB chemo-prophylaxis to all children with HIV infection when initially diagnosed, and after each TB exposure. Aside from chemoprophylaxis, the prevention of childhood TB relies mainly on effective case detection and treatment of TB in the adult population.

By coordinating global organizations, the STOP-TB Partnership aims to eliminate TB as a public health problem by 2050. In 2013, the WHO published the first targeted roadmap outlining the steps to 'end childhood TB deaths', emphasizing the need for increased investment in the development of effective, novel, child-friendly diagnostics and therapeutics.

Question 33.2

Tuberculosis

A 3-year-old girl is referred because her grandfather has recently been diagnosed with smear-positive pulmonary tuberculosis. She lives with her older brother, parents and grandfather. She has been asymptomatic and has a normal examination.

Which of the following would not be useful in determining her management? Select ONE answer only.

A. Chest X-ray

B. Interferon-gamma release assay (Quantiferon or T-spot)

C. Mycobacterial M, C & S of her grandfather's sputum

D. Mycobacterial M, C & S of her nasopharyngeal aspirate

E. Tuberculin skin test (Mantoux)

Answer 33.2

D. Mycobacterial M, C & S of her nasopharyngeal aspirate.

Contact tracing is a vital part of tuberculosis control programmes. Household contacts of a smear-positive pulmonary TB case are at highest risk of acquiring infection. Once infection has occurred, the majority of individuals are able to contain it within the lungs, with a small number developing progressive primary disease. This is more likely in children under 5 years of age, and in those who are immunocompromised. Children are also more likely than adults to develop extrapulmonary TB. In older children and adults, the infection becomes latent and disease can occur later by re-activation. This is most likely in the first two years following initial infection or during any periods of immunocompromise including old age (immunosenescence).

The purpose of contact tracing is to identify active cases of TB, as well as those who are latently infected. Active cases can be identified on clinical assessment and chest X-ray. Microbiological confirmation can be achieved using induced sputum or gastric aspirates, and sometimes bronchoscopy, but not via nasopharyngeal aspirate. A positive microbiological sample is required to confirm drug susceptibility. Obtaining positive isolates from the source case are therefore useful, and therefore knowing culture and sensitivity of the grandfather's sputum is important.

Measles

Tomoka has presented with clinical features that would also be compatible with a diagnosis of measles. Deaths from measles are disproportionately high in low-resource settings, where vaccination coverage is suboptimal and levels of malnutrition are high. Severe complications are more common in children with impaired cellular immunity (such as malnourished children) and include pneumonia, laryngotracheo-bronchitis, and keratoconjunctivitis. Treatment with vitamin A reduces morbidity and mortality in children through promoting epithelial integrity. Systemic anti-biotics may also be indicated, allied with eye/mouth care. The control of measles relies on herd immunity through vaccination, and outbreaks may occur when more than 10% of the population are susceptible. Eradication is possible, as measles does not cause latent transmissible infection, and humans are the only reservoir of infection. Despite dramatic progress in reducing mortality, the World Health Assembly target of reducing measles mortality by 90% between 2000 and 2010 was not met. Recent large outbreaks in Africa were likely due to poor vaccination coverage in certain high-burden countries (Nigeria, Ethiopia, Democratic Republic of Congo) as well as inadequate funding for supplemental immunization activities, such as mass vaccination campaigns.

Which intervention programmes would be of greatest benefit for Tomoka's health?

Expanded programme of immunization (EPI)

Vaccination could have prevented several of the important infectious pathogens potentially responsible for Tomoka's clinical presentation. Approximately

	Birth	6 weeks -2 months	10 weeks -3 months	14 weeks -4 months	6–9 months	1 year	2 years	3 years	12–13 years	13–18 years
Chad	BCG OPV	DTwPHibHep OPV	DTwPHibHep OPV	DTwPHibHep OPV	Measles YF					
Malawi	BCG	DTwPHibHep OPV Rotavirus PCV	DTwPHibHep OPV Rotavirus PCV	DTwPHibHep OPV PCV	Measles					
India	BCG OPV	DTwPHibHep OPV	DTwPHibHep OPV	DTwPHibHep OPV	Measles OPV JapEnc*		DTwP OPV JapEnc*	DTwP OPV	TT	TT
United Kingdom	BCG* Hep B*	DTaPHibIPV PCV Rotavirus MenB Hep B*	DTaPHibIPV MenC Rotavirus Hep B*	DTaPHibIPV PCV MenB Hep B*	MMR PCV MenB HibMenC	Influenza	DtaPIPV MMR	HPV	TdIPV MenACWY	

Legend

BCG = Bacille Calmette-Guerin vaccine, **OPV** = Oral Polio vaccine, **Hep B** = Hepatitis B vaccine, **DTwPHibHep** = Diphtheria/Tetanus/whole cell Pertussis/Haemophilus influenzae b/Hepatitis B vaccine, **PCV** = Pneumococcal conjugate vaccine, **DTaPHibIPV** = Diphtheria/Tetanus toxoid/Acellular pertussis/Haemophilus influenzae b/Inactivated polio vaccine, **MenB** = 4 component meningococcal B vaccine, **MenC** = Meningococcal C conjugate vaccine, **YF** = Yellow Fever vaccine, **JapEnc** = Japanese Encephalitis vaccine, **MMR** = measles, mumps and rubella vaccine, **HibMenC** = Haemophilus influenza b/Meningococcal C booster, **DTwP** = Diphtheria/Tetanus toxoid/Whole cell pertussis booster, **DtaPIPV** = Diphtheria/Tetanus toxoid/Acellular pertussis/ Inactivated polio booster, **HPV** = Human Papillomavirus vaccine, **TdIPV** = Tetanus/Diphtheria toxoid/Inactivated polio booster, **TT** = tetanus toxoid booster, **MenACWY** = Meningococcal ACWY conjugate vaccine

*Given to high-risk groups

Fig. 33.2 Comparison of country-specific EPI vaccination schedules for Chad, Malawi, India, and the United Kingdom, 2015. *(Adapted from WHO data, 2013 – http://apps.who.int/immunization_monitoring/globalsummary/schedules)*

2–3 million deaths per year are prevented by immunization. In 1974, the success of the smallpox eradication programme prompted the World Health Assembly to establish the Expanded Programme of Immunization (EPI). The goal of EPI is to provide universal access to relevant vaccines for all at risk. In 2012, more than 80% of infants had been vaccinated against diphtheria, tuberculosis, pertussis, polio, measles and tetanus. However, vaccination coverage within countries and between countries is inequitable. In 2010, vaccine-preventable diseases were responsible for the deaths of an estimated 1.5 million children, and approximately 19.3 million children did not receive three doses of the diphtheria–tetanus–polio (DTP) vaccine, with more than one third of these children living in Africa. In 2013, the Global Alliance for Vaccines and Immunization (GAVI), Decade of Vaccines Collaboration and WHO formulated the Global Vaccine Access Plan (GVAP); this aims to achieve universal access to all immunizations by 2020.

Vaccination schedules vary between countries. Figure 33.2 demonstrates how vaccination schedules vary across two low-income countries (Chad and Malawi), a middle-income country (India) and a high-income country (United Kingdom). Complex factors govern each individual country's choice of EPI schedule, including balancing the limitations of the national health budget against the relative contribution of endemic diseases to morbidity and mortality.

Polio is likely to be the next vaccine-preventable infection to be eradicated. The Global Polio Eradication Initiative aims to eradicate polio by 2018, by concentrating efforts on two countries accounting for 99% of cases: Afghanistan and Pakistan. As part of these efforts, GAVI will also assist with the replacement of live oral polio vaccine with injectable inactivated polio vaccine in 124 countries, to eliminate vaccine-derived cases of polio.

There is a need for more evidence to define optimal vaccination schedules. It has been shown in observational studies that neonatal BCG vaccination is associated with significant reductions in all causes of child mortality. The putative mechanism of this phenomenon is heightened host immune surveillance following the stimulatory effect of BCG on the immune system. There is further evidence to suggest that DTP reduces some of the survival advantage conferred by the neonatal BCG vaccination. The analyses underlying such associations are controversial but highlight the need for more high quality randomized studies comparing vaccination schedules.

Recognition and treatment of sick children, e.g. ETAT (Emergency Triage, Assessment and Treatment) courses

Tomoka is acutely unwell and her survival at a busy rural health clinic may depend upon effective triage and, if necessary, prompt resuscitation and treatment. Child mortality is highest within 24 hours of acute illness. The WHO Emergency Triage, Assessment and Treatment (ETAT) training course using scenario-based teaching is a system of paediatric life support adapted to the commonest causes of hospital admission in southern Africa. The implementation of ETAT at a busy emergency department in a Malawian tertiary hospital led to a 50% reduction in inpatient mortality. In Kenya, Uganda and Rwanda, the course has been expanded (ETAT+ – Emergency Triage Assessment and Treatment plus Admission), to include initial hospital treatment.

Case history

Fluid resuscitation as supportive therapy

Tomoka, age 10 months, is referred urgently to her local district hospital in Uganda. On arrival, she is noted to be febrile, with a capillary refill time of 3 seconds, a raised respiratory rate of 60 breaths/min and heart rate of 150 beats per minute. Should Tomoka receive intravenous fluid bolus resuscitation?

The key evidence to address this scenario comes from the FEAST trial, which randomized 3000 children over the age of 3 months with fever

and impaired circulation to receive intravenous fluid bolus, or no bolus. Interim analyses demonstrated the unexpected finding of increased mortality at 48 hours in the fluid bolus group (relative risk 1.45; 95% confidence interval: 1.13–1.86) and thus the study was halted early. In light of the findings of the FEAST trial, Tomoka should not receive a fluid bolus, and this is endorsed by the ETAT+ guidelines. However, the study's definition of shock has been debated – for an acute infectious illness with severely impaired circulation (all of: cold periphery, capillary refill time >3 seconds, weak peripheral pulse and AVPU score <A), then 20 mL/kg over 1–2 hours is recommended. Furthermore, fluid bolus resuscitation is still recommended for shocked children with diarrhoea, burns or trauma.

How can effective interventions be integrated at a consultation at the clinic?

Integrated management of childhood illness (IMCI)

Tomoka's presentation may potentially involve a number of different pathologies with overlapping clinical features: pneumonia, diarrhoea, TB, measles, HIV and malaria. Figure 33.3 summarizes the range of evidence-based interventions that tackle these major threats to child survival. Tomoka also has several wider health issues that need to be addressed in the consultation, such as nutritional assessment, vitamin A status, deworming and immunization status. The programmatic response to the complex health needs of children such as Tomoka was previously characterized by fragmented, multiple vertical programmes with little overall integration. To address this, the Integrated Management of Childhood Illness (IMCI) approach was developed by the WHO and UNICEF during the early 1990s.

IMCI is a comprehensive system to assess the sick child for common conditions in the primary healthcare setting, while addressing wider health issues such as the assessment of nutritional status and provision of feeding advice. Healthcare workers are also reminded to consider other systematic nutritional interventions, such as regular vitamin A administration and deworming. In addition, IMCI prompts healthcare workers to assess HIV, TB and immunization status during every patient contact. Many individual countries have adapted IMCI protocols to include relevant clinical conditions according to their individual local epidemiology. For example, dengue

| Prevention | Community Management | Hospital Management |

Expanded Programme on Immunization (EPI)

Integrated Management of Childhood Illness (IMCI)

Emergency Triage, Assessment and Treatment (ETAT) — ETAT+

Pneumonia
Water, Sanitation and Hygiene (WASH), Breastfeeding Promotion, Vaccination (Hib, PCV, measles, rotavirus, cholera), Vitamin A and Zinc supplementation, Household Food Security, School Feeding Programmes, Deworming — Antibiotic therapy, Detection of very severe pneumonia and hospital referral — Antibiotic and oxygen therapy

Diarrhoea — Oral Rehydration Therapy (ORS) and continued feeding

Malnutrition — Ambulatory management of uncomplicated malnutrition with ready-to-use therapeutic food (RTUF) — WHO Ten Steps to Recovery for inpatient management of severe complicated malnutrition

Malaria
Insecticide Treated Bed Net, Vector control, indoor residual spraying, etc. — Access to near-patient Rapid Diagnostic Testing (RDT) for malaria, Access to Artemisinin Combination Therapy (ACT)

Tuberculosis
Effective adult TB control programmes, BCG vaccination, Contact Tracing and Isoniazid Preventative Treatment — Effective childhood TB case detection and access to high-quality laboratory services, Child-friendly TB treatment programmes

HIV
Prevention of Mother-To-Child Transmission (PMTCT) — Access to HIV serological (antibody) and virological (antigen) testing, Child-friendly antiretroviral treatment programmes

Fig. 33.3 Prevention, community management and hospital management of the major threats to child survival.

fever is highlighted as an important cause of fever or shock in the Indian adaptation of IMCI. Neonatal health also plays an important part in the Indian version, which has thus been dubbed IMNCI (Integrated Management of Neonatal and Childhood Illness).

IMCI categorizes acute clinical conditions, such as diarrhea, into simple clinical 'traffic light'-coloured classifications depending on severity, each with a corresponding management pathway. The other key elements of IMCI include healthcare worker training, systems development and engagement with the community and families. In Tanzania, IMCI has been shown to be cost effective while improving the quality of referral patterns. Given the efficacy of IMCI, there is an urgent need to improve its coverage as well as promoting local adaptation and integration with private sector services.

Malnutrition

Malnutrition is an underlying factor in approximately half of deaths in under-5-year-olds. Undernourished children are significantly more likely to die from common childhood conditions, e.g. diarrhoea, respiratory tract infections, malaria, measles, TB and HIV.

Undernutrition is also associated with impaired and suboptimal cognitive development. The current global burden of morbidity and mortality associated with malnutrition lies predominantly with undernutrition in low-resource settings, and overnutrition in wealthy countries and in the rapidly increasing middle class in middle-income countries. In 2012, there were an estimated 51 million children with wasting and a further 162 million with stunting; 80% of these were living in either south Asia or sub-Saharan Africa.

The aetiology of undernutrition is usually multifactorial. Poverty is the most important underlying predisposing factor, exacerbated by lack of food security created by civil conflict, drought and natural disasters. Protective factors that reduce the probability of a child becoming undernourished include longer duration of breastfeeding, higher maternal age at first birth and up-to-date immunization status. The period from conception to the child's second birthday, or 'first 1000 days', has been targeted for nutritional interventions. The most effective preventative interventions include breastfeeding promotion and supplementary feeding programmes, including micronutrient supplements, e.g. vitamin A. Helminth infections (such as hookworm) have been associated with malnutrition and impaired school performance, and periodic systematic

Fig. 33.4 Malnutrition: the link between pathophysiology, clinical features and management.

deworming is recommended alongside vitamin A administration in many countries.

Undernutrition has profound physiological implications. Figure 33.4 summarizes the key pathological processes involved in macronutrient deficiency and common micronutrient deficiencies. The physiological changes or 'reductive adaptation' that occur in the severely undernourished state heavily influence management.

The WHO has simplified the case definitions for malnutrition. The definition of severe acute malnutrition includes full-blown clinical conditions such as marasmus and kwashiorkor, as well as children who present with less obvious clinical signs but are below defined anthropometric thresholds. Weight-for-age is a sensitive and specific index of acute malnutrition. It is usually expressed as standard deviations from the mean (or Z-score), or as percentage of the expected (or median) value. Severe malnutrition is defined as a weight-for-height more than 3 standard deviations below the median on the WHO growth chart. Height-for-age is a measure of stunting and an index of chronic malnutrition. The measurement, calculation and interpretation of such anthropometric measures necessitate proficient numeracy skills, and are prone to error. Therefore, the WHO advocates the use of a highly effective proxy measure of severe malnutrition in children aged 6 months to 5 years: measurement of the mid upper arm circumference (MUAC). This is relatively simple and quick to perform, and does not require specialized equipment beyond a tape measure (Fig. 33.5). The regular assessment of MUAC is recommended in all children between 6 months and 5 years of age; measurement below 115 mm correlates highly with severe acute malnutrition.

Question 33.4

Kwashiorkor

Which of the following clinical features would suggest increased risk of death? Select ONE answer only.

A. A 'flaky-paint' skin rash with hyperkeratosis (thickened skin) and desquamation
B. Angular stomatitis
C. Distended abdomen and enlarged liver
D. Hair sparse and depigmented skin
E. Oedema of the feet

Answer 33.4

E. Oedema of the feet.

Some children with acute protein–energy malnutrition develop oedema and these children have kwashiorkor (rather than marasmus). Although all forms of malnutrition are life-threatening, the risk of death with kwashiorkor is higher than it is in children with marasmus.

Oedema is the key clinical feature which distinguishes kwashiorkor from marasmus.

Though kwashiorkor and marasmus are easily recognizable clinically, severe malnutrition only represents the 'tip of the iceberg' (Fig. 33.6); moderate malnutrition is more prevalent and often goes unnoticed, and is associated with a greater number of associated deaths. The most effective method of detecting moderate malnutrition is systematic regular anthropometric assessment, a key feature of IMCI protocols.

Regardless of the anthropometric severity of malnutrition, the presence of certain clinical risk factors 'complicate' malnutrition and have been shown to significantly increase the risk of mortality: lethargy, high fever, severe dehydration, palmar pallor or pneumonia. 'Complicated' malnutrition is an indication for admission to a hospital or specialized feeding centre. The WHO Ten Steps to Recovery addresses the priorities for the inpatient of complicated severe acute malnutrition

– the 'stabilization phase' (hypoglycaemia, hypothermia, dehydration, early feeding, antibiotics, electrolyte and micronutrient supplementation) and the 'rehabilitation phase' (catch-up growth, sensory stimulation and preparation for discharge).

There is growing evidence that 'uncomplicated' malnutrition should be treated in community-based supplemental feeding programmes. The emerging cornerstone of these programmes is the use of ready-to-use therapeutic foods (RUTF), which are sweet-tasting, energy-dense pastes that are enriched with micronutrients. Commercial RUTF preparations are inexpensive and relatively imperishable, and are an important nutritional intervention particularly for organizations working in difficult circumstances, such as conflict or natural disaster. School feeding programmes are also a sustainable nutritional intervention, using local produce to feed children during their school day, and can improve school attendance, concentration and performance as well as gender equity in access to education.

Neonatal health

Case history

A low-birth-weight baby

Adina is born in a health centre after an uncertain but probably less than 9-month gestation in rural Ethiopia. Her mother is 16 years old. Adina weighs 1.6 kg and has signs of mild respiratory distress. What are the main threats to her survival?

They are described below.

Fig. 33.5 MUAC measurement on a child at a primary health care clinic. It is colour-coded to facilitate recognition of malnutrition (red is <115 mm).

"Visible"

"Hidden"

Marasmus and Kwashiorkor

Complicated severe acute malnutrition

Uncomplicated severe acute malnutrition

Moderate malnutrition "not growing well"

Mild malnutrition "growing but sub-optimal"
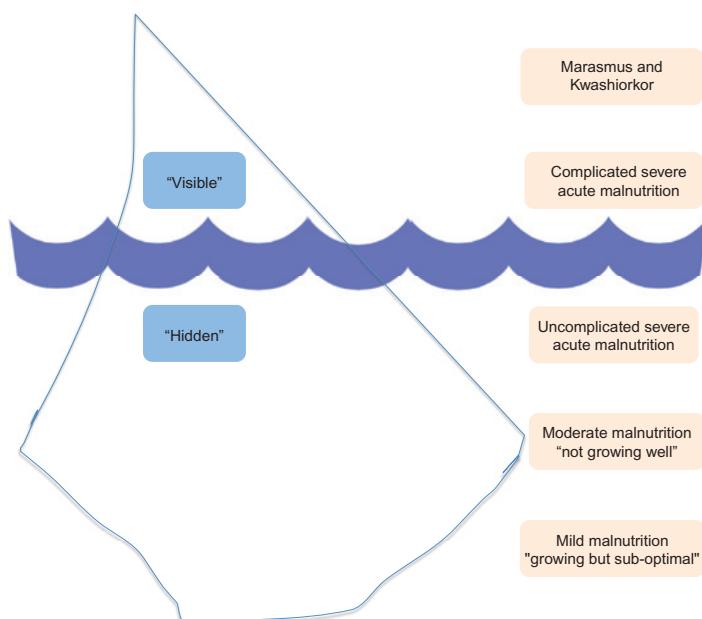
Fig. 33.6 Severe malnutrition represents the 'tip of the iceberg'. Most children with moderate malnutrition remain 'hidden'.

How many neonates die?

In 2012, there were 2.9 million neonatal deaths globally and the global neonatal mortality rate fell from 33 deaths per 1000 live births in 1990 to 21 deaths per 1000 live births in 2012. Deaths within the first 28 days of life comprised 44% of under-5 deaths globally in 2012. The vast majority of these deaths (99%) occur in low-income countries.

Why are newborns dying?

The decline in neonatal mortality has been strikingly slower than the decline in under-5 mortality. The highest risk of death is within the first 24 hours of life, with 75% of neonatal deaths occurring within the first week. The leading causes of neonatal death are preterm delivery (29%), severe infections such as sepsis and pneumonia (25%) and perinatal asphyxia (23%). Neonatal tetanus is a major cause of death in many areas. Intrauterine growth restriction is an important co-morbidity.

There is a strong link between maternal and child health. A young, stunted mother, who is anaemic during pregnancy due to repeated malaria infections and has not accessed antenatal care, is at increased risk of obstructed labour, will have poor reserves to overcome postpartum haemorrhage, and is at increased risk of sepsis. Her baby will be at increased risk of intrauterine growth restriction and prematurity, perinatal asphyxia and developing neonatal tetanus. If the mother dies, the risk of her child dying rises substantially.

Poverty and poor maternal education are major determinants of maternal and neonatal mortality, as well as for child mortality, as discussed above. The planning of effective interventions has been informed by the three delay model: delay in recognition of severe illness, delay in seeking and accessing care and delay in receiving care within the health facility. Neonatal mortality rates are lowest in countries with the highest rates of institutional delivery and skilled birth attendants. However, research has demonstrated that low-cost community educational tools are also effective at reducing mortality. A meta-analysis of trials of the effect of participatory women's groups on maternal and newborn survival in Nepal, India, Bangladesh and Malawi involving almost 120,000 births showed that local non-medical female facilitators who have received a short training course reduced neonatal and maternal mortality by raising awareness of the common problems in pregnancy and finding locally feasible solutions. Neonatal deaths fell by 23% and maternal deaths by 37%. It has been estimated that up to 41,000 maternal deaths and 283,000 neonatal deaths could be averted annually in a cost-effective and sustainable manner if women's groups were introduced to 74 high-mortality countries. Improving access to family planning and increased birth spacing also improves neonatal outcomes.

Many neonatal deaths (between 41% and 72%) can be prevented with skilled birth attendants at delivery and good, basic care of the newborn infant. Collection of epidemiological data and its application to results of trials have allowed evidence-based interventions to be evaluated (Table 33.2). Neonatal intensive care is required for very few babies. In the UK, the neonatal mortality rate had fallen to below 15 per 1000 live births before neonatal intensive care was introduced.

Only 14% of babies born in low-resource countries are low birth weight (<2.5 kg); however, they account for 60–80% of deaths. The major problems for babies born preterm and growth restricted (such as Adina in the case history above) are need for respiratory support, infection, thermoregulation, hypoglycaemia, hydration and feeding. The majority of deaths in moderately preterm babies are preventable by establishing breastfeeding, maintaining warmth and by prevention and early treatment of infections. Helping Babies Breathe is a training programme which aims to equip community workers and midwives with essential skills in basic neonatal resuscitation with airway opening manoeuvres and mask ventilation. A training course on early newborn care (WHO Essential Newborn Care) has also been developed, but training alone does not necessarily reduce mortality rate. The risk of infection can be minimized by diligent handwashing. Kangaroo mother care, where the baby is nursed on its mother's chest 24 hours a day, improves thermoregulation and reduces cross-infection. Support to establish breastfeeding, or frequent nasogastric or cup feeds of expressed breast milk, will avoid dehydration and hypoglycaemia. If the condition of a premature baby such as Adina deteriorates, she would require intravenous antibiotics, oxygen therapy and possibly respiratory support. Basic respiratory support such as 'bubble CPAP' can be used for respiratory distress syndrome in low-resource settings. Oxygen therapy is often provided using oxygen concentrators. Oxygen cylinders should be available to provide oxygen therapy when power cuts occur, but are expensive. Exclusive breastfeeding reduces the risk of later deaths from infections.

Neonatal tetanus has been estimated to cause 200,000 neonatal deaths per year, predominantly after the first week of life. Promotion of clean delivery practices, clean cord care and administration of 2 doses of tetanus toxoid vaccine to the mother prevents neonatal tetanus. The fall in neonatal mortality observed in India was achieved largely from a reduction in tetanus deaths. *Clostridium tetani* is an obligate anaerobic Gram-positive bacillus which is ubiquitous in the

Table 33.2 Evidence-based interventions for saving newborn lives

Intervention	Grade of evidence	Reduction (%) in all causes of neonatal mortality/major risk factor
Antenatal		
Folic acid supplementation	IV	Incidence of neural tube defects (72%)
Tetanus toxoid immunization	V	Perinatal mortality (33–58%) Neonatal tetanus (88–100%)
Syphilis screening and treatment	IV	Prevalence dependent
Intermittent presumptive treatment for malaria	IV	Neonatal mortality (32%)
Pre-eclampsia/eclampsia prevention	IV	Prematurity (34%) Low birth weight (31%)
Detection + treatment asymptomatic bacteriuria	IV	Prematurity/low birth weight (40%)
Intrapartum		
Antibiotics for premature rupture of membranes	IV	Incidence of infections (32%)
Corticosteroids for preterm labour	IV	Respiratory distress syndrome Neonatal mortality (40%)
Detection and management of breech by caesarean section	IV	Perinatal/neonatal death (71%)
Labour surveillance	IV	Early neonatal deaths (40%)
Clean delivery practices	IV	Neonatal mortality (58–78%) Incidence of neonatal tetanus (55–99%)
Postnatal		
Resuscitation of newborn baby	IV	Neonatal mortality (6–42%)
Breastfeeding	V	Neonatal mortality (55–87%)
Prevention and management of hypothermia	IV	Neonatal mortality (18–42%)
Kangaroo care	IV	Incidence of infections (51%)
Community-based pneumonia case management	V	Neonatal mortality (27%)

(From Darmstadt GL, et al. Evidence-based cost-effective interventions: how many newborn babies can we save? Lancet: Neonatal survival 2005.)

environment and forms spores resistant to disinfectant and heat. Though it is not possible to eradicate the organism from the environment, the WHO have set a goal of worldwide elimination of the disease, defined as less than 1 case per 1000 live births in every district of every country. Once infected, the case fatality rate for neonatal tetanus is 100% for out-of-hospital cases, and approaches 60% even with full hospital care involving benzodiazepines, tetanus immune globulin and respiratory as well as feeding support.

Perinatal asphyxia and other intrapartum-related conditions are not only a major cause of neonatal mortality but also of long-term neurodisability.

Neglected issues in global child health

Adolescent health

What are the major threats to adolescent health?

Historically, the health of adolescents (defined by the WHO as young people aged between 10 and 19 years)

has received less attention than that of younger children, despite the importance of adolescence as the 'foundation of adult health'. The leading causes of death in adolescence globally are injuries (both road traffic accidents and suicide) as well as maternal causes.

How can adolescent health be improved globally?

Interventions against non-communicable diseases should target adolescence, when long-term patterns of health behaviour are being established. This includes initiatives to maintain physical activity and good nutrition, to discourage alcohol and tobacco abuse, to improve mental and sexual health. Access to education and national wealth are the strongest determinants of adolescent health. Supportive families, schools and peers are needed to ensure good health outcomes. Programmes specifically targeting adolescents are required, taking into account relevant intercountry epidemiology. In HIV-endemic countries, programmes addressing HIV prevention in adolescents will be particularly important.

Mental health

What is the burden of mental health in childhood and adolescence globally?

There are difficulties in obtaining reliable data on the burden of mental health disorders in low-resource settings. However, figures suggest that suicide is a leading cause of death in young people living in India and China. Among non-fatal illnesses, the largest disease burden in adolescence is due to mental health disorders, with 75% of all mental disorders first manifesting in this age group.

Neglected tropical diseases

The neglected tropical diseases (NTDs) (Box 33.2) are a group of infections prevalent in low-resource settings across Asia, Africa and the Americas. The WHO's Department of Control of Neglected Tropical Diseases describes 17 NTDs. Of these, two are targeted for eradication (dracunculiasis, also called guinea-worm disease, by 2015, and yaws by 2020) and four for elimination (blinding trachoma, human African trypanosomiasis, leprosy and lymphatic filariasis) by 2020.

The WHO describes several key strategy areas for trying to tackle NTDs, including: preventive chemotherapy; innovative and intensified disease management; vector control and pesticide management; safe drinking water, basic sanitation and hygiene services; and zoonotic disease management. Two examples of particularly prevalent neglected disease threats to children are described below.

Helminthiasis

Around 1 billion children live in areas that are stable for transmission of soil-transmitted helminths. Worm infections are most common in school-aged children and worms account for 20% of disability-adjusted life years (DALYs) lost due to communicable diseases in these children. Studies have shown associations between helminth infection and undernutrition, anaemia, poor growth, school attendance and poor performance in cognition tests. In deworming programmes, drug therapy is given to all children attending school. There is some debate about the level of their effectiveness, but the World Bank and the WHO promote helminth control programmes in developing countries as a cost-effective intervention.

The most commonly used drugs for the treatment of common helminths are albendazole or mebendazole, which can be administered as a single tablet to all children, regardless of size or age. Only in the most heavily infected communities is treatment required more than once a year.

Trachoma

Trachoma is the leading preventable cause of blindness globally. It is caused by repeated and persistent infection with *Chlamydia trachomatis* resulting in progressive keratoconjunctivitis and scarring (trichiasis). The major risk factor is poor facial hygiene across communities. Children are disproportionately affected, as transmission is facilitated by living in close proximity to an affected family member. The WHO has set 2020 as the target for global elimination, by means of the SAFE strategy: surgery for trichiasis, antibiotics for active trachoma, facial cleanliness and environmental improvement. There is good evidence for these interventions, e.g. mass annual antibiotic (azithromycin) distribution appears to be an effective and safe method of reducing the prevalence of trachoma.

Vulnerable children

Several problems facing vulnerable children in a global context – child labour, street children and armed conflict – will be considered. Advocacy for them and all children can be considered within the context of the United Nations Convention on the Rights of the Child.

Child labour

The International Labour Organization defines child labour as 'work that deprives children of their childhood, their potential and their dignity, and that is harmful to physical and mental development.' It refers to work that:

- is mentally, physically, socially or morally dangerous and harmful to children
- deprives children of opportunities to attend school
- obliges children leave school prematurely
- requires children to attempt to combine school attendance with excessively long and heavy work.

Box 33.2 WHO neglected tropical diseases

Buruli ulcer *(Mycobacterium ulcerans* infection)
Chagas disease
Dengue/severe dengue
Dracunculiasis (guinea-worm disease)
Echinococcosis
Food-borne trematodiases
Human African trypanosomiasis (sleeping sickness)
Leishmaniasis
Leprosy
Lymphatic filariasis
Onchocerciasis (river blindness)
Rabies
Schistosomiasis
Soil-transmitted helminthiases
Taeniasis/cysticercosis
Trachoma
Yaws (endemic treponematoses)

It is estimated that in 2010 about 213 million children were involved in child labour. Approximately 115 million perform hazardous work; the number of children involved in hazardous work is declining. Most child labourers work in agriculture (60%), with only 20% of working children in paid employment and the majority as unpaid family members.

Street children

Case history

George is an 8-year-old boy living on the streets of western Kenya. His mother died 2 years ago, so he lives with his father, who has an alcohol problem. George decided to run away to the streets of the nearby city from his rural home 12 months ago and has been living and working there since. During the day, he tries to scavenge for food and to earn money by doing odd jobs and by begging. At night he tries to find a quiet, safe place to sleep where he uses cardboard and old blankets to keep warm. He has recently started sniffing glue.

What is meant by a 'street child'?

The term 'street child', used by the Commission on Human Rights in 1994, described 'any girl or boy […] for whom the street (in the broadest sense of the word, including unoccupied dwellings, wasteland, etc.) has become his or her habitual abode and/or source of livelihood, and who is inadequately protected, supervised or directed by responsible adults.' There is, however, continuing debate about the definition of 'street children' and also the stigma that often accompanies this label. Many now regard children to be either 'of' the street (those most vulnerable children who live and work on the streets) or 'on' the street (those children who go to the streets for work but have a home or family connections to return to).

The number of street children globally is difficult to estimate with precision and depends on the definition used, but estimates vary from 30–170 million. A study conducted in eastern and southern Africa in 1999 in 65 towns and cities that interviewed over 3000 street children found that their ages ranged between 6 and 17 years, the majority being 9–14 years old; three quarters were boys. The majority worked on the streets during the day and returned home at night, but 8% worked and lived on the streets.

What causes children to live on the streets?

Groups working with street children describe elements that drive children to the streets ('push factors') and those that encourage them to try to leave ('pull factors'). They are poverty and family breakdown, but warfare, conflict and natural disasters are also responsible for increasing numbers. Street children are at particular risk of poor nutrition, accidents, violence and sexual abuse and have poor access to healthcare. They are amongst the most vulnerable of children.

Armed conflict and children

Globally, more than 1 billion children under the age of 18 live in countries or territories affected by armed conflict. Approximately 300 million are less than 5 years of age. In countries affected by armed conflict, children are the most vulnerable to the effects of war and violence. They may be affected as the witnesses and victims of conflict, they may be used as 'human shields' or may themselves be 'recruited' or forced into being participants in conflict as combatants or in military support roles. Conflict-affected countries and territories have shown less progress towards the Millennium Development Goals (MDGs) and invariably suffer poorer child health and education indicators.

'Six grave violations' – what are they?

In an effort to try to better protect children in conflict and to aid the gathering of evidence to try to bring justice to the perpetrators of violence against children, the United Nations Security Council has identified six categories of violations – the so-called 'six grave violations':

1. Killing or maiming children
2. Recruitment or use of child soldiers
3. Attacks against schools or hospitals
4. Rape and other grave sexual violence
5. Abduction of children
6. Denial of humanitarian access

The true measure of a nation's standing is how well it attends to its children – their health and safety, their material security, their education and socialization, and their sense of being loved, valued, and included in families and societies into which they are born.

UNICEF Innocenti Report Card 7 (2007)

Looking to the future: Sustainable Development Goals

The Millennium Development Goals (MDGs) ended in 2015. Although the MDG4 target of a two-thirds reduction in under-five mortality was not reached, a decline by more than half, from 90 to 43 deaths/1000 live births between 1990 and 2015 was achieved.

The Millenium Development Goals have been replaced by 17 Sustainable Development Goals (SDGs) for 2016–2030, which have a broader agenda and include all countries, not just those of low and middle income. The SDGs include not only ending poverty and hunger, achieving inclusive and equitable education, and water and sanitation for all, but also achieving gender equality and combating climate change among others. Only one has health as its primary focus, namely SDG3, to 'ensure healthy lives and promote well-being for all at all ages'. It includes the sub-target to end preventable deaths of newborns and children under 5 years of age by 2030, with all countries aiming to reduce neonatal mortality to at least 12 per 1000 live births and under-5 mortality to at least 25 per 1000 live births. The impressive reductions in child mortality seen with the MDGs were largely because of political pressure to meet specific targets; whether the same attention will be paid to achieving the more numerous SDG3 sub-targets remains to be seen. The specific neonatal focus is because progress in reducing mortality has lagged behind that of older children.

Further reading

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Richard D W Hain
With contributions by
**Megumi Baba, Joanne Griffiths,
Susie Lapwood, YiFan Liang, Mike Miller**

CHAPTER

34

Palliative medicine

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Be aware of life-limiting conditions and their epidemiology
- Know about the principles of symptom control – pain, nausea and vomiting, dyspnoea, constipation, skin conditions and emergencies
- Be aware of the ethical issues in children with life-limiting conditions
- Know about the practical issues around the death of a child
- Be aware of bereavement and grief

Philosophy of palliative medicine

A child's illness profoundly impacts on child and family, particularly when the illness might lead to death. The science of medicine is increasingly able to intervene to cure even serious illness. However, a significant number of children cannot be cured. They have a 'life-limiting condition' (LLC), an illness which leads to premature death and/or a prolonged period of chronic illness. If cure is the only solution medicine can offer, doctors will never meet the needs of children living with LLC. Cure is a powerful way to improve the lives of ill children; fortunately, it is not the only way.

> **Key point**
>
> *Palliative care* (Box 34.1) refers to the support healthcare can offer where cure is not possible. *Palliative medicine* refers to the contribution that doctors can make to that care.

Unlike most medical specialties, palliative care is not defined by organ system, aetiology or age group, but by a philosophy of care. That complicates definitions. There have been many attempts to define which medical conditions are included in LLC. The most widely used is the ACT/RCPCH system, which defines four categories of LLC based on the trajectory of the condition. Conditions in the different categories are:

- Category I – those for which death and cure are both possible outcomes (e.g. cancer).
- Category II – might be living a normal or near-normal life in the present moment despite having a condition that will inevitably lead to premature death (e.g. Duchenne muscular dystrophy).
- Category III – relentlessly progressive towards death without any such normal period.
- Category IV – heterogeneous and unpredictable because the underlying condition is not progressive; premature death results from the cumulative effects of the condition, rather than from the condition itself (e.g. cerebral palsy).

The exact proportions are not clear (see below), but some reports suggest that categories I and IV each account for roughly a third of all LLCs, with II and III together making up the remaining third.

The multidimensional nature of palliative care means that it is informed by research in a wide range of disciplines, from anthropology – for example, Bluebond-Langner's seminal work on how children see dying – to bioethics, moral philosophy and theology. Over the last fifteen years, it is perhaps in the fields of opioid pharmacology and epidemiology that the impact of scientific research is most obvious to paediatricians.

One of the barriers to good symptom management has traditionally been the belief that morphine should be withheld from children wherever possible, and that codeine was safer because it was weaker. A series of studies of morphine in children has shown that there is no pharmacological basis for a reluctance to prescribe morphine in children. In contrast, recent clinical studies have shown that the metabolism of codeine is dangerously unpredictable. Studies have made it clear that conventional practice in respect of opioids in children perversely recommended an alternative to morphine that was both less effective and more dangerous.

Epidemiology is beginning to shape palliative care. The ACT/RCPCH categories are descriptions of types of condition, rather than a list of diagnoses. They are not precise enough for epidemiological purposes. That has meant that, until recently, it was impossible to develop services for children with LLCs based on evidence. That has recently changed as a result of studies. One assigned an ICD10 code to around 400 of the commonest LLCs presenting to hospice and palliative care teams in the UK. Another used an analysis of prospective 'hospital episode' data. The result was that for the first time we now know that 32 in every 10,000 children in England are living with a LLC and that its prevalence has increased by almost a third in the last decade.

Palliative care in children provides a good illustration of the need for clinical practice to be informed by science, even when cure is no longer possible. Pharmacology and epidemiology are fields of research whose findings have begun to transform the way we can care for children with LLCs.

Symptom control

Pain

Pain management:

- Is an essential component of palliative care.
- Requires assessment, communication, planning and a sound knowledge of pharmacology and physiology.
- Is often under-recognized in children with disability.
- Can dramatically improve quality of life for child and family if done well.

According to the International Association for the Study of Pain, pain is 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.' It is:

- Subjective (whatever the child says it is)
- Influenced by past pain experiences and concerns about personal well-being or that of others
- Influenced by context (different situations).

Key point

Total pain expresses the concept that pain always occurs in the context of emotional need, fears, past experiences and understanding of the pain as well as biological experience.

All children, including the extremely preterm, are able to feel pain. Pain in palliative care is usually neither wholly acute nor entirely chronic. It has elements of both, and may be complicated by the existential context of deterioration towards death.

Assessment of pain

Assessment of pain in children requires:

- Detailed history (also from the child, if possible)
- Observation of the child (Box 34.2), ideally in a variety of settings

- Examination
- Consideration of all possible contributing factors (including psychological, spiritual and social)
- Discussion with parents, especially in the non-verbal child
- Use of pain assessment tools appropriate for age and cognitive ability.

The two most commonly-used types of pain scale are 'faces'-type tools and scales based on observation of behaviour patterns associated with pain in non-verbal children, such as the Paediatric Pain Profile. Faces-type tools are based on a Likert scale and illustrate varying pain intensity using drawings of children's faces. Unlike the Paediatric Pain Profile, most 'faces'-type scales were validated for assessment of acute pain in cognitively normal children, rather than in children with LLCs.

Management of pain

Consider and treat specific reversible causes

- Constipation
- Gastro-oesophageal reflux
- Orthopaedic, especially hip dislocation

Consider non-pharmacological measures

- Attention to reversible sources of fear and anxiety
- Counterirritants (hot or cold packs, acupuncture or TENS), distraction techniques
- Behavioural techniques (cognitive behavioural therapy, relaxation, visualization or art therapy)

Pharmacological approach: the pain ladder

> **Key point**
>
> The WHO pain ladder (Fig. 34.1) is the basis for rational management of palliative pain. It expresses the concept that increases in the intensity of pain should be matched by changes both in the type of analgesic, and the manner in which they are prescribed.

There are three steps on the WHO pain ladder. As pain intensity increases and the effect of prescribing on one step becomes inadequate, the prescriber should move to the next step. Each step is characterized by:

- A specific class of analgesic
- A specific approach to dosing (regular versus 'as needed')
- The need to consider adjuvants (Box 34.3) appropriate to the nature of pain

> **Key point**
>
> An adjuvant is a medication or other intervention that is not an analgesic but, used alongside analgesics, its actions can reduce pain in certain specific situations.

WHO analgesia ladder

	Step 1 *Mild pain*	Step 2 *Moderate pain*	Step 3 *Severe pain*
Drugs	Simple analgesics	Opioids	Opioids
Breakthrough dose	As indicated	0.1mg/kg OME 1-4hrly	1/10 to 1/6 of total daily background dose, given 1–4 hrly
Background dose	None	Usually none	Starting dose 1 mg/kg/24h OME, then increased as determined by breakthrough requirements

OME = Oral Morphine Equivalent (measure of opioid potency)

Fig. 34.1 WHO analgesia ladder showing use of analgesics according to severity of pain. Recently, the WHO ladder recommends only simple analgesics and opioids. Opioids are no longer divided into minor and major, as high dose of a weak opioid is pharmacologically equivalent to a low dose of a strong one. Simple analgesics are: paracetamol, NSAID, aspirin where appropriate. Opioids are: morphine, diamorphine, fentanyl, buprenorphine, methadone. Codeine is no longer recommended in most places owing to pharmacogenetic variation in its hepatic activation to morphine, which leads to inconsistent effectiveness. Tramadol is an opioid but has additional non-opioid analgesic properties that make it equivalent to morphine, but it is often poorly tolerated.

Box 34.3 Adjuvants to analgesics

These depend on characteristics of pain:

- *Bone pain* – NSAID, radiotherapy (if metastatic cause), bisphosphonates (especially in presence of osteopenia), steroids (if metastatic cause)
- *Nerve pain* – Anticonvulsants, antidepressants, NMDA antagonists (ketamine, methadone), baclofen, steroids (if cause is pressure, e.g. from tumour oedema)
- *Muscle spasm* – Baclofen, benzodiazepines, botulinum toxin
- *Cerebral irritation* – Phenobarbital, benzodiazepines
- *Neurolytic and other interventions* – Regional nerve blocks and spinal blocks

For prescription of major opioids (Box 34.4), there are three phases, namely: initiation, titration and maintenance. The opioids can be given as immediate release (e.g. oramorph, buccal diamorphine), continuous release (e.g. MST, transcutaneous patch, syringe driver). There should always be both regular (background) and 'as needed' doses. This is a specialist skill and should be undertaken in discussion with the local or regional palliative care team.

Nausea and vomiting

- Nausea and vomiting are distressing symptoms that may cause more upset than pain.
- Full control of nausea and vomiting is more difficult than that of pain – negotiating acceptable goals with the family may be necessary.
- In children with cognitive impairment, feeds are a common cause – liaise with dietitians to manipulate volumes/rates/type of feed.
- Constipation is another common cause.

Key point

Mediators of nausea and vomiting act through receptors in the gastrointestinal tract, liver and brain (chemoreceptor trigger zone and vomiting centre). Rational management of nausea and vomiting relies on knowledge of receptors.

Nausea and vomiting due to:

- *Gastrointestinal tract damage* (chemotherapy, radiotherapy) is often mediated through 5-HT_3 receptors and blocked by 5-HT_3 antagonists (ondansetron, granisetron)
- *Liver swelling/damage or toxins* (infection, metabolic, uraemia, drugs) are often mediated through dopamine receptors and blocked by

Box 34.4 Common fears and myths about morphine

- *'It is the 'death drug'.'* Explanation with family to increase understanding about benefits and side-effects.
- *'It will stop my child breathing.'* Respiratory depression is extremely rare when opioids are used for pain. It is avoided by careful titration of dose.
- '*It has all kinds of side effects.*' There are adverse effects, but fear of them is often disproportionate to the reality:
  - Drowsiness: The child is likely to be drowsy for 3–5 days when first starting strong opioids or when doses are increased.
  - Nausea and vomiting: This can occur when first starting, is less common than in adults and wears off.
  - Constipation: Laxatives are necessary and can be titrated according to need.
  - Other side effects should be monitored but are rare (e.g. pruritus, urinary retention, nightmares)
- '*It is addictive*.' Explain to the family about issues relating to addiction and dependence. Physical dependence is not usually a primary concern in the palliative care setting, but opioids should always be weaned slowly if the pain resolves to avoid withdrawal.
- '*Once you start morphine, there's nothing to turn to later when the pain becomes really bad.'* Tolerance probably occurs if opioids are used for long periods. The remedy is to increase the dose of opioids. Families may find it beneficial to understand the principle of tolerance rather than assuming that escalating doses of analgesia imply disease progression.
- *'People will break in and steal it.'* Discuss safe storage, particularly in the home setting.

dopamine blockers (domperidone, metoclopramide, haloperidol). Because metoclopramide blocks dopamine receptors in the CNS as well as peripherally, it is both more effective than domperidone and more likely to cause adverse neurological effects.

- *Vestibular problems* (travel sickness, vertigo) and *raised intracranial pressure* is largely mediated through acetylcholine and histamine (H_1) and is blocked by anticholinergics, anti-H_1 (cyclizine acts at both receptors) medications.

Additional factors to consider are:

- Levomepromazine (phenothiazine) blocks most receptors and is good second-line treatment, or first-line if cause is multifactorial/not known

- Functional delay – can use prokinetics (dopamine antagonists, erythromycin)
- Efferent (motor) pathway is through vagus nerve (acetylcholine) so anticholinergics are often partially effective irrespective of cause
- Steroids can be valuable by reducing:
  - Oedema (e.g. in raised intracranial pressure)
  - Tissue damage
  - Release of emetogenic mediators

  but adverse (Cushingoid, etc.) effects after prolonged administration of steroids can limit their usefulness.

  In bowel obstruction, consider:

- Anticholinergic to relieve spasm (hyoscine butylbromide (buscopan))
- Analgesic to relieve pain (strong opioid parenterally)
- Anti-secretory to reduce hypersecretion (octreotide)

  Gastro-oesophageal reflux (GOR) is common but does not always cause discomfort. The risk is increased by prone position, decreased activity, medication and liquid feeds (all more likely among debilitated patients). A presumptive diagnosis and treatment of GOR may be appropriate in pain and discomfort related to feeding without an obvious cause. In reflux, consider:

- Antacid to relieve pain (ranitidine, proton blockers)
- Prokinetic to improve gastric emptying (domperidone, metoclopramide)
- Dopamine blocker to reduce reflux (domperidone, metoclopramide)

Question 34.1

Nausea and vomiting

The following are used in the treatment of nausea and vomiting:

A. Acupressure
B. Cyclizine
C. Dexamethasone
D. Domperidone
E. Haloperidol
F. Methotrimeprazine (Nozinan®)
G. Metoclopramide
H. Nabilone
I. Octreotide
J. Ondansetron

For each of the scenarios below, choose the most appropriate first-line intervention. Select ONE answer for each. Note: Each answer may be used more than once.

1. Nausea and vomiting in an eight-year-old boy receiving cisplatin for cancer
2. Nausea and vomiting associated with feeding in a boy with severe quadriplegic cerebral palsy with dystonic movements.
3. Nausea and vomiting in a 14-year-old with advanced metastatic Ewing's sarcoma that is causing compression of the stomach from liver infiltration.

Answer 34.1

1. J. Ondansetron. 5-HT$_3$ antagonists, as chemotherapy induced.
2. D. Domperidone. Treatment for gastro-oesophageal reflux. Metoclopramide generally contraindicated because of dystonia.
3. G. Metoclopramide. Liver and gastric outlet obstruction. Significant long-term adverse effects unlikely because of age and probable short prognosis.

Dyspnoea

The profound and multidimensional significance of difficulty breathing is illustrated by the dual meanings of words like 'inspire' and 'expire'. In paediatric palliative care, respiratory arrest is the most common mode of death and altered pattern of breathing is one of the critical signs that death is approaching. Dyspnoea is a common and distressing symptom.

Key point

Dyspnoea is a subjective sensation of uncomfortable breathing. Like pain, dyspnoea is 'what the child says it is'. It is not an objective phenomenon.

Regarding dyspoea:
- Different factors contribute to the symptom, including physical, psychosocial and existential/spiritual factors.
- Fear and anxiety play a significant part in its pathophysiology (they can be both cause and effect of dyspnea, causing a vicious cycle).
- Breathing can be *abnormal* (e.g. tachypnoea) without being *uncomfortable* and vice versa.

Causes of dyspnoea in children with life-limiting conditions (Fig. 34.2) can be:
- Reversible (e.g. chest infection, fluid overload, pressure from metastatic tumour)
- Inevitable (e.g. muscle weakness in Duchenne muscular dystrophy)
- Irreversible but amenable to palliation (e.g. secretions pooling in the hypopharynx in the last hours/days of life, causing 'death rattle').
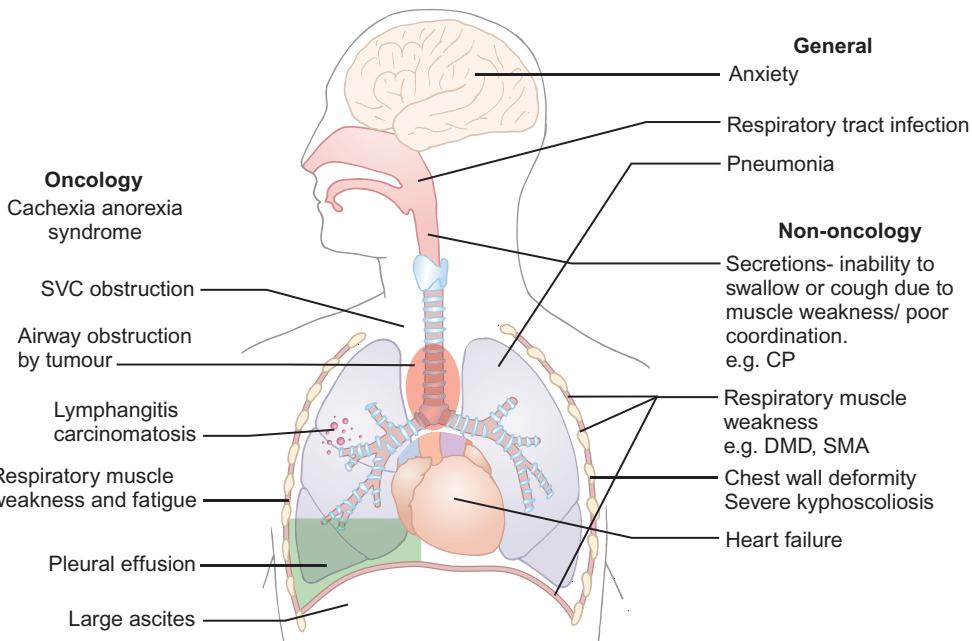
Fig. 34.2 Causes of dyspnea. CP, cerebral palsy; DMD, Duchenne muscular dystrophy; SMA, spinal muscular atrophy; SVC, superior vena caval.

Assessment

None of the assessment tools to measure dyspnoea is widely used in paediatrics. Assessment should include:

- Cause
- Severity
- Impact on life quality
- Meaning to the child/family (e.g. intimation of approaching death)
- Relieving and exacerbating factors

Management

Management of dyspnoea:

- is multidimensional
- is multidisciplinary
- requires carefully considering burden versus benefit of any intervention (e.g. the distress of dyspnoea caused by pleural effusion must be set against the distress of thoracocentesis). General approaches will usually offer benefit irrespective of the cause.

Non-pharmacological approaches

Non-pharmacological approaches to dyspnoea include:

- Explanation and reassurance through exploration of the situation with the child and family
- Other psychological interventions to reduce and manage anxiety, such as relaxation therapy
- Physiotherapy, positioning
- Environmental control, e.g. position, room temperature and humidity, use of fan
- Complementary therapy

Pharmacological

Pharmacological treatment of dyspnoea is as follows:

- Opioids (25–50% of analgesic dose) reduces breathlessness without affecting oxygen saturation or pCO_2. Families and professionals may need explanation about this.
- Low-dose benzodiazepines, especially midazolam (ask advice from specialist paediatric palliative medicine team)

  Dyspnoea due to:

- *Muscle weakness* (e.g. Duchenne muscular dystrophy, spinal muscular atrophy) – may be helped by non-invasive positive pressure ventilation if cause is respiratory muscle weakness
- *Anxiety* – may respond to discussion and other non-pharmacological approaches or to benzodiazepines
- *Hypoxia* – often responds to oxygen
- *Respiratory infection* – may be ameliorated using antibiotics or physiotherapy
- *SVC (superior vena caval) obstruction* (usually by tumour) – may be improved by steroids, radiotherapy or a stent
- *Bronchospasm* – is improved by bronchodilators
- *Malignant pleural effusion* – often improved by thoracocentesis (usually temporarily) and pleurodesis

- *Kyphoscoliosis and chest wall deformity* – may require orthopaedic intervention and physiotherapy
- *Excessive respiratory secretions* – may respond to appropriate hydration, anticholinergics like hyoscine hydrobromide and glycopyrronium, physiotherapy, suctioning and positioning

Question 34.2

Dyspoea

Which of the following statements is true about treating dyspnoea in children receiving palliative care? Select ONE answer only.

A. Anticholinergics should be prescribed alongside antibiotics for dyspnoea due to chest infection to reduce secretions.

B. Dyspnoea responds to lower doses of opioids than pain does.

C. Oxygen provides symptomatic relief irrespective of the oxygen saturation.

D. The main function of opioids in dyspnoea is to reduce the respiratory rate.

E. Thoracocentesis is not appropriate for drainage of pleural effusion.

Answer 34.2

B. Dyspnoea responds to lower doses of opioids than pain does.

Oxygen is only useful in dyspnoea if hypoxia is the cause. The main function of opioids in dyspnoea is to reduce the sensation of breathlessness. Thoracocentesis should be considered, though it is often not appropriate to carry it out and pleural effusions may rapidly recur. Anticholinergics should not be prescribed alongside antibiotics as they may interfere with each other's actions.

Constipation, anorexia, cachexia, hiccough

Delayed emptying of the bowel resulting in a colon filling with faeces, especially if hard, is a significant cause of distress. Children with life-limiting conditions are likely to have multiple risk factors:

- Reduced motility
- Reduced fibre intake
- Relative dehydration
- Abnormal central neurological control
- Medications that slow gut transit time.

Opioid-induced constipation

It is usually good practice to start a simulant laxative (e.g. docusate or Movicol®) at the same time as starting opioids. Naloxone and methylnaltrexone antagonize constipating effect of opioids, but their effectiveness is variable and can jeopardize pain control.

Skin symptoms

Key point

Skin may be the primary condition causing life-limitation (Box 34.5) or the source of symptoms in life-limiting conditions. Skin symptoms can have marked psychological sequelae.

Pruritus

- A difficult symptom to control
- Similar transmission to pain sensation; can also have a primary or neurogenic origin
- Careful assessment may identify amenable causes, e.g. opioids, uraemia, cholestasis or topical sensitivity
- Education about general skin care, nutrition and hydration is important
- Wide-ranging therapies, e.g. topical medications, antihistamines, antiepileptics, ultraviolet phototherapy or acupuncture

Wounds

- Malignant wounds are relatively rare in paediatrics
- Pressure ulcers are more common:
  - Occur when pressure compromises tissue blood flow
  - Most common at bony prominences
  - Prevention is through education, nutrition and vigilance
- Wound management focuses on controlling distressing related symptoms
- Symptoms include pain, exudate, odour, bleeding; antifungal agents may reduce odour

Box 34.5 Epidermolysis bullosa

- The most common of life-limiting skin conditions
- Extreme skin and mucosa fragility resulting in complications
- Blistered areas and wounds heal with scarring
- Scarring leads to contractures, progressive and permanent disability
- Problems include severe pain, blistering throughout the gut, renal failure, cardiomyopathy and squamous cell carcinoma

- Vital to manage emotional reactions, e.g. fear, anxiety, depression, anger and lowered self-esteem
- Tissue viability nurses can often advise as to suitable dressings

Emergencies

Even in palliative care, situations arise that demand urgent intervention. In palliative care, an 'emergency' is a symptom or set of symptoms that is serious, and for which there is a specific therapeutic approach, but occurs so rarely that the approach is likely to be unfamiliar to most paediatricians.

Cord compression

- Context – usually malignant disease
- Onset often insidious (increasing pain, urinary retention, incontinence of urine or faeces, numbness)
- Needs urgent discussion with oncology team
- High-dose dexamethasone as temporary measure while radiotherapy and/or surgery are considered
- Likelihood of functional recovery small if symptoms have been present for more than 48 hours

Acute haemorrhage

- Context – usually malignant disease, often haematological (like acute myeloid leukaemia), or occasionally erosion of major blood vessel by solid tumour
- Very rare in reality, but fear is common, especially if there has been haemoptysis or oozing gums
- Consider procoagulants (tranexamic acid)
- Consider localized radiotherapy
- Ensure green towels are available at bedside (blood less obvious than on white sheets)
- Ensure patient has access to appropriate doses of anxiolytic (midazolam) by rapidly available route

Crescendo pain

- Rapidly increasing pain, often complicating (or complicated by) anxiety
- May need 'rapid titration' of intravenous opioids against pain
- Requires inpatient admission and liaison with specialist paediatric or adult palliative care team

Symptomatic hypercalcaemia

- Rare in children but can complicate malignant disease
- Signs are confusion, dehydration and worsening pain

- Needs admission and management with fluids and bisphosphonates

Acute intestinal obstruction

See above for information on acute intestinal obstruction.

Terminal seizures

- Relatively common in the final few hours of life in children with many metabolic conditions
- Often not possible to control entirely; need to reassure parents that although seizures are frightening to watch they are unlikely to be distressing to the person experiencing them
- If necessary, use continuous subcutaneous infusions of phenobarbital, midazolam or both (but see below). If both are required, a second syringe driver is necessary as phenobarbital cannot be given in the same driver as midazolam.

Where possible, management of palliative care emergencies in children with life-limiting conditions should always be undertaken in discussion with the local or regional palliative care team.

Ethics at end of life

The moral theories that underpin medical ethics fall into four categories that differ in where they put the moral focus:

- Moral rules (deontological – e.g. 'You should never hurt a child under any circumstances')
- Practical outcome of a moral decision (consequentialist – e.g. 'It is right to hurt this child if it will benefit her enough, or benefit enough other children')
- Certain acts (e.g. 'Hurting children is always wrong, irrespective of the benefit it might have')
- Nature of the decision-maker (virtue theories – e.g. 'A good paediatrician would avoid hurting her patient unless it was unavoidable to help the child')

Key point

Although there are different moral theories that underlie ethics, they tend to overlap in their most important conclusions. An understanding of theory is important because it allows a structured and reasoned approach to considering ethical quandaries in practice. This is considered further in Chapter 35, Ethics.

In the UK, moral theories form the basis for three practical systems of ethics that relate to children at the end of life:

- The 'four principles' approach – not designed for children
- The 'children's rights' approach – legal rather than ethical
- The RCPCH guidelines: *Making decisions to limit treatment in life-limiting and life-threatening conditions in children: A framework for practice* (2015)

All rely on the concept of a child's 'best interests' – that is, what course of action will, on balance, do the child most good and/or least harm.

The concept of 'best interests' is complicated in children:

- Interests are conceived more broadly than life-prolongation, so physical benefits need to be weighed against emotional/spiritual ones
- Life quality is subjective, but many children with LLCs are not able to express preferences
- The interests of parents and children are not always separable. Even where they are separable in principle, they may not be in practice.

Two ethical quandaries are particularly likely in palliative care: double effect and withdrawing and withholding life-sustaining treatment.

Double effect

Since all medical interventions have more than one possible result, and since it is logically possible for the doctor to intend only one of them, it is inevitable that any intervention will have consequences that are *foreseen* but not *intended*. Rarely, the effect of some of these may be to shorten a patient's life.

Whether a consequence is foreseen or intended can depend in part on how directly it flows from the action. The principle of double effect relies on a sound understanding of therapeutics and pharmacology; it does not simply permit all consequences of an action.

Key point

The distinction between intended and foreseen consequences is ethically significant. In palliative care, it relies on correct prescribing in strict accordance with current knowledge of symptom management.

Withdrawing versus withholding life-sustaining treatment

The decision to withdraw treatment is not the same as the decision to withhold it, but if the 'best interests' test is applied, the answer will always be the same.

However, healthcare professionals often feel differently about withholding treatment rather than withdrawing it. It is important to acknowledge the difference in the way the two decisions are perceived, and impact on the healthcare team and the family, but it should not influence the ethical decision that is made unless that difference impacts on the child's own interests.

The period prior to death and practicalities around death

There are four key things to consider as it becomes clear that the end of a child's life is approaching:

- Recognition that death is imminent
- Place of care
- Advanced care planning
- Practical therapeutics

Recognition that death is imminent

That death has become imminent needs to be recognized, though predicting the exact time of death is rarely possible. It is best to avoid being too precise or using numbers ('I think it will be about three months'), but it is unhelpful to refuse to speculate at all ('We will just have to take it day by day'). However, one usually knows the time frame, and parents usually have a realistic idea from their own observations about what is happening, by gauging their child's deterioration in the last month or week. By finding out what families think, it is often possible to find oneself reassuring them instead of having to give estimates. Seeking advice from nursing colleagues is also often helpful; they are especially skilled at recognizing changes in circulation and breathing pattern that indicate death may be close.

Sometimes parallel planning is required. It is perfectly reasonable to suggest, for example, that the child may die in the next few days from a chest infection, but that if this does not happen, death might not be for some weeks.

Place of care

The three places where a child can be cared for in the last few days of life are home, hospice, or hospital ward. While most families in the UK express a preference that the child should die at home, an increasing number of children's hospices offer end-of-life care in a 'home from home' environment that also offers appropriate medical support.

Every effort should be made to accommodate the family's preferences. If those preferences are unrealistic, this should be discussed well in advance. The most

appropriate forum for those discussions is in the context of advance care planning discussions, often centred around completing an 'end-of-life care pathway'. Some families change their mind at the time of death itself.

Advanced care planning

Issues around advanced care planning are:

- *Discussions at the end of life itself* mean a child's clinical status is precisely known, but there is little time for sensitive discussion.
- *Exploration that takes place well in advance* allows plenty of time, but as there is often little precise information about how it will happen, discussions are necessarily largely hypothetical.

Neither discussion on its own is adequate. There must be both early discussions that are largely hypothetical, and urgent discussions at the end of life that are informed by the precise circumstances at the time.

Advanced care planning should include consideration about emergency care, including preferences in respect of end-of-life interventions (particularly invasive ventilation). When there is no time for those discussions, the medical team will usually proceed with maximum intervention as a way of 'buying time', and perhaps keeping more options open while such discussions take place. Inevitably, this means that some children are subjected to highly unpleasant interventions from which they cannot benefit, simply because there has been no time for adequate discussion about them.

Anticipated symptoms at the end of life and how they can be managed should also be considered.

Advanced care planning documents are available and provide a structured approach to difficult discussions. They also provide a record of the conclusions reached, which can be disseminated to relevant professionals so that communication is optimized. This includes ambulance and police services, allowing them to respond appropriately and sensitively to a death that is expected.

Practical therapeutics at the end of life

At the end of life, assess which medications are essential. The *enteral route* is to be preferred where possible, but as end of life approaches, the enteral route is often no longer possible as the child cannot take medications orally and absorption may be erratic. Some oral medications (e.g. steroids) are also often no longer necessary when death is imminent.

The subcutaneous continuous syringe drive is then the preferred route driver for background medications.

Many of the commonest medications used in the last few hours of life are compatible with one another in the same syringe driver:

- *Opioids* like morphine or diamorphine
- *Anxiolytics* like midazolam
- *Antiemetics* like levomepromazine

The *transdermal route* provides an attractive alternative to subcutaneous infusion for some drugs, e.g. fentanyl, buprenorphine and hyoscine.

The *subcutaneous route* can also be used for breakthrough medications, but the *buccal route* is usually preferable. It permits rapid absorption that avoids first-pass, is not dependent on safe swallow or predictable gastrointestinal absorption, and parents/carers can easily be shown how to administer drugs. Diamorphine and midazolam are commonly given by this route.

The need for artificial nutrition and hydration should be carefully reviewed. Artificial nutrition in the last few hours usually confers little benefit and can complicate symptom management. The risk of continuing with full hydration is that some symptoms, particularly 'death rattle', can be made worse. The benefits of discontinuing fluids are, for some families, offset by their anxiety around the possibility of dehydration. This can be reduced if fluids are reduced to 50%–75% of maintenance, rather than being discontinued completely. If necessary, hydration can be given subcutaneously to avoid the need for hospital admission or repeated attempts at intravenous access.

'Death rattle' – upper airway secretions making an unpleasant sound – does not usually distress the patient, but often merits treatment for the sake of those caring for the child. Treatment is by anticholinergic therapy via a transcutaneous patch or subcutaneous syringe driver.

Question 34.3

Emergency care plans

Which of the following statements about emergency care plans are true (T) and which are false (F)?

A. Once signed, they allow doctors to withhold intensive care without further discussion.

B. They are legally binding on doctors.

C. They are legally binding on patients.

D. They have legal significance.

E. They make inappropriate interventions less likely.

Collusion

Key point

All children and young people should be given the opportunity to talk about their condition and death, but no child or young person should be forced to talk about it if they choose not to.

Collusion refers to the 'conspiracy of silence' that may exist between parents and doctors, in which the nature and/or severity of a child's diagnosis are kept from him/her (Box 34.6).

It should never be assumed that a child does not want to know what is going on. The challenge is how to find out whether the child or young person wants to talk about their illness and death, without talking about it. That can only be done by allowing an opportunity to choose to explore it or not.

Factors to consider regarding collusion are:

- Patient and empathic communication by all members of the team may help encourage the child to feel confident that topics are not 'beyond discussion'.
- For some children, the best way of actively encouraging exploration may be to involve

Box 34.6 Reasons for collusion

- To protect child or young person from painful news
- Fear that he/she will 'give up' if he/she knows the truth
- To avoid having to discuss a difficult topic with the child
- To avoid parents having to face the truth themselves

Many of the reasons, therefore, have the child's own best interests at heart, but such silence is usually counterproductive.

colleagues in psychology, particularly play therapists.

- All children should have the opportunity to talk about their condition, but no child should be forced to talk about it if they do not wish to.

Key points about avoiding collusion

Once collusion has developed, it can be hard to undo. Where possible, it is preferable to avoid it happening in the first place:

- Involve the young person from the start in all discussions about their illness
- Share any new information with the patient and family simultaneously
- Encourage the family themselves to discuss issues openly
- Allow the patient to correct the parents' misunderstandings where possible, in their presence.

At the same time, it is important to:

- Respect genuine coping strategies
- Be sensitive to the rare circumstances when the consequences of even raising the issue would do more harm than good.

Bereavement, grief and mourning

Key point

Bereavement, grief and mourning are not the same:

- *Bereavement* describes the state of having lost someone or something dear.
- *Grief* is the emotional and social reaction to bereavement.
- *Mourning* is the external expression of grief.

No parent expects to bury their child, yet in England and Wales alone, there are about 4000 deaths of infants and children annually, so that about 8000 parents each year face the death of their own child, and 5000 children face the loss of a sibling. The death of a child symbolizes the loss of a future, as well as of the individual in the present.

Grief begins at communication of the diagnosis, for both the child and the family, in anticipation of losing:

- The child him/herself, who would have been expected to grow and develop towards independence as a young adult
- The child's skills and independence.

Theoretical models of grief

- *Bowlby's attachment theory*: When an attachment is threatened or destroyed, the reaction is to cry and search for the lost person.
- *Parkes' four phases of grief*: Numbness, yearning, disorganization and despair, reorganization and recovery.
- *Worden's four tasks of grieving:* Accept the reality of the loss, experience the pain of grief, adjust to the environment without the deceased present, withdraw emotional energy and reinvest in another relationship.

Practical models

- *Dual process model*: Grief is seen as a dual process, comprising a loss-orientated response and a restoration-orientated one. The bereaved person oscillates between the two, and is able both to confront the loss and be distracted from it.
- *Continuing bonds*: Emphasizes that resolution of grief involves a continuing bond, which the survivor maintains with the deceased. Through grief, the bond may be transformed from something painful into something that may give solace and inspiration.
- *Growing around grief*: Emphasizes that the grief does not shrink, but life eventually grows around it.

Box 34.8 Complicated grief

Complicated grief has been defined as a deviation from the normal grief experience in time course, intensity or both.

In a child, this may manifest as behavioural regression, excessive self-criticism, self-harm, taking on a parental role, truanting, silence and withdrawal or overt depression.

Risk factors for adverse outcomes may include:

- *Features of the loss:* e.g. sudden, violent, mutilating, random or prolonged death
- *Features of the bereaved person:* e.g. multiple losses, previous psychological or behavioural problems, child less than 5 years old or adolescent
- *Features of the relationship:* e.g. complicated, ambivalent or abusive relationships, unsupported or conflicted family, attachment issues, death of a parent, mental illness in surviving parent, death of father (for adolescent boys), death of mother (for young children).

Bereaved children, and parents experiencing the death of a child, are at increased risk of adverse outcomes.

Protective factors may include:

- A 'good death', use of rituals, death in a hospice, resilient personality factors, consistent care from residual parent, religious faith

- Children experience similar emotions and difficulties to adults, but without adult skills of verbalization.
- Hence, grief may not be noticed or may present as behavioural or physical problems.

Children may suffer *anticipatory* grief when they understand that death is inevitable, and then on the actual loss of a loved one.

Factors influencing how a family grieves the death of a child

Factors include:

- How they coped with prior losses
- Whether they have experienced the death of another child
- How effective family support systems are
- Whether members of the family have a spiritual understanding or religious faith

Bereaved parents may be at risk of guilt, anger, depression, anxiety, and post-traumatic stress. *Surviving siblings* may have a variety of psychosocial difficulties, e.g. guilt, anxiety, depression, post-traumatic stress symptoms, sleep problems and social withdrawal.

Families also undergo significant changes following the death of a child (e.g. increased parental and marital

Grief may be experienced by:

- The child him/herself with a life-limiting illness
- A sibling or close friend
- Parents or other family members.

There are many theories regarding grief. The traditional theories tended to concentrate on 'coming to terms' and 'letting go', whereas current theories concentrate on developing a new relationship within the bereaved person's life. Some models of grief are listed in Box 34.7.

Children's responses to death and bereavement

In children:

- Responses to death and bereavement are very variable and change with age, intellect, communication skills and emotional maturity, as well as the significance of the loss, the nature of the death, previous personal and family experiences of loss and trauma, their own resilience and the support they receive.

strain). Their grief may be complicated (Box 34.8). The death of a child causes a reorganization of the family.

Helping

Families may be helped by:

- Support for all family members beginning at diagnosis, using opportunities to encourage communication, encouragement to make the most of the present, to create memories, and to plan and prepare for a good death.
- Practical suggestions before and after the death which could include making a memory box, making a family record, making handprints, writing a child's 'will' to give them choice over what happens to treasured possessions, permanency planning (helping children understand what will happen to them when a loved one dies), and supporting children in telling the story of the person's end of life and afterwards.
- Seeing the body and attending the funeral; may be helpful for a child to allow them to begin to say goodbye, to accept the finality of the death, to understand what has happened and to be less afraid. But this should be the child's choice.
- Being offered choices and control, including children.
- Offering, in the case of a child's death, to inform others and provide support to parents, siblings, grandparents, carers, close friends, school staff

Answer 34.4

A. False B. False C. False D. False E. False

A. Codeine is a pro-drug of morphine and has an unpredictable metabolism due to variation in the enzymes that convert it into its active form. Morphine is therefore safer and more predictable.
B. In children, cord compression usually has a slow onset and is caused by an expanding soft tissue mass.
C. Intensive care should always be considered for a child when the benefit is likely to outweigh the risk of harm, irrespective of the nature of the child's condition.
D. Seizures are distressing for the child and family and should be treated. It may sometimes hasten the child's death, but the primary aim is to provide symptomatic relief.
E. This would be deceitful and therefore unprofessional, and a wrong guess is likely to undermine the relationship more than admitting uncertainty. However, vague answers or deflecting rather than addressing the question is also unhelpful.

and all who shared in the child's life for as long as they need it. For immediate family members, this can be several years.

- Being informed about the resources locally and nationally to support grieving children and families.

Conclusion

In this chapter, we have shown that palliative medicine relies on a sound understanding of pathophysiology and therapeutics combined with a skilled and empathic approach to communication. Families faced with losing a child are living through some of the most difficult times people can experience. Doctors are able to accompany them as 'knowledgeable companions'. Paradoxically, the key to being able to help is to acknowledge that medical treatment can sometimes fail to cure, and that for some children cure is impossible. However, the prospect of a cure is not the only thing medicine can offer such a family. There are many other ways for a doctor to help, and it is these which comprise palliative medicine, and which have been described in this chapter

Further reading

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Question 34.4

Palliative care in children

Which of the following statements regarding palliative care of children are true (T) and which are false (F)?

A. Codeine is preferable to low-dose morphine for moderate pain
B. Cord compression is typically sudden because it is likely to be caused by collapse of the vertebrae from osteopenia or metastatic disease.
C. Intensive care should not be considered if a child is receiving palliative care.
D. Seizures in the terminal phase should not be treated, as treatment may hasten the child's death.
E. When parents ask about prognosis, in order to retain their trust it is better to make an educated guess than to admit you are uncertain.

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Joe Brierley

Ethics

LEARNING OBJECTIVE

By the end of this chapter the reader should:

- Understand ethical issues relating to clinical care and conducting trials and research with children.

Paediatrics and child health, perhaps more than any other speciality, has recently been the focus of difficult decision-making. Children born months too early or living from infancy on machines are now commonplace. Newspapers carry stories about carers refusing evidence-based radiotherapy for their children's brain tumours in favour of alternative therapies or about the historic and contemporary abuse of children by celebrities and politicians. Major changes in our laws and practice have followed scandals in which parents discovered that their deceased children's organs had been retained without their knowledge – allegedly as part of a research study – and that children had died in heart centres where operative mortality was significantly greater than elsewhere.

What can *ethics* offer in all this? It is first useful to define the term. One of the simplest definitions is that ethics is the branch of philosophy that deals with matters of right and wrong, and therefore medical ethics is a branch of ethics that deals with matters of right or wrong in medicine. Ethics textbooks cannot escape some ancient Greeks and so two other definitions feature here:

An attempt to find out our chief end or highest good.
Aristotle

How we ought to live.
Socrates

The Socratic concept is especially worthy of reflection as it could be suggested that *paediatric ethics* could at one level be about how paediatricians ought to practise (live).

Healthcare professionals often ask whether a particular treatment or practice is 'ethical.' The answer being sought is whether the treatment or practice is morally acceptable – i.e. *is it right?* This is ultimately defined by society as a whole, through the values that are upheld as being important. For example, a society that regards equal distribution of resources as an important value will strive to develop a healthcare system that allows equal access to healthcare. Within such a society, any action that prevents access to healthcare on the grounds of wealth, gender, race, sexuality, etc., would be deemed unethical. In a different society, where healthcare is only provided on monetary payment, inequality in healthcare access may not be judged to be unethical.

In order to answer the question of whether an action is ethical or not, one needs to have an understanding of:

- *What terms such as right and wrong, good and bad, mean.* Most people, as moral agents, will have their own intuitive sense of what these terms mean, but they are usually influenced by the society within which people exist.
- *Moral theories* to determine what is right or wrong, good or bad. There are several moral theories, such as consequentialism, deontology, virtue ethics and feminist ethics. These different moral theories provide guiding principles by which an action can be judged.
- *Practical application of moral theories* to determine whether an action is ethical, i.e. right or wrong, good or bad. Ethical principles can provide an appropriate framework in order to achieve this.

This chapter provides a brief introduction to commonly used moral theories. It looks at the 'four principles' approach to medical ethics, using this approach to apply moral theory to medical situations. It explores some common clinical scenarios within paediatrics and child health which pose ethical dilemmas. They illustrate the use of moral theories and ethical principles to provide guidance regarding appropriate action. There is rarely an answer that is completely black or white – however, this approach demonstrates how actions can be ethically justified. In the final part of the chapter, the issues surrounding medical research involving children are considered.

Moral theories

There are several moral theories that can be used to make ethical arguments. Those most often used in medical ethics are consequentialism, deontology, virtue ethics and feminist ethics.

Consequentialism

Consequentialism judges acts to be right or wrong according to the results/consequences produced. An act leading to a positive outcome is morally more acceptable than one that produces a negative outcome. According to critics of consequentialism no act is, therefore, non-permissible. Consequentialists can argue back that if abhorrent acts are allowed and generalized there would be less overall benefit to people.

A positive outcome depends on what value is being optimized, e.g. pleasure, happiness, wealth, etc. A hedonist will always act in such a way as to maximize *pleasure* over other values, such as, say, honesty. Often, in consequentialist arguments, a calculation needs to be made to determine the net benefit, taking into account the benefits and negative effects of any action. Utilitarianism, a form of consequentialism, aims to maximize the overall utility in the world that an action can bring about. The utilitarian 'greatest happiness principle' suggests that one should always act to provide the greatest happiness to the greatest number. Consequentialism is popular as it is practical. Logically, it is analogous to 'evidence-based medicine'. It allows the application of judgement in the form of a calculation to justify any action – nothing is universally forbidden. Consequentialism, however, is not without drawbacks. Expensive therapies with low probabilities of success do not fare well against the utilitarian yardstick. For example, intensive care is resource hungry, with high levels of mortality (especially in adults) and morbidity. Public education programmes about chronic disease management, such as asthma and diabetes, in comparison may be more cost

effective in reducing long-term morbidity and mortality and utilitarians would prioritize the latter over the former. However, if intensive care provided the only chance of survival for a critically ill child, would any parent favour the utilitarian argument? Furthermore, it is unclear how the utilitarian argument can be limited – closing hospitals in the UK or decreasing national spending on nuclear weapons and redistributing the savings to the lowest income countries in the world might arguably yield greater happiness for a greater number.

Deontology

Unlike the outcome-based approach of consequentialism, deontology provides a rule-based approach. Morality is based on the intentions of actions, not the consequences. Actions are therefore:

- Obligatory – must be carried out, e.g. resuscitation of a patient in the event of an unexpected cardiac arrest
- Permissible – neither obligatory or forbidden, e.g. the treatment of 'colic' with gripe water
- Supererogatory – morally praiseworthy if performed, e.g. donating a kidney to a relative
- Forbidden – not permissible under any circumstances, e.g. actively killing a patient.

Immanuel Kant, the major proponent of deontology, formulated what is known as the categorical imperative – according to Kant, it is an absolute duty to act morally. If any action is immoral, then we ought not to perform it. The two formulations of the categorical imperative that are important in medical ethics are:

- The formula of the universal law – to act only if the principle of the action can be applied universally to all. For example, lying to a patient to provide false reassurance about their prognosis cannot be applied universally – if all doctors lied to their patients about prognosis, patients would not trust their doctors and therefore would not be reassured by what they said.
- The formula of the end in itself – when any action involves a person, to never treat the person *only* as a means to an end, but always at the same time as an end. For example, administering a placebo to a child to reassure their parent is not morally acceptable, unless the child was benefiting from the treatment at the same time.

The doctrine of double effect is the converse of the above example. An action can be justified even if it causes serious harm, if the harm is a side effect of bringing about a good end. The use of high doses of opiates to alleviate the pain of a terminally ill patient

could be deemed moral, even though it could lead to respiratory depression and death.

Virtue ethics

Unlike deontology and consequentialism, virtue ethics does not focus on acts *per se*, but on the character of the moral agent, i.e. the person morally responsible for the act. Having a given virtue predisposes a person to act in a certain way – for example, a generous person is likely to donate towards charity. Virtues are defined by the person's actions, but also their attitudes and internal values. Therefore, actions are morally appropriate if they conform to a virtuous individual's habits of valuing, assessing and acting according to the virtue in question. In other words, an action is honest if it is consistent with the actions of an honest individual.

It is worth noting, however, that individuals are unlikely to be able to always act according to a given virtue. Negative desires may be a result of circumstances and context. The virtuous will attempt to fight the negative desires and perform the right act accordingly. Virtue ethics therefore accepts the complexity of practical situations, which duty- or consequence-based theories may not.

Feminist ethics or ethics of care

This approach is often contrasted with other classic approaches in its communitarian, contextual and caring approach. Some have argued they are perfect for child health dilemmas (Brierley and Larcher 2011) as they focus less on individualistic rights-based solutions, but rather view the child in its true context as part of a family with parents, brothers and sisters, of a community with family and friends and of a society of other co-dependent people. However, there is a need to ensure the child is not merely considered as the property of its parents. The influential Gillick case clearly established that 'parental rights are derived from parental duty…and…exist only so long as they are needed for the protection of…the child.' (Gillick v West Norfolk and Wisbech Area Health Authority, 1985).

Indeed, for paediatricians, one also needs to clarify the law surrounding decision-making for children. (Further details can be found by reference to GMC and BMA guidance and healthcare law textbooks.) Parents or those with parental rights are privileged to make healthcare decisions (e.g. consent) for their children, as long as they are acting in that child's best interests. If they are not, such as refusing radiotherapy for a treatable brain tumour, the courts will ensure treatment occurs.

Over the age of 18 years, children become autonomous adults and can decide for themselves. Treatment without consent constitutes the tort of battery – unless they can be shown to lack capacity. Young people between 16 and 18 years are presumed to be able to consent, but cannot refuse medical treatment held to be in their best interest. Their parents can consent, though clinicians would be wise to seek help from the courts before treating if the situation is not an emergency, and even then rapid decisions to treat have recently been made (An NHS Foundation Hospital v P, 2014).

It is possible that many involved in child health might consider the ethical aspects at variance from the stark legal situation, given attempts to introduce 'assent taking' from children un-/not yet able to consent in both research and clinical practice.

Although the decision in the Gillick case was limited to provision of contraceptive advice, Lord Justice Scarman's reasoning has become influential to the extent that children deemed Gillick-competent can now consent to treatment at any age, though in reality such maturity is generally only attained over the age of 13 years. He stated:

> As a matter of law, the parental right to determine whether or not the minor child below the age of 16 will have medical treatment terminates if and when the child achieves sufficient understanding and intelligence to understand fully what is proposed.
>
> *Lord Justice Scarman*

Any paediatricians faced with ethical dilemmas involving young people must have a clear understanding of and the ability to test for both capacity and the child's competence to consent to what is proposed. Certainly, one place where ethics and the law coalesce is in children of any age having a right to be involved in decision-making about their healthcare (Gillick v West Norfolk and Wisbech Area Health Authority, 1985).

The four principles of medical ethics

Perhaps the most influential concept in modern medical ethics, and not without its critics, is principlism. In the 1970s, Beauchamp and Childress formulated their four principles of biomedical ethics, which have become the dominant cornerstone of ethical consideration in healthcare practice. The principles are often used as a framework to deliberate on ethical questions about therapies. The four principles are:

i. Respect for autonomy

Autonomy is the ability to self-govern. In order to possess autonomy, an individual must be able to have

desires, be able to formulate options that can realize those desires and be able to select the most appropriate option. Autonomous actions should be intentional, fully understood and devoid of controlling influences. In order to exercise autonomy, a patient must be able to express the problem for which they wish to have treatment, understand the various treatment options and consent to the most appropriate option. Consequently, it would be unethical to treat a patient against their wishes, fail to present the available treatment options to them, or influence or disregard their consented option. For children, this might be the relative autonomy (if that can exist) of a Gillick-competent child, or the autonomy of parents to decide for their children – restricted by the need to act in the child's best interests, however this might be determined.

ii. Non-maleficence

The principle of non-maleficence is embodied in the maxim *primum non nocere*, or above all, do no harm. Harm is defined as an abrogation of one's interests. Within medicine, this would include causing pain, death, incapacity, etc. However, 'causing' death may not always be against a patient's interests; if a patient's condition is unbearable to the point that they wish to die, then continuation of life-sustaining treatment may be both maleficent and disrespectful of their autonomy. Therefore, non-maleficence could be interpreted as not acting against a patient's interests, and is the same for adults and children.

iii. Beneficence

In addition to *not acting against* the patient's interests, one of the ends of medicine is *to act in* the patient's interests, by promoting their welfare. This is the principle of beneficence. Beyond the requirement to provide positive benefit, beneficence also encompasses utility, whereby benefits and risks are balanced to provide an overall positive result. An act of beneficence may therefore involve a reduction in risk to a patient, e.g. vaccination or thrombo-prophylaxis for children or adults.

iv. Justice

The principle of justice involves the fair and consistent treatment of all people within a population. In medical ethics, the principle mainly refers to distributive justice, or the fair and equitable distribution of resources within a population. The fairness of distribution is based on specific principles, e.g. clinical need. The equity is based on treating equals equally, i.e. patients with the same degree of clinical need get the same degree of care irrespective of ability to pay, of religion, of racial group or indeed age.

The four principles are not independent of each other. For example, surgery is not performed on a patient who does not consent, even if he is unlikely to survive without it, out of respect for his autonomy – despite this meaning arguably not acting in a beneficent way. The four principles approach does not set a hierarchy for the principles when they come into conflict with each other, which has often been the focus of criticism. However, the principles aim to provide a framework for ethical deliberation. The emphasis on each principle will depend on the context. For example, in a society where autonomy is held in highest regard, respect for autonomy may overrule considerations of beneficence. Conversely, in societies where medicine has a more paternalistic identity, beneficence may take precedence over autonomy.

Case history

The extremely preterm infant

You are called as the neonatal registrar to talk to parents who have presented to the delivery suite. Juliet is a 38-year-old woman, who is 22^{+5} weeks pregnant with her third pregnancy. She has just had a leak of liquor, and her cervix is 4 cm dilated. She has two healthy children, 2 and 5 years old, with her husband George. You counsel the couple regarding the poor prognosis of babies born at 22 weeks. If Juliet delivers in the next few hours then the baby will not be considered viable. Even if he or she is born with a heartbeat, you will not resuscitate him/her. However, if the baby is born after 23 weeks, he/she will have a better chance of survival. They will still be at high risk of all the complications of extreme prematurity (sepsis, intraventricular haemorrhage, retinopathy of prematurity, bronchopulmonary dysplasia). You quantify the risks according to national and local audit figures. You offer to resuscitate the baby if born after 23 weeks, provided that Juliet and George agree to this.

Juliet and George feel that this is their last attempt at adding to their family. They have strong religious beliefs and are convinced that their baby will survive. They are unhappy with your decision not to resuscitate their baby if he/she is born in the next few hours. They want you to do everything to help their child survive.

Ethical dilemmas:

- Who should decide whether the baby should be resuscitated or not?
- What considerations should be taken into account?
- Should the parents' age, social background or religion have an impact on the decision?
- What if the parents did not want the baby to be resuscitated, as they did not feel they could look after a baby with chronic health problems?

These are complex ethical questions without a right or wrong answer. However, the law may provide boundaries to the relevant ethical arguments. Therefore, the answers may be different in different countries.

In the UK, according to the Abortion Act 1967, a pregnancy can be terminated up to 24 weeks of gestation (or beyond to protect the physical or mental health of the woman, or if the child is likely to be born with severe disabilities). This can be the choice of the pregnant woman, and this is respected to protect her autonomy. The unborn fetus has no legal rights (rightly or wrongly – this is still a topic of debate). However, once the child is born, he/she becomes an individual person, subject to rights and interests like anybody else. As with most children up to a certain developmental age, a newborn baby is not autonomous: they do not have the ability to govern themselves, form their own opinions of how they should live, or execute actions according to those opinions. Others have to decide for them and look after them, which is the role and responsibility of parents, as enshrined in the Children Act 1989. The guiding principle for these decisions is the welfare of the child; in medical ethics terminology synonymous with the principles of beneficence and non-maleficence.

Whilst most parents will act in the best interests of their child, this may not always be the case. Compromises are made to meet the interests of the family unit, e.g. rather than sending their son to a school with a better reputation 30 miles away, parents may decide to send him to his sister's school, closer to home, so that they can travel together. Although this may not be in the individual child's best interests, it does not form an argument for placing the child in foster care – staying in his own family is likely to be far more favourable.

Similarly for medical choices, most parents will take decisions for their children in their best interests. The medical team may need to intervene if the parental decision puts the child at risk of significant harm (known as the 'no harm principle'). Applying this to the case above, we need to determine what risk of harm the child is being placed in after birth. According to the EPICure 2

data from 2006, the survival to discharge from hospital of babies born at less than 23 weeks of gestation is very rare. At 23 weeks, the survival chances are close to 20%, at 24 weeks 40% and at 25 weeks over 60%. In cases where babies have been resuscitated at, or especially below, 22 weeks, even the institution of maximal intensive care has rarely helped. Intensive care therapy can be harmful – most procedures such as intubation, intravenous line insertion and heel pricks are distressing, even though babies may be provided with analgesia to minimize pain. This is largely justified if the chance of survival is reasonable – the baby has potential of a life 'worth living'. However, as babies born at 22 weeks are unlikely to survive, one could consider that the burdens of intensive care outweigh the potential benefits. Such a life may be considered not worth living. One must also be mindful of justice – neonatal intensive care is not a limitless resource. If a baby with an extremely poor chance of survival takes the last available neonatal cot and denies one with a reasonably good chance of survival, both may end up suffering. In order to maximize benefits, we may need to limit who we can offer intensive care to.

Many extremely premature babies will develop chronic health needs. They may remain dependent on their parents for longer. This has an impact on the parents, who may have to give up their jobs to look after their child, and siblings, who may miss out on opportunities as their parents have to devote resources to the less able child. Therefore, although we must try and protect the welfare of individual children whom we as healthcare professionals are looking after, we must be aware of the interdependence between the child and their family. Ultimately, this may affect the welfare of the child – a child with health needs will need dedicated care from their family, which may be compromised if the family did not want the child to be resuscitated at birth, for example.

Based on the evidence (albeit that of EPICure 1995) and such ethical considerations, the Nuffield Council of Bioethics in 2006 formulated the guidelines in Box 35.1. The guidelines were formulated by a working group of healthcare professionals, ethicists, lawyers and parents. They are guidelines and not legally binding. It is possible that with time and improving medical care they will need revision. Nonetheless, they form a consensus opinion, and therefore will carry weight in a court of law.

In the above case there are strong ethical arguments, based on current evidence, to not resuscitate the baby if born before 23 weeks. This should be discussed with the parents, explaining the reasoning behind the decision. This is best done by a paediatrician with experience in the area, respectfully and with empathy for the parents.

Box 35.1 Guidelines for providing intensive care to extremely premature neonates in the UK according to the Nuffield Council of Bioethics

At 25 weeks and above

Intensive care should be initiated and the baby admitted to a neonatal intensive care unit, unless he or she is known to be affected by some severe abnormality incompatible with any significant period of survival.

Between 24 weeks, 0 days and 24 weeks, 6 days

Normal practice should be that a baby will be offered full invasive intensive care and support from birth and admitted to a neonatal intensive care unit, unless the parents and the clinicians are agreed that, in the light of the baby's condition, it is not in his or her best interests to start intensive care.

Between 23 weeks, 0 days and 23 weeks, 6 days

It is very difficult to predict the future outcome for an individual baby. Precedence should be given to the wishes of the parents. However, where the condition of the baby indicates that he or she will

not survive for long, clinicians should not be obliged to proceed with treatment wholly contrary to their clinical judgement, if they judge that treatment would be futile.

Between 22 weeks, 0 days and 22 weeks, 6 days

Standard practice should be not to resuscitate the baby. Resuscitation should only be attempted and intensive care offered if parents request resuscitation, and reiterate this request, after thorough discussion with an experienced paediatrician about the risks and long-term outcomes, and if the clinicians agree that it is in the baby's best interests.

Before 22 weeks

Any intervention at this stage is experimental. Attempts to resuscitate should only take place within a clinical research study that has been assessed and approved by a research ethics committee and with informed parental consent.

Case history

The non-immunized child

Henry, a 10-month-old child, is admitted to the paediatric ambulatory care ward following a generalized febrile seizure associated with a 3-day coryzal illness. The seizure stopped spontaneously after 2 minutes. This was his second seizure. You realize from the history taken at presentation that Henry has never been immunized. His mother, who is at his bedside, does not feel immunization is necessary. She believes that natural immunity alone is effective in preventing childhood infections, and vaccines carry an unnecessary risk of side effects. Her 4-year-old daughter had some of her early vaccines, but did not have her MMR or booster vaccines. She has never suffered any severe illnesses needing hospital, and is now fit and well.

The family seem fairly well informed about health choices. Henry is well grown and there are no other causes for concern about his care. There has been no social services involvement in the family. You remain concerned that Henry has not been immunized. He has already had two febrile seizures. While you understand that being immunized may not have prevented them, you are concerned that it increases Henry's predisposition to more serious illnesses. You express this to Henry's mother, who thinks immunization itself can increase the risk of seizures. She also thinks that these are likely viral illnesses, for which there are no vaccines.

It is difficult to argue with Henry's mother. However, you are still concerned that Henry's health is being affected by his mother's choices. His father is not at the bedside, but has not expressed any wishes for Henry to be immunized.

Ethical dilemma:

- Should Henry's mother's opposition to immunization be pursued further, in the form of child protection proceedings?

The question at hand could be framed in public health terms, namely should immunization be made compulsory? Currently in the UK, an immunization schedule is offered to parents, but is not compulsory. Parents are required to consent to vaccines being administered as proxy decision-makers for children. If they do not consent, the vaccines are not administered. Notably, when parents have disagreed on immunization and the dispute has ended up in court, the UK courts have ruled for the children to be vaccinated in their best interests.

Most interactions between the public and healthcare involve an illness or medical problem. Immunization as part of a schedule is an intervention administered to a well person to prevent future illness. It does this in two ways: by preventing the disease being vaccinated against in that individual, and by generating herd immunity, so that the disease is not propagated within the population.

What is the extent of these benefits to the individual? The vaccines offered protect against disease, but the protection is not absolute. Vaccine failure can occur due to failure of adequate immunity to develop. The vaccines protect against a limited number of serotypes; for example, the current pneumococcal vaccine protects against the 13 most common serotypes in the UK. The protection diminishes with age. For some diseases, such as polio, there is sufficient

herd immunity in the UK that it is highly unlikely that a child will contract polio if not vaccinated against it. Rubella is classically a mild, self-limiting viral illness. However, vaccination is offered to achieve herd immunity to prevent the teratogenic effects of rubella. The benefits to the individual child receiving the vaccination against rubella are arguably minimal.

On the other hand, vaccines are not wholly without risk. Having an intramuscular injection is painful. All vaccines can cause local reactions, which can cause prolonged discomfort. Some vaccines can result in mild flu-like symptoms, including fever. Vaccines can cause anaphylaxis reactions. Some postulated associations, such as seizures and pertussis vaccine, or MMR and autism, have been discredited, with the burden of proof against them.

Parents are responsible for taking decisions, including medical decisions, for their children until their children are deemed competent enough to decide for themselves. It is likely that they will take decisions in the child's best interests. However, (as stated in the Case history above) sometimes this may not be the case. This is accepted in order to protect the interests of the family – a decision may not be in a child's best interests, but may protect the interests of a sibling, the parents or the family

as a whole. If a decision places the child at risk of significant harm, then external agencies (the medical team in an emergency, or more likely the courts, through social services) should intervene. Choosing not to immunize their children cannot be deemed to cause significant harm to their child. For diseases such as pertussis, measles, pneumococcal disease and meningococcal C disease, the child is at greater risk of contracting the disease, though this is difficult to quantify. Not all parental behaviour is fully risk-averse. For example, parents are allowed to smoke, exposing their children to the detrimental effects of passive smoke. In the case of diseases such as polio, where not vaccinating a single child does not confer any increase in risk to the child as long as approximately 95% of the population is immunized, can a parent be forced to vaccinate their child to maintain child immunity for the protection of the community? It is difficult to do so, as it would involve treating an individual for the good of another. This is against Kantian morality, where people should never be treated 'merely as a means to an end, but always at the same time as an end'.

Therefore, in the above case, Henry's mother cannot be forced to immunize Henry. Nevertheless, the overall benefits and safety of immunization should be reiterated to her again.

Question 35.1

The child with asthma

Louis, a 6-year-old with known asthma, is admitted to the paediatric intensive care unit following a cardio-respiratory arrest secondary to status asthmaticus. You find out that he has not been using his steroid inhaler for the last month as he had run out of inhalers and his mother did not get a new prescription.

Which of the following options is the best course of action now? Select ONE answer only.

A. Arrange for an emergency protection order for the child.

B. Call the police, as the mother should be arrested for wilful neglect.

C. Do nothing, as it is within the zone of parental discretion to withhold treatment.

D. Report the general practitioner to the GMC for not realizing that the steroid inhalers had not been prescribed for over a month.

E. Speak to the mother to find out what the circumstances are and if help could be provided to prevent this from recurring.

Answer 35.1

E. Speak to the mother to find out what the circumstances are and if help could be provided to prevent this from recurring.

It is common to feel frustrated and upset when it is clear that a child has come to harm as a result of poor care. However, it is vital that clinicians keep calm and exercise judgement before proceeding. Parents may make decisions that are 'at odds' with a clinician's beliefs but are still ethically justified (see discussion about vaccination above). Obtaining more information at this stage in a professional manner is important before proceeding.

Case history

Apnoea in a child with spinal muscular atrophy

You are called as the paediatric registrar on call to attend to a 3-month-old child, Jack, who has been diagnosed in the last two weeks with spinal muscular atrophy (SMA) type 1. Jack has been brought to the paediatric admission unit with episodes at home where he has stopped breathing. On your arrival, you witness that Jack has got oxygen saturations in the low 90s despite high flow oxygen. He has shallow breathing with up to 10-second pauses between breaths.

The nurse looking after Jack is worried and suggests calling the anaesthetists with a view to intubate him. Jack's parents understand that SMA 1 is a life-limiting condition. They had met with the palliative care nurse a week ago but had not discussed an emergency care plan (see Chapter 34, Palliative medicine). They are upset and do not know what the best course of action is. You understand that SMA 1 is a life-limiting condition, but as this is Jack's first presentation to the acute ward, you wonder if Jack should be intubated and ventilated.

Ethical dilemmas:

- Who should decide whether he should be intubated or not?
- Would it be ethical to intubate a child with a life-limiting condition?
- Would not intubating the child be worse than withdrawing care after the child has been ventilated?

SMA is a progressive motor degenerative disease, with type 1 being the severest form. Most children will be diagnosed before 6 months of age and will develop respiratory insufficiency. They are usually cognitively normal, but, due to their motor weakness, are unable to express themselves, including sensations of pleasure or pain. Currently there is no cure.

Children with SMA could potentially be ventilated indefinitely and kept alive for months to years before their respiratory function deteriorates with increasing ventilatory requirements. The questions in the above scenario are whether or not he should be ventilated in the acute situation and whether he should be provided with long-term ventilation. Both need careful consideration. The guiding principle is to protect the best interests of the child. This is achieved by acting with beneficence, and limiting actions that are maleficent. Determining the best interests of children is difficult, but more so in children with SMA. They are unable to express feelings of pain with facial expressions or crying like other children. There is a risk that they could be exposed to pain inadvertently without us knowing. Acute intensive care involves invasive procedures such as intubation, physiotherapy and blood sampling. The pain can be minimized using analgesia and sedation, but this reduces patient awareness of all sensations. Long-term ventilation will still require suctioning and physiotherapy. Non-invasive ventilation with a face mask carries the risk of pressure sores. Ventilation via a tracheostomy will need routine tracheostomy care, including tracheostomy tube change and suctioning. Also, he would be unable to suck or swallow, play, or participate in any of the activities that children of a similar age may derive pleasure from. Therefore, long-term ventilated children with SMA type 1

may be exposed to burdens that they may find intolerable, without experiencing the benefits of being alive. Long-term ventilation will require dedicated long-term care, usually from the parents. The principle of justice also requires consideration, as respiratory support both acutely and long-term may use scarce resources in a public health service.

Although there is an international expert consensus statement for the management of SMA, this is neither binding nor followed consistently, with differing attitudes in different countries and health systems. The consensus statement recognizes the need for long-term ventilation, but suggests the use of non-invasive ventilation to minimize the need for invasive procedures. As long-term ventilation will require dedicated care by parents and the best interests of the child are difficult to determine, parents should have a say in the treatment choices for a child with SMA. The decision for long-term ventilation needs to be carefully discussed between the family and the medical teams soon after the diagnosis of SMA type 1, preferably in a non-acute setting.

Question 35.2

Ventilatory support in SMA type 1

Jack's parents do not want him to be intubated as they feel this will lead to pain and distress. What action do you take? Select ONE answer only.

A. Discharge Jack home, as there is nothing else you can do for him and it is better for him to be at home.

B. Ignore their wishes and intubate him, as you do not think they have had enough time to think about this decision

C. Ignore their wishes and intubate him, as you think it is in Jack's best interests to be ventilated, as without support he will die.

D. Involve the palliative care team and discuss with his parents how Jack's symptom care should best be managed.

E. Start high doses of morphine and midazolam so that Jack dies relatively quickly.

Answer 35.2

D. Involve the palliative care team and discuss with his parents how Jack's symptom care should best be managed.

If it is decided that the child should not be ventilated to avoid the burden that comes with it, then the emphasis of care should be on the alleviation of symptoms for the child. The Royal College of Paediatrics and Child Health guidelines to aid the withholding and withdrawal of life-sustaining care lists five situations where withholding or withdrawing of care can be considered: brain death, the permanent vegetative state, the 'no chance' situation, the 'no purpose' situation and the situation involving 'unbearable suffering'. In SMA type 1, the child has no chance of disease-free survival and their symptoms are likely to progress. It is possible that subjecting them to ventilatory support may cause unbearable suffering. Therefore, withholding life-sustaining care can be considered in children with SMA type 1.

In an emergency, or if the parents are unable to reach a decision regarding the long-term management of their child, despite discussion with experienced clinicians, the default option would be to provide ventilatory support to preserve the sanctity of life. This would allow his parents time to decide how Jack should be managed long term. Ethically, and legally in the UK, withholding and withdrawing care are viewed as being equivalent. Therefore, if they decide his care should be palliative, care can be withdrawn on the same basis as listed above.

Question 35.3

Brainstem death

Which of the following answers is correct? Select ONE answer only.

Brainstem death testing in Mohammed requires:

A. A court order to allow for testing to take place

B. Both his parents to be present at the time of testing

C. The absence of peripheral pulse

D. The absence of a respiratory drive

E. Two doctors not directly involved in Mohammed's care to perform the test

Answer 35.3

D. The absence of a respiratory drive.

See case history on Mohammed below.

Case history

Ventriculo-peritoneal shunt

You are the registrar on the paediatric intensive care unit. Mohammed, a 13-month-old child, has been admitted from the operating theatre following an emergency ventriculo-peritoneal (VP) shunt revision. He developed hydrocephalus following neonatal meningitis, and needed a VP shunt at 3 months of age. The last 5 days he has been unwell with a slight fever and vomiting. His mother was told that he had gastroenteritis. Twelve hours ago, he presented to his local emergency department as he was unrousable, and had an 18-minute bradycardic arrest while he was about to be intubated. A CT scan of his head showed acute hydrocephalus with evidence of brainstem herniation. After discussion with the paediatric intensive care retrieval and neurosurgical teams, the local team rapidly transferred him to the operating theatre at your hospital.

On admission, you note that Mohammed has fixed and dilated pupils. His heart rate and blood pressure are stable but there is little variation. He is on inotropic support and ventilated. The anaesthetist handing over care to you says that his pupils have been unreactive since his arrest. Mohammed's parents are at the bedside. They are upset, and understand that Mohammed may not survive. They ask you what will happen next.

You are worried about Mohammed's pupils being fixed. You do not think that he is likely to survive. However, his ventilator settings are low and he is only on a small amount of inotropic support with noradrenaline (norepinephrine).

Ethical dilemma:

- Is Mohammed still alive? How do we demonstrate this?

Whether Mohammed is still alive may seem an odd question to ask. Mohammed has a heart rate, you can feel a pulse and he is being ventilated mechanically. He is sedated and paralysed, so it is difficult to demonstrate 'signs of life'. Intuitively, he is still alive. However, there is no legal definition of death – the law recognizes physicians' ability to determine death using appropriated codes of practice, currently this is the Academy of Medical Royal Colleges (AOMRC) document *A code of practice for the diagnosis and confirmation of death*. While the persistence of a heartbeat is commonly felt to be evidence of survival, does this mean that a patient on cardiac bypass or ECMO with no cardiac output is dead?

The major pathophysiological issue in Mohammed's case is the fact that his brainstem seems to have herniated prior to the VP shunt revision, which is likely to have caused brainstem

ischaemia – the fixed pupils are evidence of this. Without a functioning brainstem, life cannot be sustained without support, i.e. Mohammed is unlikely to breathe without a ventilator or alter his cardiac output without inotropes.

To tackle this ethical quagmire, a group of physicians at Harvard Medical School (known as the Ad Hoc Committee of the Harvard Medical School) drew up a set of criteria to define 'brain death' in 1968. They defined brain death as an irreversible coma, with no discernible central nervous activity. The criteria consisted of three components:

i. Unresponsiveness and unreceptivity: the lack of motor response to a painful stimulus
ii. No movements or breathing: no respiratory effort after removal from mechanical ventilation, despite a higher than baseline pCO_2.
iii. No reflexes, namely the lack of brainstem reflexes, e.g. gag, corneal reflexes, oculo-cephalic reflexes and pupillary reaction to light.

A confirmatory fourth component was a flat or isoelectric electroencephalogram. The Committee recommended that the examination be repeated a second time to allow confirmation, 24 hours after the first instance.

In reality, the tests confirm two aspects of loss of brain function – the capacity for consciousness (cerebral cortex dysfunction) and the loss of the capacity to breathe (brainstem dysfunction). In order to determine irreversibility, absence of reversible causes needs to be demonstrated. These include hypothermia; severe electrolyte, endocrine or metabolic disturbances; and pharmacological agents, such as central nervous system depressants (e.g. barbiturates) and muscle relaxants, at significant levels.

These accepted tests, performed according to AOMRC guidelines, enable the definition (and confirmation) of human death using neurological criteria (neurological determination of death (NDD)). The criteria have been adopted almost universally, with minor variations. In some countries a confirmatory test, such as an electroencephalogram or cerebral perfusion scan, is mandated (not in the UK). In most countries, the criteria can be adopted for infants above term, whereas in the UK a more conservative approach limits it to children older than 2 months of age (corrected for gestation above 37 weeks). For younger children, an RCPCH working group is currently establishing whether UK practice should be changed.

Rather than circulatory or brainstem death, the death of a human is a single entity for which healthcare professionals may use different criteria: either circulatory determination of death (CDD), the method we are more familiar with (no pulse, no breath sounds, with pupils fixed and dilated), or

else NDD. For NDD or brainstem testing, the examination needs to be carried out by two doctors, one of them a paediatrician, although there is no longer any recommended time interval between examinations.

For Mohammed, NDD evaluation cannot be undertaken, as he is muscle relaxed. He has therefore not been verified as dead and, ergo, ought to be considered as alive! The tests will need to be deferred until there is no ongoing neuromuscular blockade (tested by bedside peripheral nerve stimulation). Also, if Mohammed received significant barbiturates (e.g. a thiopentone infusion), drug levels will need to be measured before NDD. After discussion with the consultant, muscle relaxants are stopped and you explain to Mohammed's parents that once all the drugs have worn off, a series of tests will be performed to identify the brain activity necessary for Mohammed to survive. If there is no brain activity, he would be certified as having died.

 Case history

Organ donation

After speaking to Mohammed's parents in the case history above, they are understandably distraught. The next morning they ask whether there is any possibility for Mohammed to donate any of his organs – one of Mohammed's cousins had received a liver transplant a year ago for biliary atresia. They can be informed that this might indeed be possible. You had already informed your local specialist nurse in organ donation (SNOD) about the plan for NDD. In accordance with both NICE and UK Paediatric Intensive Care Society best practice, they will come and see the family shortly and will 'approach' the family in collaboration with the consultant to discuss donation.

Once the muscle relaxant and other drugs have worn off, the consultant and another independent senior colleague each carry out the set of brainstem tests. Unfortunately, Mohammed has no motor responses, no spontaneous respiratory effort despite prolonged ventilator disconnection and no intact brainstem reflexes. He satisfies brainstem criteria and is verified as dead, the time of death being when the *first set* of tests was completed.

His parents have very kindly agreed to organ donation. There is a wait for a few hours for the theatres to be set up for the organs to be harvested.

Ethical dilemma:

- Is it ethical to continue intensive care after a patient has been declared dead?

Again, this exposes the ethical problems relating to defining death. Some philosophers have

questioned whether brain death criteria were formulated to redefine death for the purpose of making more organs available for transplant. The Harvard Committee identified both the need for organs for transplant and the scarcity of intensive care resources in their introduction to the definition of brain death. However, there is no explicit reference to either being their motivation in drawing up the criteria for brain death.

There is often a period of time between completing NDD and organ donation. This can be used to optimize organs for transplantation, but if the child is dead, is it ethical to continue intensive care beyond this point?

Once again, according to Kant, a person should never be treated purely as a means to an end. In this case, continuation of intensive care is for the sole purpose of facilitating organ donation. In practice, the care of organ donors is more than maintaining them in status quo; in order to optimize the function and quality of donated organs, additional treatment may be needed. Common problems in brain-dead patients include diabetes insipidus, hyperglycaemia, cortisol insufficiency, disseminated intravascular coagulopathy and shock. One can argue that the dead cannot be harmed by their body being maintained on organ support. On the other hand, intensive care beds are scarce; what if the last available bed is being occupied by a dead patient? However, the consequentialist argument is surely stronger – Mohammed's organs and tissues are likely to benefit more than one other person. Continuing organ support for a few extra hours leads to more overall good than discontinuing care immediately. Also, organ donation is an altruistic act, with donation reflecting the wishes of the deceased or their family. Therefore, it is also assumed that someone who wanted to be a donor when they die would have been willing to have their body maintained on a ventilator following NDD to facilitate donation. This can be difficult to argue in children, but parents, as proxy decision-makers, can act with the same altruistic motive if that is in the child's best interest, although that child is now, of course, deceased.

Cadaveric organ donation is also possible using donation after circulatory definition of death (DCDD). Prior to the introduction of 'brain death', all cadaveric organ donation was from donors whose heart had stopped beating. Initially termed non-heart-beating donation, the more correct DCDD is now preferred. The limitation with DCDD is the degree of organ ischaemia occurring during both the dying process and between death and organ harvesting, compared with donation after neurological determination of death (DNDD), where organs are harvested from an intact circulation. Most dying patients are unsuitable donors, but following elective cessation of life-sustaining therapy (LST) in the intensive care unit, DCDD can be considered in cases where care is being withdrawn under planned circumstances, where an NDD donor waiting for organ harvest has a circulatory arrest prior to disconnection from the ventilator or, very rarely, if a patient suffers an arrest in intensive care and is not amenable to resuscitation, but retrieval can be organized rapidly.

The main ethical consideration in DCDD is that the decision to withdraw LST must be made in the child's best interests before any consideration of donation. The major ethical controversy is determining the interval between when the circulation stops and death can be verified and when organs can be harvested. In the UK, this currently follows 5 minutes of uninterrupted asystole, though there have been attempts in the USA to introduce shorter intervals. This takes us back to what is rather a fundamental ethical rather than clinical question – what and when is human death? (See Truog and Miller 2008.)

Research ethics

Research into child health is crucial to advance the care of children. It must often involve children themselves, rather than relying on extrapolation from adult research. However, the protection that is generally afforded human research subjects, namely the need for fully informed consent, is not *directly* afforded to children. Whether the requirement for such consent from those with parental responsibility is equally strong protection is unresolved.

The abuse of human subjects for medical research in the twentieth century, as well as societal demands, led to the most influential document about human subject research: the Declaration of Helsinki. This remains the overarching standard pertaining to human subject research today. Whilst the Declaration initially mandated that the free consent of the research subject was required – effectively banning research with children – later iterations have facilitated a symbiotic relationship between the researcher and the research participant, which in child health research can often be considered as 'the family' rather than the individual child. Clear guidance for the 'ethical' conduct of research is offered by many bodies, including the RCPCH, the Medical Research Council and, within the next few years, the Nuffield Council of Bioethics, following extensive consultation involving all interested parties.

In the UK, the current process of ensuring ethical acceptability for research is the mandatory research ethics committee review of all patient/human subject research in hospitals. These committees operate under the auspices of the Health Research Authority (HRA), and are independent of the institutions with which they were previously associated. They are composed of expert and lay members, and specific experts if required, e.g. in qualitative research or specific paediatric expertise. Forms for completion to lead to review are available on the HRA website, as is advice and information on how to complete a 'good application.'

Many of the challenges for paediatric researchers regarding research ethics review are not complex questions of the ethical acceptability of a study. Instead, they more often involve not completing forms in *lay language* as requested, providing unclear age-appropriate information sheets for child participants and parents and inconsistencies about the study protocol. For studies with material ethical concerns, the chair of a committee, the 'paediatric expert member(s)' for paediatric flagged committees and the Health Research Advisory Panel are readily available for advice.

Research with 'no material ethical issue' can undergo *proportionate review* within weeks of application by a research ethics committee – usually electronically – and can be given a rapid favourable opinion. Other research is reviewed formally by the committee, a meeting to which the research team is invited. If possible, it is wise to attend, as matters that can take weeks of correspondence can often be dealt with rapidly.

Research ethics committees look for age-appropriate child as well as family participant information sheets, with clear explanations of vital facts about the study – such as the reason for the study, time course and practical aspects of participation and a clear consent form for all aspects of the study and options to withdraw.

Once a favourable opinion is reached, sometimes after a provisional opinion and alterations as requested, the study can proceed, subsequent to other authorizations as guided by the local research and development office of the institution. This is a separate process from the research ethics review. For clinical trials of investigative medicinal products (CTIMPs) or medical device trials, this might involve the Medicines and Healthcare products Regulatory Agency (MHRA).

Consent for paediatric research studies can be confusing, as it is distinct from consent in clinical practice. The law regarding consent for CTIMPs is clear. The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), implementing the European Clinical Trials Directive, came into force in 2004 and, although subjected to a series of amendments, remains in place. Regarding children, those with parental responsibility give consent. Though many

advocate the use of 'assent' forms (agreement in principle prior to formal consent) and this is recommended in the Declaration of Helsinki, there is no legal basis for their use in these trials. In non-CTIMP research, there are no legal standards or case law, though again there is helpful guidance from the GMC and the Royal College of Nursing.

The law in this context arguably defines a minimal standard, and children have an absolute right under the UN Convention of the Rights of the Child to be informed about their healthcare and this is pertinent to participation in healthcare research.

Previous concepts, such as therapeutic research (i.e. which directly affects the treatment an individual child receives) and non-therapeutic research (that will not directly benefit the child involved), have largely disappeared. Once-contentious research issues, such as 'non-therapeutic' CT scans or anaesthesia for children, are now considered in studies to which parents can consent. However, some ethical experts are concerned that researchers now have almost unfettered access to vulnerable children.

These issues are fortunately being addressed in the UK with the admirable work of the Medicines for Children Research Networks (MCRN), which has led to a collaborative relationship between research teams and children and their families.

Involvement of children in research is also considered in Chapter 37, Clinical research.

Summary

In this chapter, we have provided a definition for medical ethics and have outlined the various theoretical and practical frameworks for making ethical arguments. Through a series of vignettes, we have highlighted some ethical questions that we face in paediatric medicine. Any, and all, aspects of paediatric practice contain an ethical component. Whilst we might easily perceive ethical dilemmas in complex and challenging scenarios, such as in the cases described above or in research, most ethical issues arise in the day-to-day care of children.

Further reading

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Elizabeth Starkey, Imti Choonara, Helen Sammons

Pharmacology and therapeutics

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Understand the principles of pharmacokinetics in children
- Know the major pathways of drug metabolism in children and how they vary with age
- Know about some of the commoner adverse drug reactions that occur in children
- Understand the mechanisms by which adverse drug reactions occur in children
- Know the principles of safe prescribing
- Be aware of the most frequent types of medication error
- Understand the pharmacology of some of the commonly used drugs in children
- Understand the importance of the rational use of medicines in children

Introduction

Understanding how the body handles different medicines is important for all clinicians when prescribing medications. For effective and safe prescribing, we need to make sure that we do not under-dose a medication, making it ineffective, but also that we do not give a dose that causes toxic effects. In paediatrics, significant physiological and developmental differences add to the challenges of safe prescribing. The key parameters of clinical pharmacology will be described below and the differences seen in the different paediatric age groups will be highlighted.

Pharmacokinetics

Pharmacokinetics (PK) describes the course of a drug within the body; this is expressed as the dose given and concentrations in different parts of the body (usually plasma). It includes how it is absorbed, distributed, metabolized and finally excreted. These will each be discussed separately, along with the common equations used. Pharmacokinetics allows us to understand the profile of a drug's concentration over time and recommend a drug dosing regimen or, when faced with a novel paediatric drug therapy, provides us with knowledge to prescribe safely and effectively. Mathematical formulae are available that describe the

inter-relationship between clearance, volume of distribution and elimination half-life.

Absorption

If a drug is given intravenously, 100% of the dose will enter the blood stream, but for any other route less than 100% of the dose will be absorbed. This is because it must overcome chemical, physical, mechanical and biological barriers; the percentage that enters the systemic circulation is known as its *bioavailability*.

Absorption is the process of drug movement from the site of administration or application into the systemic circulation. It is often reduced following oral administration in the neonatal period. Additionally, in the neonatal period, pH is elevated within the stomach. This increase in gastric pH affects the bioavailability of medicines. This higher gastric pH increases the absorption of weak base drugs such as penicillins and decreases the absorption of acidic drugs such as phenobarbital and phenytoin, which may therefore require a larger oral dose. Fortunately, in sick neonates most medicines are given intravenously and therefore absorption is not usually a clinical problem.

For children, there are other developmental changes to drug absorption that occur in different systems. Intramuscular absorption depends on skeletal muscle

blood flow; neonates have poor muscle bulk and poor muscle density, reducing bioavailability. Percutaneous absorption is enhanced in childhood due to the larger surface area of the skin relative to the body weight, and better skin hydration and perfusion. Young infants and neonates also have increased absorption due to their skin being thin. This increases systemic absorption and therefore potential side effects of topical medications.

A historical catastrophic example of this is the topical disinfectant hexachlorophene in neonates, which caused neurotoxicity and death. Developmental changes in pulmonary structure and capacity in young patients may also alter the patterns of inhaled drug absorption (see also Chapter 17, Respiratory medicine).

Question 36.1

Volume of distribution

Which of the following is true with regards to volume of distribution (Vd)? Select ONE answer only.

A. A larger Vd requires a higher loading dose of a drug.

B. A large Vd implies a drug primarily resides in the systemic circulation.

C. Neonates have a higher Vd with lipophilic drugs.

D. Neonates have a lower Vd for hydrophilic drugs.

E. Vd equals the total amount of drug in the body multiplied by the concentration found in the plasma.

Answer 36.1

A. A larger Vd requires a higher loading dose of a drug.
  A larger Vd implies good distribution within the tissues and subsequently will require a higher loading dose for a drug to get an adequate target concentration. Neonates have higher body water, therefore they have a lower Vd for fat-soluble drugs and higher Vd for water-soluble drugs (see below).

Volume of distribution (Vd)

This is not a physiological volume, but rather an apparent volume into which the drug would have to distribute to achieve the measured concentration. The volume of distribution is usually defined in litres or litres/kg. It is calculated by dividing the amount of drug by the plasma concentration:

$$\text{Volume of distribution (L)} = \frac{\text{Amount (mg)}}{\text{Plasma concentration (mg/L)}}$$

A small volume of distribution indicates a drug is largely retained within the systemic circulation, whereas a large volume of distribution means a drug is well distributed into other peripheral compartments. Water-soluble drugs, such as gentamicin, therefore have a volume of distribution that is similar to the extracellular fluid volume. Drugs that are highly bound to plasma proteins, such as phenytoin, have a low volume of distribution. Differences between paediatric and adult patients stem mainly from the fact that neonates and young children have a higher proportion of body water and lower concentrations of plasma proteins. Knowing the volume of distribution of a drug is useful when determining what loading dose is to be given. This is calculated from the following formula:

$$\text{Loading dose} = \text{Vd} \times \text{Target concentration} \times \text{Body weight}$$

For example, in order to achieve a peak gentamicin concentration of 10 mg/L in a neonate weighing 1 kg, where the volume of distribution is known to be 0.5 L/kg, one would multiply 10 mg/L by 0.5 L/kg by 1 kg. This equates to 5 mg.

If some of the drug is already present in the patient, one can subtract the measured plasma concentration from the target concentration in order to calculate the dose that is required.

Clearance

Total body clearance is the ability of the body to remove a drug from the plasma or blood and is the sum of drug clearances of each organ. For many drugs, this is equal to hepatic clearance plus renal clearance. Renal clearance is determined by the clearance of an unchanged drug in the urine, whereas liver clearance can occur via biotransformation to a metabolite, which is subsequently excreted via the urine, and/or excretion of the unchanged drug into the biliary tract.

It is defined as the volume (usually of plasma) that is completely cleared of drug in a given time period. In adults, clearance is therefore described in relation to volume/time (L/hour). In paediatric patients, clearance is also described in relation to body weight (either as L/hour/kg or mL/min/kg). Clearance can be used in conjunction with the target steady state

concentration (C_{SS}) to calculate the rate of administration of a drug given intravenously. This is shown in the following equation:

$$\text{Dose rate (mg/hour)} = \text{Target } C_{SS} \text{ (mg/L)} \times \text{Clearance (L/hour)}$$

Or for children, where a dose and clearance are expressed in relation to body weight:

$$\text{Dose rate (mg/hour)} = \text{Target } C_{SS} \text{ (mg/L)} \times \text{Clearance (L/hour/kg)}$$

This formula is appropriate for the administration of drugs given intravenously.

For example, the maintenance dose of an intravenous aminophylline infusion to achieve a theophylline level of 10 mg/L in a 20 kg child where clearance is 0.087 mg/kg/hour is 10 mg/L × (0.087 × 20) = 17.4 mg/hour.

For drugs that are given orally, one needs to take account of the bioavailability as well as the dosage interval between different doses. If a drug is given via regular bolus intervals, the 'average' target C_{SS} is used as steady state fluctuates between the peak and trough and the dosing interval (π) is also added into the equation. The maintenance dose can therefore be calculated by the following formula:

$$\text{Maintenance dose} = \frac{\text{Target } C_{SS} \text{ (mg/L)} \times \text{Clearance (L/hour)} \times \text{Dosing interval}}{\text{Bioavailability}}$$

Maturation of renal function occurs during childhood. The maturation process of kidney structure and function is associated with prolongation and maturation of the tubules, increase in renal blood flow, and improvement of filtration efficiency. This knowledge allows us to provide a rational dose schedule for drugs exclusively eliminated via the kidneys. In general, the neonate will need longer dose intervals than the infant to maintain target concentrations.

For example, the dose of benzylpenicillin changes from 25–50 mg/kg 12 hourly in a neonate <7 days to 8 hourly in a 7–28-day neonate and 4–6 hourly in children over a month old.

Question 36.2

Half-life and elimination of drugs

A new antibiotic, X, has been developed. It has exceptional antimicrobial activity but is toxic in higher doses. The half-life is 2 hours in children.

After how long will 97% of this new antibiotic, X, be eliminated from the child? Select ONE answer only.

A. 4 hours
B. 6 hours
C. 8 hours
D. 10 hours
E. 12 hours

Answer 36.2

D. 10 hours.
   See below for discussion.

Question 36.3

Half-life and elimination of drugs

A new agent has come to the market as a treatment for severe pain. It is intended to be given as a single dose rescue treatment. There have been no large studies in children but in the literature its plasma half-life is 12 hours.

What percentage of the dose is still in the body after one day? Select ONE answer only.

A. 87.5%
B. 75%
C. 50%
D. 25%
E. 10%

Answer 36.3

D. 25%
   50% of the drug is eliminated every 12 hours, therefore 25% left in the body after two half-lives.

Half-life

Half life is a secondary pharmacokinetic parameter and is the time taken for the drug concentration (usually in the plasma) to decrease by half. Therefore, 50% of the dose will be eliminated in one half-life. It is inversely related to the clearance and can be calculated using a drug's volume of distribution and clearance with the following equation:

$$\text{Plasma half-life} = \frac{0.693 \times \text{Volume of distribution}}{\text{Clearance}}$$

(Note: the value 0.693 is the natural logarithm of 2)
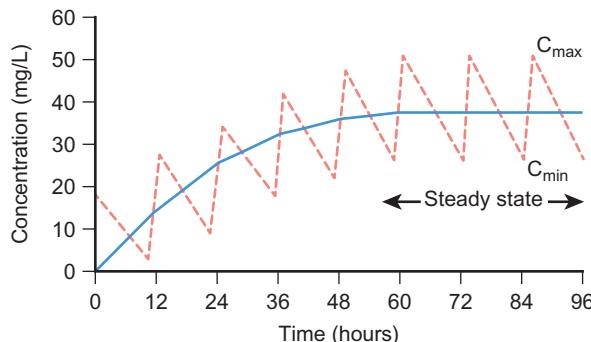
Fig. 36.1 Concentration–time profile of a drug given by continuous and intermittent dosing with a half-life of 11.5 hours. Steady state is reached at 57.5 hours (11.5 × 5 hours). With the intermittent drug dosing, repeated doses increase the peak and trough concentration due to drug accumulation. *(From Starkey ES, Sammons HM. Practical pharmacokinetics: what do you really need to know? Arch Dis Child Educ Pract Ed 2015;100(1):37–43, with permission. © BMJ.)*

Half-life can be used to determine the time it takes to achieve steady state and the time for a drug to be completely eliminated. It takes around 3–5 times the drug's half-life to reach steady state and the same for it to be completely eliminated in constant dosing. Five half-lives is the time required for 97% of the drug to be eliminated (Fig. 36.1). For instance, the $t_{1/2}$ of intravenous midazolam is of the order of 1.1 hours in 3–10-year-olds, therefore it takes around 3.3 to 5.5 hours to reach steady state.

The half-life helps the clinician to establish an appropriate drug dosing interval. When a medication is given every half-life, the plasma concentration will have a twofold fluctuation over the dosing interval (see Fig. 36.1). For drugs with a half-life <6 hours, it is sometimes not practical to give frequent doses, so sustained release formulations are given (e.g. theophylline). In drugs with a very long half-life (e.g. amiodarone), a daily treatment may be appropriate. A loading dose helps to reach the steady state more quickly. The $t_{1/2}$ of phenobarbital in neonates is 67–99 hours, so without a loading dose it could take 8–20 days to reach a steady state. Although drug half-lives are quoted in the literature, they represent average values mainly in adults and should be used cautiously.

The pharmacokinetic principles outlined above assume that the drug follows first-order or linear pharmacokinetic characteristics. This means that the steady-state concentration changes in direct proportion to a drug dose alteration. However, for some drugs, the relationship is more complex. For example, phenytoin saturates the metabolizing enzymes at clinical doses. Subsequent increases in dosing cause a disproportionate elevation of the steady-state concentration. This is known as zero order or saturated kinetics.

Drug–food interactions

Interactions between food and drugs can unintentionally reduce or increase the effect of an oral medicine, resulting in potential therapeutic failure or toxicity. Firstly, food intake also impacts on drug absorption by stimulating gastrointestinal secretions, pancreatic hormones, and bile salts (which lower gastric pH), as well as delaying stomach emptying and increasing gastrointestinal transit time. The size and content of a meal, especially those with a high fat content, also play a role and can reduce a drug's rate of absorption.

Secondly, food has the ability to affect a drug's bioavailability by interaction with the food constituents. A good example is the reduction in bioavailability of tetracyclines following dietary calcium caused by chelation. Food–drug interactions affecting metabolism, distribution or elimination are not very common, apart from interactions with grapefruit juice. Grapefruit juice contains potent inhibitors of the cytochrome P450. CYP3A4, a P450 enzyme, may markedly increase the bioavailability of drugs that it metabolizes, including ciclosporin, midazolam and carbamazepine.

Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) consists of measuring plasma concentrations of the drug in order to improve its efficacy whilst reducing its toxicity (Box 36.1 outlines criteria for use). TDM is recommended for certain antibiotics, including the aminoglycosides and glycopeptides, in order to reduce potential toxicity. It may be beneficial in patients with poorly controlled epilepsy who are receiving carbamazepine,

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Box 36.1 Criteria for the use of therapeutic drug monitoring (TDM)

- Good correlation between serum concentrations and pharmacological effect.
- A narrow margin between serum concentrations that cause toxic effects and those that produce therapeutic effects.
- Marked pharmacokinetic intra- and inter-individual variability.
- The pharmacological effects of the drug are not readily measurable.
- It provides a rapid and reliable method for the analysis of the drug.

phenytoin or phenobarbital. Interpretation of the plasma concentration of a drug requires details of the time of administration of the drug and time of collection of the blood sample, as well as an understanding of why TDM has been requested.

Drug levels should only be taken once the drug has reached its steady state, unless there are concerns regarding toxicity. In general, trough levels measured just prior to drug administration provide accurate interpretation of drug concentrations. Peak levels are less accurate due to individual variability and are reserved for treatments with short half-lives where peak levels are associated with efficacy or toxicity, e.g. gentamicin.

TDM for aminoglycosides

This class of drug is bactericidal and works by irreversibly binding the 30S subunit of the bacterial ribosome, and interfering with bacterial protein synthesis. Aminoglycosides are mainly used for the treatment of severe Gram-negative infections, with tobramycin and gentamicin having some activity against *Pseudomonas* infections. Tobramycin is used frequently in children with cystic fibrosis. Gentamicin also works synergistically with β-lactams for the treatment of Gram-positive *Staphylococci* infections. This is why benzylpenicillin and gentamicin are used in combination for the treatment of group B streptococcal neonatal infections.

TDM is essential when using aminoglycosides because of the significant oto- and nephrotoxicity that can occur with these agents. It is thought that toxicity is associated with high trough concentrations. Studies in adults suggest that ototoxicity is more frequent than nephrotoxicity. Ototoxicity has been described following single doses and is thought to occur in 5–10% of adults who receive aminoglycosides. Both prolonged and repeated courses are thought to be risk factors for toxicity. Aminoglycosides used to be given three times daily but current practice is to give them once daily. This larger daily dose produces a higher peak level than the standard regime, which in turn increases the rate and extent of bacterial cell death. It also lengthens the post-antibiotic effect (suppression of bacterial regrowth) without increasing the risk of any drug toxicity. When multiple daily dose regimens are used, as well as a pre-dose (trough concentration), one should measure a one-hour (peak) post-dose concentration. Most hospitals in the UK provide a clinical pharmacy service to help interpret the plasma concentration and give advice regarding dose adjustment. The beneficial effect of discussing management with a clinical pharmacist has been demonstrated. In

> **Box 36.2 An example of how to alter vancomycin doses following TDM**
>
> Pre-dose (trough) after 2nd–3rd dose:
> - <5 mg/L – increase frequency if able, if not, increase the dose by 10–20%
> - 5–10 mg/L – increase dose by 10–20%.
> - 10–15 mg/L – continue as in therapeutic range (sometimes need 15–20 mg/L in less sensitive MRSA strains – consult microbiology if cultures available)
> - 15–20 mg/L – reduce dose by 10–20%
> - >20 mg/L – check trough before commencing and reduce frequency
> Check electrolytes to identify acute kidney injury.

addition to minimizing toxicity, one needs to ensure that the individual patient receives a dose that is effective in treating the significant bacterial infection that the patient is likely to be suffering from.

TDM for glycopeptides

Glycopeptides are another group of antibiotics that require therapeutic drug monitoring and include vancomycin and teicoplanin. They act by interfering with the bacterial cell wall synthesis in Gram-positive bacteria. They bind to the end of the pentapeptide chains that are part of the growing cell wall structure. This inhibits the transglycosylation reaction and prevents incorporation.

Vancomycin and teicoplanin are used in intravenous form for the treatment of serious infections caused by Gram-positive cocci such as *Staphylococcus aureus* and coagulase-negative *Staphylococcus.* Vancomycin is the main treatment for patients with MRSA infections. It can also be given orally for the treatment of pseudomembranous colitis in the colon, usually caused by *Clostridium difficile*, which is rarely seen in children.

Like aminoglycosides, glycopeptides are nephro- and ototoxic and hence require TDM (Box 36.2). Variations in protocol occur throughout different hospitals about how to monitor and adjust vancomycin dosing, and local policies should be followed. Teicoplanin is less toxic than vancomycin but still requires monitoring. Adverse drug reactions due to vancomycin include red man syndrome, characterized by flushing and erythematous skin usually of the upper body and face. This is caused by a non-specific mast cell degranulation and can be avoided with a slow infusion rate.

Question 36.4

Drug metabolism

The following (A–H) is a list of drug metabolism pathways:

A. Acetylation

B. Glucuronidation

C. Hydration

D. Hydrolysis

E. Methylation

F. Oxidation

G. Sulfation

H. Reduction

Pick the mechanism from the list described above that best matches the descriptions below:

1. The major phase 1 pathway utilized by cytochrome P450 enzymes in the liver.
2. The major phase 2 pathway responsible for elimination of paracetamol in teenagers.

Answers 36.4

1. F. Oxidation
2. B. Glucuronidation
   See below for discussion.

Drug metabolism

Most drugs need to be converted into more water-soluble compounds to become inactivated and excreted from the body. This can take place in a variety of sites (e.g. gastrointestinal tract, skin, plasma, kidney, lungs), but most are metabolized in the liver via hepatic enzymes.

Two phases of drug metabolism are traditionally distinguished – phase 1 and phase 2. Phase 1 involves altering the structure of the drug, for example oxidation and hydrolysis. The major pathway is oxidation, which involves the cytochrome P450-dependent (CYP) enzymes that are present mainly in the liver. Phase 2 reactions conjugate the drug to another molecule (for example, glucuronidation of paracetamol in older children). Drugs may undergo metabolism and subsequent elimination by a combination of phase 1 and phase 2 pathways (Fig. 36.2). This deliberate simplification of drug metabolism does not imply that only the parent compound itself is active and that metabolites are not. Some drugs are inactive and need to be metabolized to exert their effect; for example, carbamazepine, and enalapril. Other drugs may have
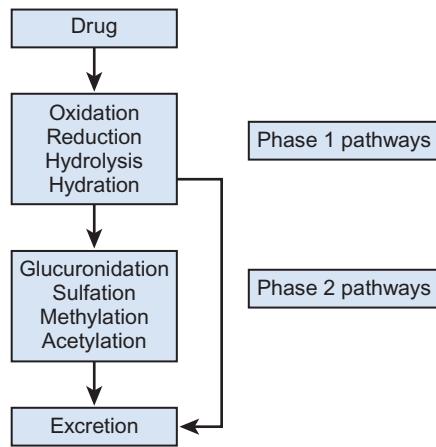
Fig. 36.2 Drug metabolism.

metabolites with the same therapeutic effect as the parent compound, such as morphine and its metabolite morphine-6-glucuronide. Finally, some metabolites may be responsible for adverse drug reactions. Paracetamol is metabolized to the reactive metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI), which is associated with acute liver injury after overdoses (see below).

Phase 1 enzymes

The most abundant and best studied phase 1 system is the cytochrome P450 (CYP450) family which consists of at least 56 genes that code for functional enzymes. *More than half of all metabolized drugs are subject to CYP450-mediated metabolism*. The most common subfamilies are CYP1A, CYP2A–2E and CYP3A/CYP3A4. They are responsible for the metabolism of many drugs, such as midazolam, ciclosporin, fentanyl and nifedipine (Table 36.1). CYP1A2 accounts for 13% of total enzyme activity in the liver. Caffeine and theophylline are metabolized via the CYP1A2 pathway (see Table 36.1).

Phase 2 enzymes

These are a different set of enzymes and less is known about them. Glucuronidation and sulfation are the two major phase 2 pathways. Examples include UDP-glucuronosyltransferases (UGT), sulfotransferases (SULT) and glutathione-S-transferases (GST). The majority of these encompass large numbers of different enzymes which are differently regulated and metabolize different drugs.

The effect of age on metabolism

The majority of drug-metabolizing enzymes develop in a different pattern and rate. However, there are three

Table 36.1 Drug metabolism pathways

Pathway	Drug
Oxidation	
CYP3A4	Carbamazepine Diazepam Erythromycin Fentanyl Midazolam Nifedipine Ondansetron Rifampicin
CYP1A2	Caffeine Theophylline
CYP2C9	Phenytoin Ibuprofen
CYP2D6	Amitriptyline Codeine Selective serotonin reuptake inhibitors
Glucuronidation	Paracetamol Morphine
Sulfation	Paracetamol

distinct patterns that have emerged from research studies. Individual enzymes show maximum activity either prenatally, postnatally or throughout development. Within the *prenatal* pattern, enzyme activity is high in the fetal liver as well as just before and after birth and then it declines. An example of this is CYP3A7.

The second group has a *postnatal* pattern. Here, the levels of the enzyme are low at birth but increase to adult ranges over the next few weeks or months. This is seen in a large number of enzymes, including CYP1A2, CYPC2C, CYP2D6 and CYP3A4.

Finally, in the *constant* pattern, activity remains stable from early fetal life through adulthood; examples are CYP3A5 and SULT1A1.

Age-related changes in drug metabolism have a major impact on a drug's effect. The majority of these are observed in neonates and infants, when typically the largest changes in enzyme activities occur. An important example of this is chloramphenicol. Historically, chloramphenicol was used to treat neonatal infections using adult doses of 12.5–25 mg/kg four times a day. Neonates have immature levels of UGT2B7, which converts chloramphenicol to the excreted water-soluble chloramphenicol glucuronide. Large numbers of babies developed cardiovascular collapse and irregular respiration, and in some cases died; this became known as grey baby syndrome because of chloramphenicol toxicity as a result of this immature metabolism. Consequently, dosing in neonates has been reduced to 12.5 mg/kg twice daily for those under one month of age, and is rarely used in neonates.

Drug–drug interactions

Drug–drug interactions may also result in significant variation in drug metabolism. Several drugs are known to either induce or inhibit enzyme activity. When these drugs are metabolized by the same enzyme, the blood levels of the drug and metabolites may change accordingly. Macrolide antibiotics, proton pump inhibitors and some of the antifungals, such as ketoconazole, are well known drug inhibitors, whereas phenobarbital, carbamazepine and dexamethasone are well-known inducers.

Children's vulnerability to metabolic drug–drug interactions alters as liver enzymes mature and pathways change. However, this does not necessarily mean that younger children are always at higher risk of drug–drug interactions. For instance, if enzyme activity in the neonatal period is low, then an enzyme inhibitor is less likely to have a large impact. Therefore, some interactions seen in adults may not be evident in neonates and younger children.

Drug excretion

Two organ systems are responsible for most drug excretion: the liver (via bile) and the kidneys (via urine). For many drugs and metabolites, the kidney is the most important route of excretion. The kidney has three physiologic functions: glomerular filtration, tubular secretion, and tubular reabsorption; and elimination of medicines require a balance of these. Drugs vary in where they are primarily eliminated. Some are eliminated by glomerular filtration (e.g. aminoglycosides) with clearance of these correlating well with glomerular filtration rate. Others are eliminated by proximal tubular secretion (e.g. penicillins, furosemide). Tubular reabsorption of drugs also affects total body clearance.

Maturation of renal function is a dynamic process that begins during fetal organogenesis, with all physiologic functions of the kidney decreased in newborns (see Chapter 19, Nephrology, for more details). The maturation process of kidney structure and function is associated with prolongation and maturation of the tubules, increase in renal blood flow, and improvement of filtration efficiency. By approximately one year of age, the kidney is functioning at adult levels. Understanding renal development and anatomy is essential to provide a rational dose schedule for drugs that are exclusively eliminated via the kidneys. In general, the neonate will need longer dose intervals than the infant to maintain target concentrations. An example, as described above, is the different dose regimens for benzylpenicillin with age, reflecting the improving renal function and excretion.

Disease and drug disposition

The metabolism of some drugs is influenced by co-existing diseases. There are some obvious examples. Liver disease will clearly have a big effect on the profile of drugs that are metabolized within the liver and renal disease will affect the clearance of any drug that is eliminated by the kidney. There are some important specific examples:

- Certain illnesses, such as cystic fibrosis (CF), can affect drug metabolism. Clearance of most drugs is thought to be higher in children with CF, resulting in higher dosages required to yield a therapeutic benefit and achieve similar serum drug concentrations to children without CF. Tobramycin dosing increases from 2–2.5 mg/kg three times a day to 8–10 mg/kg three times a day to provide optimal bacterial penetration within CF bronchial secretions.
- Liver and renal failure can reduce the ability to metabolize drugs and delay the elimination of them. This therefore dictates reduced dosages; for example, reduced dosing of cephalosporins, aminoglycosides in those with severe renal failure.

Clinical conditions, e.g. shock and hypothermia have been found to down regulate the liver enzyme. For example, clearance of the CYP3A substrate midazolam is significantly lower in paediatric intensive care patients than in relatively healthy children. Some of the interventions used in the critically ill, such as cardiopulmonary bypass and extracorporeal membrane

Question 36.5

Jaundice in a 1-year-old with epilepsy

Isobel is a 1-year-old child with epilepsy, who has been admitted to the paediatric ward with a three-week history of lethargy, loss of appetite and vomiting. On examination, she is jaundiced and has grossly abnormal liver function tests.

Isobel has a complex medical history with epilepsy and developmental delay. Her seizures have been poorly controlled with a combination of carbamazepine and topiramate, so 8 weeks ago she was started on sodium valproate by her consultant paediatric neurologist in conjunction with the epilepsy specialist nurse.

What is the most likely diagnosis? Select ONE answer only.

A. Adverse drug reaction
B. Autoimmune hepatitis
C. Inadvertent valproate overdose
D. Intercurrent illness
E. Glandular fever

Answer 36.5

A. Adverse drug reaction.

Isobel has developed an adverse drug reaction (ADR) to sodium valproate. Differences in drug metabolism between young children and adults contribute to it. Valproic acid is metabolized predominately by the liver, via conjugation to a glucuronide ester and detoxification via the fatty acid oxidation pathway. The latter has reduced activity in young children. In addition, there is increased activity of some cytochrome P450 enzymes, resulting in greater production of toxic metabolic intermediates.

Of course, it is important to check that the doses prescribed are correct, but it is highly unlikely that both the paediatric neurologist and nurse specialist will have both incorrectly calculated the dose required.

Recent scientific advances which have changed paediatric clinical practice – identification of drug toxicity

A retrospective review of valproic acid hepatic fatalities in the United States identified patients at greatest risk of liver toxicity. Children under the age of 3 years receiving valproate as polytherapy were at greatest risk. Developmental delay and associated inborn errors of metabolism are risk factors. By simply avoiding using sodium valproate as first-line antiepileptic in these children, the risk of hepatotoxicity was significantly reduced.

(Dreifuss F, Santilli N, Langer D, et al. Valproic acid hepatic fatalities: a retrospective review. Neurology 1987;37:329–85.)

oxygenation (ECMO), may also impact on drug metabolism.

Drug toxicity

The World Health Organization defines an adverse drug reaction (ADR) as 'a response to a drug which is *noxious* and *unintended*, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapeutic disease, or for the modification of physiological function'. This is in contrast to a medication error, where the wrong dose of a drug has been inadvertently given or an inappropriate route of administration prescribed.

ADRs can be thought of as predictable and unpredictable. Predictable ADRs are known side effects or secondary effects of the drug or can be caused by known interactions with other medications. An example of this would be exaggerated effects of the medicine's known pharmacological action, which are

usually dose-dependent, such as opiates causing respiratory depression. Unpredictable reactions are due to an intolerance to the medicine, may be allergic/pseudoallergic in nature or be completely unexpected (known as an idiosyncratic reaction – see Question 36.5, above).

Almost 1 in 10 children in hospital will experience an ADR, of which 1 in 8 will be severe. About 2% of hospitalized children have been admitted following an ADR. Children can experience a wide variety of ADRs. Their management should involve taking a thorough medical history and clinical examination followed by consideration of the differential diagnoses for the presenting symptoms. Suspicion of an ADR is increased when symptoms appear soon after a new medication or dose escalation is introduced, and disappears when the medicine is stopped. Recurrence of the problem when the medication was taken again is helpful in confirming the diagnosis.

Children are at risk of specific ADRs that do not affect adults, in whom growth and development are not an issue. Differences in drug metabolism make certain ADRs a greater problem in children (e.g. valproate hepatotoxicity). They may sometimes reduce the likelihood of a problem (e.g. paracetamol hepatotoxicity following an overdose; there is a greater capacity for the sulfation of paracetamol in pre-pubertal children, which reduces the formation of toxic metabolites that cause liver failure following overdose). The mechanisms of ADRs specifically affecting children are illustrated in Table 36.2.

Percutaneous absorption

The newborn infant has a higher surface area to weight ratio than both adults and children. Percutaneous toxicity can therefore be a significant problem in the neonatal period. Examples of this include the use of antiseptic agents, such as hexachlorophene, which have been associated with neurotoxicity in neonates.

Protein-displacing effect on bilirubin

The sulphonamide, sulphisoxazole, was used as an antibiotic in neonates in the 1950s. It was associated with increased mortality due to the development of kernicterus. Sulphonamides have a higher binding affinity to albumin than bilirubin. Thus, the administration of sulphonamides results in an increase in the free fraction of bilirubin, which crosses the blood–brain barrier and may causes kernicterus, especially if the neonate is ill. In most areas of paediatrics, protein binding is not a significant issue. However, in neonates, especially sick preterm neonates, highly protein bound drugs should be avoided.

Impaired drug metabolism

As described above, chloramphenicol was associated with the development of grey baby syndrome in neonates as they metabolize chloramphenicol more slowly than adults and therefore require a lower dose.

Altered drug metabolism

Paediatric patients may have reduced activity of the major enzymes associated with drug metabolism in the liver. To compensate for this, they may have increased pathways of other enzymes. This is thought to be one of the factors contributing to the increased risk of hepatotoxicity in children under the age of 3 years, as illustrated in Question 36.5, above. This increased risk is raised by the use of additional anticonvulsants alongside the sodium valproate, which may result in enzyme induction of certain metabolic pathways.

Table 36.2 Major adverse drug reactions (ADRs) in paediatric patients

Year	Drug/compound	Age group	ADR	Mechanism
1886	Aniline dye	Neonates	Methaemoglobinaemia	Percutaneous absorption
1956	Sulphisoxazole	Neonates	Kernicterus	Protein-displacing effect on bilirubin
1959	Chloramphenicol	Neonates	Grey baby syndrome	Impaired metabolism
1979	Sodium valproate	Young children <3 years	Hepatic failure	Abnormal metabolism?
1980	Salicylate	Children	Reye's syndrome	Unknown
1990	Propofol	Children	Metabolic acidosis	Unknown Dose-related?
1996	Lamotrigine	Children	Skin reaction	Unknown Associated with co-medication with sodium valproate
2008	Ceftriaxone	Neonates/infants	Precipitation in lung and kidneys	Drug interaction Calcium solutions

(Modified from Choonara I, Rieder MJ. Drug toxicity and adverse drug reactions in children – a brief historical review. Paediatric and Perinatal Drug Therapy 2002;5:12–18, with permission.)

Drug interactions

Skin reactions to the anticonvulsant, lamotrigine, are more likely to occur in children than in infants. The incidence is significantly increased by co-medication with sodium valproate alongside the lamotrigine. The mechanism of this drug interaction is unknown. A drug interaction between intravenous calcium and ceftriaxone has been reported in neonates and young infants. Neonatal deaths were documented when ceftriaxone and calcium-containing fluids or drugs were given together or using the same intravenous line. There was evidence of crystalline material in the renal and pulmonary vasculature in some of these neonates at postmortem. Ceftriaxone can also contribute to biliary sludging and kernicterus in neonates, and therefore is contraindicated in premature infants, full-term infants with jaundice and in any child receiving calcium, most often seen in emergency resuscitations and PICU.

Unknown mechanisms

There are several examples of major ADRs that occur in children for which we do not understand the mechanism. Salicylate given during the presence of a viral illness will predispose children of all ages to develop Reye's syndrome, an acute non-inflammatory encephalopathy accompanied by fatty infiltration of the liver. By avoiding the use of salicylates in children with viral infections, the incidence of Reye's syndrome has been dramatically reduced. Propofol is a parenteral anaesthetic agent with minimal toxicity when used to induce general anaesthesia. Used as a sedative in critically ill children, however, it has been associated with the death of over 10 children in the UK alone. The propofol infusion syndrome is thought to be related to the total dose of propofol infused, i.e. high dose or prolonged duration is more likely to cause problems.

Fetal toxicity

The majority of medicines used during pregnancy do not result in harm to the fetus. Both health professionals and pregnant women usually overestimate the risk of drug toxicity associated with the use of medicines during pregnancy. Thalidomide, prescribed for morning sickness during pregnancy, however, is an example of how a drug that is relatively safe in adults can result in significant harm to the fetus (phocomelia) when it is given during a critical stage in pregnancy (24–27 days). The drug that is most likely to be associated with fetal toxicity at present is alcohol, which may result in fetal alcohol syndrome.

Suspected ADRs should be reported to the regulatory authorities by using the Yellow Cards at the back of the *British National Formulary for Children* (BNFc) or online at www.mhra.gov.uk/yellowcard. They can be reported by any healthcare professional or member of the public via this system. All suspected ADRs should be reported, especially if severe/serious. For newer medicines, this is indicated by a black triangle in the BNFc.

Prescribing for children

Many medicines used in children are not fully licensed for such use. Analysis has shown that approximately a third (36%) of children on general paediatric wards and most (up to 90%) of babies on the neonatal unit will receive an unlicensed or off-label medication during their stay. This is usually because the pharmaceutical company has not asked for a licence from the regulatory authorities in any indication in a child or young person. An example of this would be TPN, as it is made individually (or the standard doses are altered) for each individual. In addition, many medicines given to children are off-label, i.e. used at a different dose or route than specified within the product licence or for a different age or different indication. In many cases we prescribe in this way almost every day for children. An example of this would be diclofenac given for pain, as it only holds its licence for the treatment of juvenile idiopathic arthritis in children. Sometimes doses given are well beyond the licensed dose. For instance, inhaled salbutamol is licensed at doses of 100–200 µg via a spacer but paediatricians commonly use much higher doses during acute asthma attacks (up to 10 puffs, which is 1 mg).

The RCPCH recommends choosing the medicine for which there is the *greatest amount of evidence* to justify its use and a licensed form of a medicine is always recommended to be prescribed. The BNFc uses current evidence and the opinions of experts in the field to justify its doses, although the level of evidence is not given in the text. When a dose, for the age group in which it is being prescribed, is given in the BNFc, most paediatricians would not directly discuss the licence with the parents. Provision is given in law for doctors to prescribe, pharmacists to dispense and nurses to administer unlicensed and off-label medicines.

Since the introduction of the European Paediatric Regulation in 2007, all new medicines have to be tested on children (when judged appropriate by the Paediatric Committee). This is a carrot and stick approach. The carrot being one year's marketing extension for the drug in all ages and the stick being that a licence will not be issued in adults until a paediatric plan has been agreed. The regulation also contains legislation for older medicine (Paediatric Use Marketing Authorization (PUMA)), where ten years of marketing exclusivity is given to a company for their paediatric formulation. To date, only one medicine has been through this process, buccal midazolam.

The emergency management of seizures in children was changed by the randomized controlled trial comparing buccal midazolam versus rectal diazepam. Rectal diazepam used to be standard treatment. Buccal midazolam was more effective then rectal diazepam for terminating seizures. Buccal midazolam is now accepted as standard treatment for acute seizures.

(McIntyre J, Robertson S, Norris E, et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. Lancet 2005;366:205–9.)

Most medicines can be taken by a breastfeeding mother and will not cause a significant problem to the infant. One should not discourage mothers from breastfeeding because they are uncertain of possible toxic effects. Formularies such as the BNFc give detailed information regarding which medicines to avoid during breastfeeding. A thorough history should also be taken of all over-the-counter medicines and herbal/alternative medicines that may contain active ingredients.

Question 36.6

Medication error

Following discovery of a medication error, which of the following is mandatory (true) and which is not (false):

A. A critical incident form should be completed

B. A Yellow Card must be completed

C. The doctor responsible should have a disciplinary proceeding commenced

D. The nurse responsible should have a disciplinary proceeding commenced

E. The responsible consultant should be informed

Answer 36.6

A. True; B. False; C. False; D. False; E. True.

A Yellow Card should be completed in the event of an adverse drug reaction but not in the event of a medication error. Whilst the consultant responsible should be informed and a critical incident form should be completed, disciplinary proceedings are not usually required. It is important to learn from errors whenever possible (see below).

Table 36.3 Types of medication error reported in the press that occurred in children in the UK (1993–2000)

Type of medication error	Number	Fatal
Incorrect dose	32	13
Incorrect drug	16	5
Incorrect strength	3	1
Omitted in error	4	1
Incorrect patient	4	–
Duplicate dose	3	–
Expired drugs	3	–
Incorrect route	3	3
Incorrect container	2	1
Incorrect label	2	–
Incorrect rate	2	2
Miscellaneous	6	3
TOTAL	80*	29

*Six children experienced more than one error each.
(From Cousins D, et al. Medication errors in children – an eight-year review using press reports. Paediatric and Perinatal Drug Therapy 2002;5:52–58, with permission.)

Medication errors

Medication errors are a significant problem in paediatric patients. A review of press reports of medication errors described 29 deaths of paediatric patients in the UK over a period of 8 years (Table 36.3). Many health professionals will commit a medication error at some stage in their career and systems have been introduced to try to minimize their occurrence and impact. Incorrect dose has been found to be the most frequent type of prescribing medication error, and is also the type of error most likely to be associated with a fatality. This is because tenfold errors are a particular problem in both neonates and children. It is vital, therefore, to make sure when prescribing that you have an accurate record of the child's weight. Dose calculations, especially on the neonatal unit and when using parenteral medicines, require careful checking.

Prescription of the incorrect drug is the second most common type of medication error and is also associated with significant fatalities. This is particularly likely when drugs have similar names and great care should be taken when you are unfamiliar with a drug name. Incorrect route is a potential problem with intrathecal drugs, and great care is required for medicines administered via this route. Box 36.3 summarizes the measures that should be taken when a medication error occurs.

Commonly used medications

Having some understanding about the pharmacology of drugs commonly used in children is essential for

safe and effective prescribing. Below are a few of those that are most commonly used.

Analgesics

Paracetamol

Paracetamol is used for its analgesic and antipyretic actions and it is easily the commonest drug used within paediatrics. Paracetamol is a weaker analgesic than NSAIDs and is preferred because of its better tolerance. Its primary mechanism of action is believed to be inhibition of cyclooxygenase (COX), with a predominant effect on COX-2. Inhibition of COX enzymes prevents the metabolism of arachidonic acid to prostaglandins. In the central nervous system, inhibition of COX enzymes reduces concentrations of prostaglandin E_2, which lowers the hypothalamic set-point to reduce fever, and activation of descending inhibitory serotonergic pathways to produce analgesia. Paracetamol has limited anti-inflammatory properties. It only weakly inhibits prostaglandin synthesis. The COX-2 selectivity of paracetamol results in a lower antiplatelet activity and better gastrointestinal tolerance than is seen with NSAIDs, which are non-selective COX inhibitors. Paracetamol can be given in various forms: most commonly through the mouth but also by intravenous infusion or rectally. As paracetamol is not absorbed effectively through the gastric mucosa, it will be ineffective in children with limited or no gastric emptying. In these situations, a rectal or intravenous preparation will be required.

Paracetamol undergoes hepatic metabolism for it to be eliminated (see Fig. 7.4). There are three major metabolic pathways: glucuronide conjugation (accounting for 40–60% of a dose in adults), sulfate conjugation (20–40%), and N-hydroxylation via the cytochrome P450 isozyme CYP2E1 (<15%). This latter mechanism produces a highly toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), which requires conjugation with glutathione to form a non-toxic metabolite that can be excreted.

When large amounts of paracetamol are ingested, for example with a paracetamol overdose, glucuronidation and sulfation pathways become saturated. Glutathione stores become depleted, resulting in excess quantities of NAPQI resulting in hepatotoxicity. The treatment of paracetamol poisoning, N-acetylcysteine, increases the glutathione stores so that the buildup of NAPQI can be conjugated and excreted.

In neonates, there is both immaturity of glucuronide conjugation and CYP2E1 metabolism with compensatory increases in sulfation pathways. This immaturity of the CYP2E1 pathway produces less NAPQI, explaining why neonates have a *decreased* likelihood for paracetamol hepatotoxicity.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) have numerous actions *in vivo* and are commonly used to treat pain, inflammation and fever. Ibuprofen is the commonest NSAID used in children. Stronger NSAIDs, such as diclofenac or naproxen, are mainly used in inflammatory conditions such has juvenile idiopathic arthritis.

Inflammation
NSAIDs inhibit cyclo-oxygenase, the enzyme that transforms arachidonic acid to prostaglandins and thromboxanes. There are two forms: COX-1 and COX-2. Selective COX-2 inhibitors, e.g. celecoxib, have fewer gastrointestinal side effects than the non-selective NSAIDs such as ibuprofen and diclofenac.

Analgesia
NSAIDs have a more marked effect on pain, resulting from the increased peripheral sensitization which occurs from inflammation.

Antipyretic
NSAIDs exert their antipyretic effect by inhibition of prostaglandin E_2 (PGE_2) synthesis, which normally triggers the hypothalamus to increase body temperature during inflammation. (See also the section on fever in Chapter 3, History and examination).

Opioids

All opioids produce their actions at a cellular level by activating opioid receptors. These receptors are distributed throughout the central nervous system with high concentrations throughout the brain and spinal cord. Receptors are also found to a lesser extent through

other sites including the vas deferens, knee joints, gastrointestinal tract, heart and immune system. Since their identification, opioid receptors have had a variety of names and historically were called mu, delta and kappa receptors. In the 1990s, a fourth receptor was found and following this discovery the classification was changed. There are MOP (mu opioid peptide), KOP (kappa opioid peptide), DOP (delta opioid peptide) and NOP (nociceptin orphanin FQ peptide) receptors.

Mechanism of action of opioids

Binding of an opioid agonist to a G protein-coupled opioid receptor causes the α subunit of the G protein to exchange its bound guanosine diphosphate (GDP) molecule with intracellular guanosine triphosphate (GTP). This then allows the α-GTP complex to dissociate away from the βγ complex. Both of these complexes are then free to interact with target proteins. With a classical opioid agonist such as morphine, binding to its G protein receptor results in the inhibition of adenylyl cyclase. This in turn causes a reduction in intracellular cyclic adenosine monophosphate (cAMP) levels. Additionally, the α and βγ complexes interact with Ca^{2+} and K^+ channels causing activation of potassium conductance and inhibition of calcium conductance, respectively. The net effect of these changes is a reduction in intracellular cAMP, a hyperpolarization of the cell and, specifically for neuronal cells, reduced neurotransmitter release (Fig. 36.3).

Opioids can be classified by their potency, origin (i.e. synthetic, semi-synthetic or natural) or by function (action at the receptor). Pure opioid agonists

(morphine, diamorphine, pethidine and fentanyl) bind to opioid receptors and demonstrate high intrinsic activity as described above. Partial opioid agonists (buprenorphine, pentazocine) bind to opioid receptors but produce a submaximal effect compared to pure agonists. Opioid antagonists (naloxone) have receptor affinity but no activity and prevent agonists binding (Table 36.4).

Opioids are used for management of severe pain for any number of causes from abdominal pain from a ruptured appendix to pain from a broken ankle. It can be given in a number of different forms but the main forms in children are oral (such as oramorph) and intravenous. Intramuscular morphine is avoided in children due to the unnecessary pain of an injection. Opioids have a large number of side effects, some more serious than others, including addiction, respiratory depression and reduced consciousness, whereas constipation, nausea and vomiting are the most common. Until recently, two opioids were commonly used in paediatric practice – morphine and codeine. The latter is likely to be much less commonly used in the future (see below).

Metabolism of morphine

Morphine is extensively metabolized by the gut wall and the liver. Glucuronidation by the liver enzyme UGT2B7 converts morphine to morphine-3-glucuronide (M3G) (70%) and morphine-6-glucuronide (M6G) (10%). Morphine sulfation is another minor metabolic pathway and does not contribute to the overall clearance. M3G is an inactivated compound and excreted renally, but it is the M6G that produces
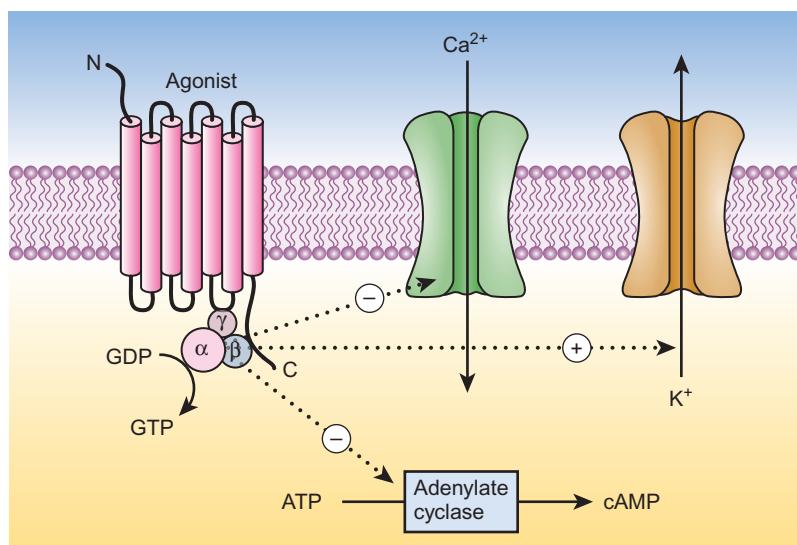
Fig. 36.3 Intracellular changes occurring following the binding of an opioid agonist to a G protein-coupled opioid receptor. *(From Pathan H, Williams J. Basic opioid pharmacology: an update. British Journal of Pain 6(1):11–16 © The British Pain Society 2012, with permission.)*

Table 36.4 Opioids with their selectivity for different opioid receptors

Opioid	Opioid receptor			
	MOP	**KOP**	**DOP**	**NOP**
Agonists				
Morphine	+++	+	+	–
Diamorphine	+++	+	+	–
Pethidine	+++	+	+	–
Fentanyl	+++	+	–	–
Partial agonist				
Buprenorphine	++	+	–	–
Antagonist				
Nalaxone	+++	++	++	

+, low affinity; ++, moderate affinity; +++, high affinity; –, no affinity; MOP, mu opioid peptide; KOP, kappa opioid peptide; DOP, delta opioid peptide; NOP, nociceptin orphanin FQ peptide.

the analgesia effect from morphine. In babies and children, the glucuronidation by UGT2B7 is immature and only small amounts of M3G and M6G are produced. Therefore, in younger children and neonates, where there is immature morphine metabolism, to obtain effective and safe analgesia, morphine doses are reduced and, due to the reduced clearance, given less frequently.

Metabolism of codeine

To obtain its analgesic properties, codeine needs to be converted into morphine by the cytochrome P450 enzyme CYP2D6. This enzyme is known to be highly polymorphic. Homozygous individuals lack the genes for this enzyme and are known as poor metabolizers. They subsequently are unable to convert codeine to morphine, resulting in no analgesia from codeine and increased side effects due to delayed excretion. On the other hand, those with gene duplications or multiplications are described as 'ultrarapid metabolizers' and are at risk of reduced or toxic effects from quick drug metabolism. This puts them at significant risk of the side effects of morphine, such as reduced consciousness and, more concerning, respiratory depression. Case reports in children post adenotonsillectomy have highlighted fatalities from respiratory depression secondary to codeine use in CYP2D6 as a result of increased morphine production. There have also been similar reports in breastfeeding neonates whose mothers were taking codeine and were CYP2D6 'ultrametabolizers'. Following alerts from the Food and Drug Administration (FDA), European Medicines Agency (EMA) and Medicines and Healthcare Products Regulatory Agency (MHRA) in 2013, codeine should not be used in any child with a history of sleep apnoea who is undergoing tonsillectomy or adenoidectomy and should only be used in children over the age of 12 years.

This is an important example of how different patients can respond differently to the same medication, known as inter-individual variability. A large amount of inter-individual variability is caused by genetic variations in activity of drug metabolism enzymes and drug transporters, as in this example.

Antibiotics

Some of the commonly used paediatric antibiotics have been discussed in therapeutic drug monitoring, but other commonly used antibiotics are discussed below, including their mechanism of action and clinical uses.

Question 36.7

Mechanism of action of antibiotics

Which of the following antibiotics acts by inhibiting cell wall synthesis? Select ONE answer only.

A. Azithromycin
B. Cefuroxime
C. Chloramphenicol
D. Gentamicin
E. Trimethoprim

Answer 36.7

B. Cefuroxime.

β-Lactams act by inhibiting cell wall synthesis, as do glycopeptides. Trimethoprim inhibits nucleic synthesis and gentamicin and azithromycin are inhibitors of bacterial protein synthesis.

Inhibitors of cell wall synthesis

β-Lactams

The compounds of this family include a β-lactam ring in their structure. The different groups within this family are distinguished by the structure of the β-lactam ring and the side chains attached to these rings. Penicillins have 5-membered rings, whereas cephalosporins have a 6-membered ring. β-Lactams are bactericidal and act by binding to enzymes known as penicillin binding proteins (PBPs) and inhibiting cell wall synthesis.

Bacterial resistance against the β-lactam antibiotics continues to increase. Mechanisms of resistance include production of β-lactamases that destroy the antibiotics, but also alterations in penicillin-binding proteins and decreased entry and active efflux of the antibiotic.

Penicillins: These are the most commonly used antibiotic within paediatrics and are used widely for the treatment of Gram-positive bacteria, including *Streptococci* and *Staphylococci* species. Amoxicillin is used for community-acquired respiratory infections. When used orally, it has been shown to be as effective as intravenous therapy for treatment of moderate pneumonias. Phenoxymethylpenicillin (penicillin V) is used for treatment of *Streptococcus* infections, such as tonsillitis, where amoxicillin has the potential to cause a rash if used in those with glandular fever.

Co-amoxiclav is an antibiotic which combines amoxicillin with clavulanic acid, the latter being a β-lactamase inhibitor. This combination allows it to be an effective treatment against those bacteria which produce β-lactamases. The most important side effect of the penicillins is hypersensitivity. Allergic reactions to penicillins occur in 1–10% of exposed individuals, with significant anaphylactic reactions occurring in less than 0.05% of treated patients.

Cephalosporins: Their broad spectrum of activity and safety profile make the cephalosporins one of the most widely prescribed classes of antimicrobials. Historically, this group of antibiotics was used in the treatment of Gram-positive bacterial infections, however more recently the third-generation cephalosporins, such as cefotaxime and ceftriaxone, have been used to treat Gram-negative infections, such as *Neisseria meningitides.*

It is the increased penetration of third-generation cephalosporins which gives them this extended range of antibiotic cover. In Gram-positive bacteria, there is only one layer of peptidoglycans, which leaves the PBPs exposed – this leaves them susceptible to treatment with nearly all β-lactams. In Gram-negative bacteria, any antibiotic has to enter the cell wall through porin pores to reach the inner space between the double peptidoglycan membrane before it can attach to the PBPs.

As described above, ceftriaxone has caused calcium deposits in the lung and kidneys in neonates when calcium infusions have been given simultaneously and therefore ceftriaxone should be avoided in young babies. It is also contraindicated in children receiving both ceftriaxone and calcium-containing medications, such as calcium infusions or TPN. Ceftazidime, another third-generation cephalosporin, also has good activity against *Pseudomonas* infections.

Cefuroxime is a second-generation cephalosporin that is less susceptible than the earlier cephalosporins to inactivation by β-lactamases. It is, therefore, active against certain bacteria that have shown resistance as well as having greater activity against *Haemophilus influenzae*. It is used widely in paediatrics for a number of infections, including severe pneumonias, infective abdominal pathology and pyelonephritis.

The principal side effect of cephalosporins is also hypersensitivity. Around 0.5–6.5% of penicillin-sensitive patients will also be allergic to the cephalosporins.

Glycopeptides

See Therapeutic drug monitoring, above, for details.

Inhibitors of protein synthesis

Aminoglycosides

This section is covered within Therapeutic drug monitoring, above.

Chloramphenicol

This drug blocks the action of peptidyl transferase thereby preventing peptide bond synthesis and

subsequently inhibiting bacterial protein synthesis. Chloramphenicol is active against a wide number of bacterial species, including *Salmonella typhi,* and *Chlamydia* species. Its current main use is for topical use in eye infections. Historically, it was used to treat neonatal infections due to its broad cover, however it was shown to be toxic (see above).

Macrolides

Antibiotics within this class are primarily bacteriostatic and act by binding to the 50S subunit of the ribosomes and subsequently they inhibit bacterial protein synthesis. These include various antibiotics, including erythromycin, azithromycin and clarithromycin. Macrolides have a similar spectrum of activity as the β-lactams and are therefore used as an alternative in those who are penicillin allergic.

Clarithromycin has better activity than erythromycin and is used as the alternative in respiratory infections. It is also better tolerated than erythromycin and is only given twice a day rather than four times. Macrolides are also the treatment of choice for atypical respiratory infections, such as *Mycoplasma*, where penicillins are ineffective. Some macrolides (erythromycin and clarithromycin) are cytochrome p450 inhibitors, especially CYP3A4, and can affect the metabolism of other drugs, e.g. warfarin.

Inhibitors of nucleic synthesis

Sulphonamides

Antibiotics in this group are bacteriostatic and act as competitive inhibitors of the enzyme dihydropteroate synthetase (DHPS) which is involved in bacterial folate synthesis. The most widely used sulphonamide within the paediatric setting is trimethoprim and it is used as a first-line treatment for urinary tract infections. It is active against Gram-negative rods, such as *E. coli*. When combined with sulphamethoxazole, it is known as co-trimoxazole and is used for the treatment and prophylaxis of Pneumocystis pneumonia.

Quinolone

This group of drugs acts by inhibiting the activity of DNA gyrase and therefore preventing supercoiling of the bacterial chromosome. This prevents the bacterial cell from putting DNA into its cell. The most ommonly used for treatment of infections in children is ciprofloxacin. Ciprofloxacin has activity against both Gram-negative and Gram-positive bacteria, but in particular *Pseudomonas* and *Neisseria* infection. Its main use is for pseudomonal infections in children with cystic fibrosis or complicated urinary tract infections.

Rational use of medicines in children

When prescribing medicines, one needs to follow the BNFc or local or national guidelines.

The rational use of antimicrobials is important to prevent the development of resistant organisms. The choice of antimicrobial agent needs to be made in conjunction with the local microbiologist, who will be aware of local resistance patterns. Please see the section on commonly used medications for further information on their mechanisms of action. The duration of antibiotic therapy also needs to be carefully considered. Most hospitals have local antibiotic guidelines that should be followed.

The rational use of medicines is important not just for antimicrobials. For example, many infants with mild gastro-oesophageal reflux are prescribed medicines that are both expensive and ineffective such as omeprazole, a proton-pump inhibitor. This is also an off-label use and the formulations that are available (dispersible tablets) make it difficult to measure an accurate dose. A liquid formulation is made by special manufacturers but this can be difficult to source and expensive. It continues to be prescribed despite the fact that proton-pump inhibitors have not been shown to be effective in reducing symptoms associated with gastro-oesophageal reflux in otherwise well infants. There are unfortunately many other instances where health professionals prescribe a medicine for which there is no evidence of effectiveness.

Further reading

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Simon Bomken, Josef Vormoor

Clinical research

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Understand the different research settings and the phases of clinical trials
- Understand how to develop a research question and frame this as a null hypothesis to be tested
- Be aware of the regulatory bodies and processes involved in trial design and approval
- Understand how to enrol a young person on a clinical trial
- Be aware of the monitoring requirements of a clinical trial
- Have a basic understanding of the approach to statistical analysis of trial data
- Appreciate the importance of trial reporting and the role that prospective registration of clinical trials has in this process

There has been a dramatic improvement in child health outcomes throughout the second half of the last century. This has mainly been driven by improvements in nutrition, housing, child safety, immunization and other public health developments. These important approaches are now being complemented by clinical trials, fuelled by the development of new 'omics' technologies, which are uncovering the molecular origins of disease faster than we are able to translate the new information into clinical benefit for patients.

Paediatricians are a critical component in ensuring that our ever improving understanding of fundamental molecular biology is translated into improvements in the health of young people. This requires that paediatricians continue to identify, and seek to answer, key questions relating to childhood development and disease. Identifying clinically relevant problems, framing questions and searching for answers from established research is at the heart of evidence-based medicine (see Chapter 39, Evidence-based paediatrics). However, many questions remain unanswered. Designing studies to address these unanswered questions is the essence of clinical research.

This chapter aims to introduce clinical research, providing a broad understanding of what underpins clinical trial conception and design, the process of obtaining trial approval, recruitment, monitoring and finally reporting of trial findings.

The role of research

Research into the causes of childhood illness underpins much of what we see as standard practice today. However, many of our daily clinical decisions are based on little or no evidence. Children are not small adults, but individuals with specific and ever changing developmental and physiological needs. Despite this, paediatricians are often obliged to extrapolate from adult trials and to prescribe drugs for which there is little clinical trial data from children. Challenges facing the development of research for young people are listed in Box 37.1.

How, then, can child-specific clinical research be driven and what does it offer to the health of young people? Paediatricians involved in caring for children with rare, complex or life-threatening disorders are constantly looking to understand that disease in more detail, to identify high-risk patients and to develop innovative management strategies. For example, molecular characterization of malignant diseases has opened the door to the application of targeted therapies in place of non-selective cytotoxic chemotherapies. Cellular and genetic manipulation of donated

stem cells will reduce the risk of rejection or graft-versus-host disease in recipients. Delivery of the wild type *CFTR* gene will reconstitute normal function, preventing the destructive lung disease seen in cystic fibrosis. However, the majority of child health research seeks to provide evidence relevant to the clinical management of children with more common diseases, forming the evidence base from which we develop our practice, and is the domain of all paediatricians (Box 37.2). Whether as chief investigator, recruiting patients

or as someone committed to improving local practice, understanding the principles and practice of clinical research is a key component of paediatrics. All paediatricians have a responsibility to improve children's healthcare and research is an essential part of this process.

Research methods

Research setting

Medical research is conducted across a number of different settings. Different components flow, in two directions, with clinical problems and observations being investigated at a fundamental level and improved fundamental knowledge being applied to the patient setting. The resultant interplay of ideas, questions, solutions and new questions (Fig. 37.1) is what defines the process of medical research. Whilst the boundaries can merge, broadly the style of research being conducted allows these different settings to be considered separately.

Fundamental (or basic) *research* seeks to develop our understanding and knowledge of the genetic, molecular, environmental or societal basis of disease. Examples include:

- Investigating the cardiovascular or central nervous system effects of neonatal asphyxia using an animal model

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Box 37.1 Challenges facing the development of research for young people

Barriers to research in young people

- Disease rarity – compounded by the increasing molecular subcategorization of conditions
- Consent required on child's behalf, often during distressing periods
- Consideration of risk vs benefit by parents on child's behalf
- Multiple sampling of blood or tissues
- Repeated follow-up causing intrusion into family/school life
- Concordance with therapy and follow-up amongst young people
- Transition to adult services research setting affecting long-term follow-up

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Box 37.2 Landmark study – the use of oral prednisolone in viral-induced wheeze

Framed PICO question: In a pre-school child with wheeze associated with a viral upper respiratory tract infection [patient], is oral steroid (e.g. prednisolone) [intervention] more effective than placebo [comparison] in terms of time to resolution of symptoms, likelihood of admission and deterioration and side effects [outcomes]?

Study design: Randomized, double-blind, intention-to-treat, placebo-controlled trial comparing the role of a short (5-day) course of prednisolone in 700 children aged between 10 months and 60 months. The stated primary outcome measure was duration of hospitalization, with secondary outcome measures assessing symptom severity and salbutamol use.

Results: The study demonstrated that there was no difference in any of the stated outcome measures between children who received prednisolone and those who received placebo. This included a sub-analysis of children at risk of asthma (e.g. previous wheeze, dermatitis or parental asthma).

Discussion: Whilst this trial was conducted in a tertiary paediatric environment, it sought to

address a common problem where there was no evidence to inform practice. Its impact comes not from high technological science, but from the importance of the clinical problem across tertiary, secondary and primary care settings. The use of a randomized, blinded and placebo-controlled design was critical in this study as many of the measured endpoints included a degree of subjectivity. This included the primary outcome measure, duration of hospitalization, as the decision to discharge a patient is based on clinician decision and therefore open to bias if the supervising clinician knew the allocated treatment. Equally, secondary outcome measures of degree of respiratory distress, total dose of inhaled β_2 agonist administered in hospital and following discharge and mean 7-day symptom score all include an element of subjectivity. The use of a placebo was essential to maintain blinding.

Reference: Panickar J, Lakhanpaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. New England Journal of Medicine 2009:360;329–38. ISRCTN58363576.
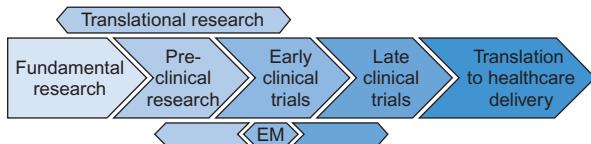
Fig. 37.1 Two-way interconnection between fundamental research and clinical research. EM, experimental medicine.

Box 37.3 Clinical biomarkers

Prognostic biomarkers – used to stratify patients according to the prognosis of their disease subtype. In childhood acute lymphoblastic leukaemia, cytogenetic analysis identifies patients at a higher risk of treatment failure, e.g. t(9;22) Philadelphia chromosome.

Predictive biomarkers – predict a patient's response to a particular treatment. Mutations of Kir6.2 causing infant-onset diabetes insipidus predicts sensitivity to sulphonylureas (Box 37.4).

Response biomarkers – provide a surrogate measure of a patient's disease status and response to the chosen therapy – fever or C-reactive protein in infection.

Pharmacokinetic biomarkers – used to assess the therapeutic or toxic effects of a drug. Antibiotics such as gentamicin or vancomycin will commonly have drug levels monitored.

Imaging biomarkers – non-invasive imaging, e.g. CT or MRI, may provide prognostic or response biomarker information.

- Identifying the cytogenetic abnormalities found in acute lymphoblastic leukaemia
- Identifying the underlying cause of the abnormally thick secretions seen in cystic fibrosis – characterization of the cystic fibrosis transmembrane regulator provided a pathological mechanism which, in turn, may offer a therapeutic option.

Translational research is a two-way process which provides a bridge between fundamental research and applied clinical research and adheres to the philosophy of 'bench-to-bedside and back again'. In the forward direction, it aims to generate supportive *pre-clinical* data prior to investigating the clinical application of:

- One of a number of different potential clinical biomarkers (Box 37.3)
- Novel therapeutic targets – if the *CFTR* gene is mutated in cystic fibrosis, is it possible to deliver a functionally normal gene to the airways and does this result in a biological improvement, e.g. in secretions?

In reverse, it aims to identify:

- Important clinical problems and frame them as research questions for fundamental investigation
- Unusual clinical situations as routes for fundamental science to develop learning of basic processes – identification of recessive genetic causes of primary immunodeficiency can identify critical elements in development of immunity.

Question 37.1

Biomarkers

A phase III clinical trial is opened to assess the benefit offered by a new insulin pump in children. The primary endpoint of the trial is the change in their HbA1c.

In this setting, HbA1c is an example of what kind of biomarker? Select ONE answer only.

A. Imaging biomarker
B. Pharmacokinetic biomarker
C. Predictive biomarker
D. Prognostic biomarker
E. Response biomarker

Answer 37.1

E. Response biomarker.

The HbA1c is being used as a surrogate measure of glycaemic control, and thus provides a measure of the effectiveness of the intervention.

Clinical research seeks to take potential diagnostic, monitoring or therapeutic strategies, identified by basic and translational research, into a representative clinical setting. It asks the question, 'Does this treatment improve the health and well-being of real patients?' Addressing this question will normally be performed in steps, or phases, with different aims at each phase (Table 37.1). Phase I and II (*early phase*) trials recruiting small numbers of patients and focusing on determining the safety and appropriate dosing/schedule of a new intervention, may be combined so that patients are initially recruited to a phase I element followed by progression to a phase II element. This is increasingly common in trials of new therapies designed specifically for rare patient or disease/molecular subgroups.

Increasingly, *experimental medicine* (see Fig. 37.1, and see Personalized medicine, below) seeks to use human trials to generate pre-clinical data. For example, a clinical trial with a primary aim of investigating the effect of a new cytotoxic anti-cancer drug can also be used to assess the pharmacokinetics/pharmacodynamics of that drug and the effect on

Box 37.4 Interventional cohort studies provide an alternative to RCTs when they are unfeasible or unethical

Scenario: You are a paediatrician working in a tertiary paediatric diabetes service.

Framed PICO research question: In children with diabetes due to mutations within the ATP-sensitive potassium channel [population], is oral sulphonylurea [intervention] as effective as standard insulin replacement [control] in maintaining or reducing HbA1c [primary outcome measure] without additional episodes of hypoglycaemia [secondary outcome]?

Method: This interventional cohort study looked at the management of 49 patients with diabetes due to mutations within the ATP-sensitive potassium channel.

Results: A significant reduction in HbA1c from 8.1% pre-treatment to 6.4% after 12 weeks of treatment (p<0.001). Forty-four patients were able to stop insulin treatment.

Discussion: This collaborative multinational study demonstrated a safe and more effective way of managing diabetes resulting from this rare group of mutations. The patients in this study, all of whom were established on 'standard' insulin therapy, provided their own controls for the primary outcome measure of HbA1c, which can be assessed using a paired Student's t-test (see Chapter 38, Statistics). Assuming that all patients were stable prior to enrolment, this approach provided the most appropriate trial design. It maximized the opportunity to study the effect of an intervention in a small population of patients with a rare condition. Randomizing patients between ongoing standard care and investigational treatment would have reduced the number in the trial therapy arm, thereby reducing the power of the study. However, a crossover approach would clearly not be appropriate in acute conditions where baseline measurements cannot provide stable data, or in life-threatening conditions where two interventions – usually current standard of care and new intervention – must be directly compared. In that situation, randomization would be most appropriate.

Reference: Pearson ER, Flechtner I, Njølstad PR, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. New England Journal of Medicine 2006:355;467–77.

Table 37.1 Trial phases I–IV with common study sizes and aims

Phase	Numbers recruited	Primary aims	Secondary aims
Phase I	<30	• Assess safety • Assess side effects • Determine maximum tolerated dose (MTD – the highest dose at which tolerable side effects are seen)	Understand the pharmacology of the drug in humans
Phase II	<100	• Assess safety • Optimize dosing schedule • Look for beneficial effect in a suitable patient population	Determine optimal supportive care for side effects
Phase III	Hundreds to thousands	• Compare new intervention with standard intervention • Compare alternative ways of delivering a standard intervention • Test applicability to 'routine' clinical setting	Ongoing safety monitoring
Phase IV	Hundreds to thousands	• Ongoing clinical efficacy in 'population-wide' usage • Ongoing safety monitoring	

similar, potentially cross-reactive pathways in normal tissue. These studies cannot be performed *in vitro* or in healthy human volunteers due to the potential toxicity.

Common trial designs

A number of different quantitative trial designs exist. Whilst the randomized controlled trial is frequently seen as the gold standard approach for investigating a new treatment intervention, each of the designs can be the most appropriate choice for a given clinical setting (Table 37.2).

Question 37.2

Trial design

The following (A–E) is a list of trial designs:

A. Case-control study

B. Cohort study

C. Cross-sectional study

D. Ecological study

E. Randomized controlled trial

Match the trial designs to each of the studies below:

1. Given current theories on autism and the finding of low-level contamination of drinking water specifically from surface sources with pharmaceuticals including oestrogenic compounds and other pollutants, researchers questioned whether drinking water might be a common source of exposure for numerous potential risk factors for autism spectrum disorders. The study collected secondary data on county-level autism prevalence in the USA and data on the percentage of drinking water derived from surface water sources for each county from publicly available data sources.

2. Mothers were identified during attendance at an antenatal clinic and divided into two groups: those who smoked during pregnancy and those who did not. Following delivery, all children were followed up for five years with yearly questionnaires about a variety of developmental outcomes.

3. Families attending an outpatient clinic were approached and asked to complete a survey regarding the amount of physical exercise undertaken each week. During the same clinic, each child was weighed and their height measured in order to evaluate associations between physical activity and overweight.

4. Following recruitment, children were allocated to receive either the current standard first-line treatment for epilepsy or a new medication under review. Investigators, unaware of which medication each participant was taking, analysed the outcome data with regards to seizure control.

5. To assess and compare the oral health status of pre-school children with and without cerebral palsy (CP), pre-school children with CP were recruited from special child care centres and a gender-matched sample of pre-school children from mainstream pre-schools were recruited as the control group.

Answer 37.2

1. D. Ecological study.
2. B. Cohort study.
3. C. Cross-sectional study.
4. E. Randomized controlled trial.
5. A. Case-control study.
   See Table 37.2 for discussion.

Box 37.5 Qualitative study

Non-compliance amongst adolescents with asthma

Scenario: A 14-year-old boy is admitted to your ward. He has 'brittle' asthma. It is the fourth time he has been admitted this year. GP records demonstrate that he is not collecting his prescriptions. You have a large number of similar adolescent patients and want to investigate compliance in adolescent patients.

Research question: 'To understand better the reasons for non-compliance in adolescents with asthma.'

Research study: In-depth interviews with a sample of 49 adolescents, aged between 14 and 20 years. All adolescents were diagnosed as asthmatic more than a year previously and were attending a hospital asthma clinic. The interviews focused around the adolescents' feelings about their illness and their illness-related behaviour, including self-management.

Key results: Reasons given for non-compliance with prescribed medication in the past or at present were: forgetfulness, belief that the medication is ineffective, denial that one is asthmatic, difficulty using inhalers, inconvenience, fear of side effects, embarrassment and laziness.

Research implementation: The results are implemented by improved education, including a peer education initiative.

Reference: Buston KM, Wood SF. Non-compliance amongst adolescents with asthma: listening to what they tell us about self-management. Family Practice 2000;17(2):134–8.

Qualitative research

Whilst most clinical research revolves around the *quantitative* analysis of clinical criteria, the interrogation of *qualitative* information can also play an important role, both in informing quantitative clinical trial design and in influencing clinical service design and provision.

Qualitative research (Box 37.5) aims to develop understanding of a defined area by collecting information, analysing it and using the output to generate new ideas or hypotheses which may or may not then be suitable for quantitative analysis. Information collecting may involve:

- Review of documented evidence
- Observational approaches – recording uninfluenced behaviours
- Interviews – usually open-ended and defined by topics rather than specific questions
- Group discussion – specifically focusing on the interactions of the group setting

Table 37.2 Common trials designs

Trial design	Approach offered	Most suitable if	Example research question
Randomized controlled trial (RCT)	Patients are randomly assigned to receive either standard intervention or the new 'trial' intervention	A new treatment is being compared with the current best treatment. This approach allows comparison of efficacy and toxicity whilst minimizing sources of bias.	PREDNOS trial: In children with new onset nephrotic syndrome [patient], is 16 weeks of prednisolone [intervention] more effective than 8 weeks [control] at reducing relapse rate [outcome]?
Crossover trial (variation of RCT)	Individuals provide both control and experimental arm by sequentially receiving multiple/all interventions at different time-points, interspersed with periods for drug 'wash-out'	The new treatment is for a chronic condition and aims to control symptoms Is unsuitable/unethical for an acute condition where life-saving treatment is on trial	In adolescents with type 1 diabetes [patient], does pump therapy [intervention] compared to basal-bolus [control] reduce nocturnal hypoglycaemic episodes [outcome]?
Cohort	Children and young people in a particular setting are recruited and followed up to determine outcome	The effect of an exposure or predisposition to a condition is being investigated May be used, especially in early phase trials, where controlling with a placebo is unfeasible or unethical (Box 37.4)	In infants [population], does supine sleeping [cohort 1] compared to prone sleeping [cohort 2] lead to a high frequency of sudden infant death [outcome]? (See Box 37.4.)
Case-control	Children and young people with a condition are compared with a control group without that condition. Controls must be matched for a number of characteristics, such as age, gender, socio-economic group	Predisposing/risk factors are being investigated. By comparing well-matched cases and controls, the differences between the groups can identify such risk factors.	In infants with pyloric stenosis [case group] compared with a matched group [control group], is there higher exposure to erythromycin?
Ecological	Data generated from a geographically (usually) defined population to identify risk-modifying factors on health outcomes	Able to identify available information about the population	Map of skin cancer deaths and sun exposure

Whilst outcome measures are not restricted in qualitative studies, the study aim, methodology and analysis are no less rigorously defined and validated than in quantitative approaches. Commonly a number of validated methods will be used independently by more than one researcher and the results triangulated to identify areas of agreement, providing a high degree of validity.

Question 37.3

Clinical research/clinical trial settings

The following (A–J) is a list of research settings:

A. Experimental medicine
B. Fundamental research
C. Phase I clinical trial
D. Phase I/II clinical trial
E. Phase II clinical trial
F. Phase III clinical trial
G. Phase IV clinical trial
H. Pre-clinical research
I. Research for patient benefit
J. Translational research

Choose the most appropriate research setting to address each of the problems below:

1. Regular intravenous antibiotics form an important part of the management of children with cystic fibrosis. However, these require frequent admissions to hospital and therefore disrupt children's social development and education. Your local respiratory team would like to assess a new home antibiotic delivery programme aimed at improving the experience of this element of care for children and their family.

2. A new targeted anti-cancer therapy has shown good efficacy in early phase trials in adults with relapsed non-Hodgkin's lymphoma. You wish to determine the tolerability of this agent alongside/in addition to your current standard therapy for aggressive mature B-cell lymphoma. Initially this study will identify the maximum tolerated dose in cohorts of three patients, followed by an extended cohort to look at short-term toxicity.

3. In order to gain the most information from your Phase II trial of a novel immune-modulatory agent in severe Crohn's disease, you design a number of associated studies to identify the

pharmacokinetics of the drug in young people (existing data are derived from adult studies) and the effect on serum markers of inflammation (response biomarkers), and you require that fresh biopsy specimens are collected at subsequent endoscopic procedures for laboratory investigations of immune cell function. This way you aim to get the most information about the efficacy of the new drug.

Answer 37.3

1. I. Research for patient benefit. This approach looks at optimizing healthcare service delivery in a patient-centred manner.
2. D. Phase I/II. Initial identification of maximum tolerated dose (Phase I) is followed by an extended early phase approach to confirm tolerability alongside otherwise very intensive therapies using an extended early phase trial approach.
3. A. Experimental medicine. This concept aims to maximize the experimental and learning opportunities available during clinical trials of new treatments by use of pharmacokinetic, pharmacodynamic, biomarker and fundamental science studies on patient-derived samples.

Designing a clinical trial
Introduction – identifying a clinical need

The origins of all clinical trials should be an identifiable *clinical need*. This is one of the key contributions to be made by translational researchers. The process of identifying a need, investigating potential solutions and then validating them is key to framing the clinical *research question* (Fig. 37.2). Whilst basic scientists may follow lines of investigation which appear interesting in the hope of further defining fundamental elements of biology, a greater expectation must be placed on the question underpinning a clinical trial. Asking a child and their family to consent to novel intervention or additional investigations can only be ethically justified if the benefit outweighs the risk. There must therefore be a reasonable expectation of patient benefit, identified as a clinical need. It may not, for example, be justified to randomize children between two established therapies with an equivalent, well-documented success rate, simply to demonstrate equivalence in a formal setting. If, however, there was a rationale for one treatment being more effective or less toxic than the other, then this would need to be investigated in a randomized clinical trial. The research question becomes:

- Treatment effect:
  - Is treatment A more effective than treatment B in this clinical setting (e.g. In pre-school children with mild chronic asthma [patient], is oral leukotriene antagonist [intervention] as or more effective then inhaled steroid [control] in preventing chronic symptoms and/or acute exacerbations [outcomes])?
- Side effects/toxicity:
  - Is treatment A less toxic than treatment B in this clinical setting (e.g. in pre-school children with mild chronic asthma [patient], does oral leukotriene antagonist [intervention] lead to greater height potential [outcome] than inhaled steroid therapy [control])?
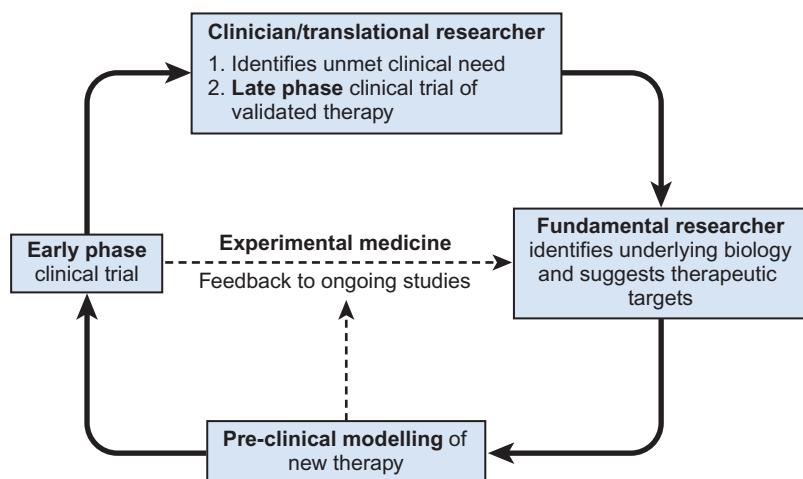
Fig. 37.2 Cyclical process of clinical trial design – identifying a clinical need, investigating the underlying biology, validating and testing a novel therapeutic approach, including feedback to ongoing fundamental studies, and undertaking late phase clinical trial.

Fundamental scientific evidence

Having identified a clinical need, basic evidence must be sought on how to approach meeting that need. Frequently this will involve a thorough search of the published literature, as there is often a large body of evidence in existence. However, this will often need to be complemented by additional studies investigating the relevance of published knowledge in the specific disease setting. Combined, these data will hopefully provide possible routes for a new intervention aimed at meeting the clinical need.

Pre-clinical modelling of the intervention

Having identified a potential novel intervention, this needs to be validated in the most appropriate pre-clinical model available. Some models will involve *in vitro* drug testing using derived cell lines. However, more complex models, often involving animal research, are frequently used as these may be felt to be more representative of the clinical setting with, for example, metabolism of drugs and complex tissue microenvironments in place of homogeneous single cell cultures (Box 37.6). However, the animal model may only partially represent the human disease and the metabolism and cellular effects of a drug may differ between animal model and humans. One approach to solving this, predominantly relevant to malignancies, is to use human diseases engrafted into immunodeficient animal models – xenografts. It should be noted that even then, factors such as differential metabolism of a drug or the altered microenvironment may limit the clinical relevance of the model.

Defining the research hypothesis

Having identified a clinical need, defined the research question and examined the basic and pre-clinical evidence available, the approach to answering the question and resolving the need must be expressed as a hypothesis (Box 37.7). A *research hypothesis* aims to state a prediction about the outcome of a research study, which can then be experimentally tested. Conventionally this hypothesis is based on the outcome of literature searches and previous, pre-clinical, studies. However, it is not statistically possible to prove the research hypothesis, as the results observed within the study might be due to chance occurrence. Instead, a study's results must be compared against the opposite situation, which is known as the *null hypothesis*. Evidence which argues against the null hypothesis is evidence in favour of the original research hypothesis, which now becomes known as the *alternative hypothesis*. Deciding what size of effect the study is looking to identify is an essential component of defining the alternative hypothesis, providing the clinically relevant outcome with which power calculations can be made and data analyses can be performed. Defining the research question and subsequently the research hypothesis is key to determining how the resultant study will be structured, performed and analysed.

Feasibility

Consideration must be given to the ability of the study team to deliver a successful trial within a suitable timeframe. The key factors to consider are shown in Box 37.8. If the expected duration of the study, including necessary follow-up, risks making the delivery of results so delayed that they may no longer be clinically relevant (if, for example, other approaches to management have improved substantially), then it may not be appropriate to initiate the trial. Options for increasing recruitment should be considered, especially widening the trial setting to include national (Box 37.9) or, commonly, international recruitment, the use of alternative trial designs and the sharing of data across trials by prospective or retrospective meta-analysis.

Preliminary statistics

One critical component of developing a clinical trial is to give consideration to defining the outcomes to be assessed and the number of patients required to demonstrate whether those outcomes are affected by the intervention on trial. By defining the outcome which the intervention is hoped to produce, statistical analyses can be tailored to address that specific question. Collecting large quantities of data and then asking multiple questions is statistically unsound and will both risk identifying effects resulting from chance and reduce the likelihood of producing a statistically significant result for the most important clinical outcome as statistical significance needs to be adjusted from when performing multiple tests (Bonferroni calculation). Ideally, outcomes should be defined as:

- *Primary outcome measures* – the main outcome(s) under investigation
- *Secondary outcome measures* – additional important impacts of the intervention

Once the nature of the outcome to be assessed is defined, preliminary data on the clinically relevant size and distribution of the effect within the study population can be used to determine the number of patients (sample size) which need to be recruited to the study. This is the *power calculation*, which will usually be required by regulatory/funding bodies as one part of demonstrating that the study is practicable.

Scenario: You are a community paediatrician who regularly cares for children with neurodisability secondary to hypoxic–ischaemic encephalopathy (HIE). You want to engage in pre-clinical research to identify new interventions to reduce neurodevelopmental complications in the population.

Research question: In newborn pigs that have undergone induced hypoxia, is there evidence of secondary brain insult despite normal pH, oxygen and glucose levels?

Background: Understanding the mechanism of injury in neonatal asphyxia requires a complex model including developing neural tissue, oxygenation, glucose metabolism and metabolic by-products. Such modelling could not be produced *in vitro* and therefore animal models of asphyxia were developed to investigate not only the pathological mechanisms, but also the response to a number of treatment options.

Using both newborn pig and newborn rat models of asphyxia, an initial insult to cerebral metabolism is following by a period of normal metabolism. However, a late or secondary cerebral energy failure was identified, despite normal blood pH, oxygen and glucose levels. As the severity of this secondary insult was shown to correlate with the risk of death, severe neurological disability or microcephaly (Roth et al 1992), it provided a possible therapeutic opportunity – a second period during which a protective therapy could be implemented.

Further research stemming from this finding: Further analysis of these models found that whilst infusing magnesium sulphate did not prevent the secondary energy failure (Penrice et al 1997), inducing moderate hypothermia did (Thoresen et al 1995), reducing neuronal apoptosis (Edwards et al 1995) and infarct size (Bona et al 1998). These studies paved the way for further optimization of cooling strategies using models prior to early phase trials investigating the safety of both selective head cooling or whole body hypothermia in newborn infants (Gunn et al 1998, Azzopardi et al 2000, Eicher et al 2005), see Box 37.13.

References:

Azzopardi D, Robertson NJ, Cowan FM, et al. Pilot study of treatment with whole body hypothermia for neonatal encephalopathy. Pediatrics 2000;106(4):684–94.

Bona E, Hagberg H, Løberg EM, et al. Protective effects of moderate hypothermia after neonatal hypoxia-ischemia: short- and long-term outcome. Pediatr Res 1998;43(6):738–45.

Edwards AD, Yue X, Squier MV, et al. Specific inhibition of apoptosis after cerebral hypoxia-ischaemia by moderate post-insult hypothermia. Biochem Biophys Res Commun 1995;217(3):1193–9.

Eicher DJ, Wagner CL, Katikaneni LP, et al. Moderate hypothermia in neonatal encephalopathy: efficacy outcomes. Pediatr Neurol 2005;32(1):11–7.

Gunn AJ, Gluckman PD, Gunn TR, et al. Selective head cooling in newborn infants after perinatal asphyxia: a safety study. Pediatrics 1998;102(4 Pt 1):885–92.

Penrice J, Amess PN, Punwani S, et al. Magnesium sulfate after transient hypoxia-ischemia fails to prevent delayed cerebral energy failure in the newborn piglet. Pediatr Res 1997;41(3):443–7.

Roth SC, Edwards AD, Cady EB, et al. Relation between cerebral oxidative metabolism following birth asphyxia, and neurodevelopmental outcome and brain growth at one year. Dev Med Child Neurol 1992;34(4):285–95.

Thoresen M, Penrice J, Lorek A, et al. Mild hypothermia after severe transient hypoxia-ischemia ameliorates delayed cerebral energy failure in the newborn piglet. Pediatr Res 1995;37(5):667–70.

The factors required to produce a power calculation are:

- The *significance level* to be used in the analysis – the value against which the likelihood of incorrectly rejecting the null hypothesis will be judged. This will be calculated from the trial data as the *p-value*.
- The *magnitude of effect* in the study population (either a direct measurement or, preferably, standardized according to the spread of the effect within the population)

- The *power* – the probability of rejecting the null hypothesis when the alternative hypothesis is correct (Box 37.10). Frequently set to be 0.8, this represents an 80% chance of correctly identifying the pre-determined clinically significant effect in the study population.

Regulatory approval

All studies involving human subjects must be subjected to rigorous regulatory oversight. This includes

Scenario: You are a respiratory paediatrician who regularly treats children with cystic fibrosis (CF).

Framed PICO research question: In children with CF [population], is retroviral delivered normal *CFTR* gene [intervention] compared to placebo [control] effective in reducing the development of chronic airway damage [outcome]?

Hypotheses:

- *Research hypothesis*: 'Retroviral delivery of a normal *CFTR* gene to the airways of children with cystic fibrosis will reduce the development of chronic airways damage.'

- *Null hypothesis*: 'Retroviral delivery of a normal *CFTR* gene to the airways of children with cystic fibrosis will not reduce the development of chronic airways damage.'

- *Alternative hypothesis*: 'Retroviral delivery of a normal *CFTR* gene to the airways of children with cystic fibrosis will delay the development of chronic airways disease by X years.'

Box 37.8 Factors contributing to the feasibility of a clinical trial

- **Incidence** – including genetic/molecular subclassification
- Number of patients (sample size) required to give the study adequate **power** (see Chapter 38, Statistics)
- Predicted **eligibility rates** – pathways of referral, additional inclusion/exclusion criteria
- Predicted rates of **consent** – affected by trial design, complexity, additional impact on family and potential risks

making applications to a number of organizations, depending on the nature of the study (Table 37.3). Furthermore, trials must be conducted within the framework defined by the International Conference on Harmonisation, a tripartite initiative between the US, Europe and Japan to define a standardized approach to clinical trial design and conduct to ensure accuracy and credibility of trial findings. The outcome, provided as the 13 principles of good clinical practice (GCP), are applied to ensure that the results from a clinical trial can universally be trusted as being of high quality (Box 37.11). The principles defined by GCP have their foundation in the Declaration of Helsinki and focus primarily on the rights, safety and well-being of participants. All professionals involved in clinical trials will be expected by the trial sponsor/research ethics committee (REC) to have evidence of up-to-date GCP training and it is a legal requirement within the UK and European Union that all trials of investigational medicinal products are conducted according to the principles of GCP.

In order to ensure that all required regulatory requirements are complied with, every clinical trial will identify a sponsor. The sponsor is 'an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial' (UK Clinical Trials Regulations). For clinical trials, the sponsor is commonly the institution hosting the clinical trials unit running the trial.

Engaging with children and young people on trial design

An increasingly important element of clinical trial design is engaging children and young people from an early stage. Many research ethics committees and funders will require this, particularly on matters such as the design of age-specific patient and parent information sheets. More importantly, however, high quality engagement, involving young people and families right from a study design stage, seeks to ensure that the research question reflects the priorities of this most important group and creates a relationship between study and patient which hopefully improves understanding, participation and concordance. The outcome should be greater patient/family satisfaction and well-being as well as higher quality data.

Trial registration

Once the trial protocol has been developed, many trials will register themselves with a publicly accessible database, such as the International Clinical Trials Registry Platform (ICTRP) or International Standard Randomised Controlled Trial Number (ISRCTN) to receive a unique clinical trial number. Currently, registration of a clinical trial is not mandatory, although clinical trials of investigational medicinal products (CTIMPs) undertaken within the EU are required to register with the European Medicines Agency for a EudraCT number (Box 37.12). The aims of these registrations are to facilitate supervision of trials, including linking with pharmacovigilance databases, supporting communication between regulatory authorities and tracking outcomes of trials through all related publications, limiting the impact of reporting bias.

Enrolling young people on clinical trials

Information sharing

The first major commitment to enrolling a child or young person on a trial is to provide both the

Widespread recruitment to clinical trials within paediatric oncology has seen a stepwise improvement in outcome for many childhood malignancies. Improvements in supportive care have been an important part of this development, including:

- Criteria for identification of febrile neutropenia and the use of broad-spectrum antibiotics
- Improved prophylaxis for *Pneumocystis jiroveci* and population immunity for measles
- Improved imaging – CT, MRI, CT/PET, isotope imaging
- Improved surgical/anaesthetic techniques – operating microscopes, coagulation diathermy, peri/intraoperative imaging
- More advanced intensive care facilities

However, many of the clinical trials conducted in childhood malignancy have provided a clear improvement in outcome. This is well demonstrated by the results of UK trials in acute lymphoblastic leukaemia (Fig. 37.3), which have recruited over 8500 children between 1980 and 2011, with the most recent complete trial, UKALL 2003, recruiting over 95% of eligible children:

- UKALL VIII – Attempted to reproduce the superior results seen in the US by using the US CCG162 protocol. Inclusion of daunorubicin in induction improved disease control, albeit at the cost of higher treatment related mortality. Extension of maintenance therapy from two to three years improved survival, although again at the cost of increased toxicity. Overall, similar results were achieved compared to the US, but neither randomization demonstrated a clear overall benefit.
- UKALL X – Examined the role of post-induction intensification. Inclusion of both early and late

intensification phases was better than one or no intensification phase. Five year event-free survival was 71% with 2 intensification phases, 62–63% with a single intensification and 57% without intensification.

- UKALL 97/99 – This trial demonstrated the superiority of dexamethasone over prednisolone, stratified patients according to white cell count and age at diagnosis: standard risk – age <10 years, white cell count $>50 \times 10^9$/L; high risk – age >10 years or white cell count $>50 \times 10^9$/L. The UK trial again adopted an apparently superior US approach with longer intensification blocks. Introduction of more extensive and sensitive cytogenetic analysis to identify high risk groups.
- UKALL 2003 – Stratified children according to minimal residual disease analysis (MRD), a molecular test for low levels of residual disease not detectable by traditional bone marrow analysis. Low risk MRD allowed for reduction of treatment intensity whilst high risk MRD resulted in escalation of treatment.

Further reading:

Hargrave DR, Hann II, Richards SM, et al. Medical Research Council Working Party for Childhood Leukaemia. Progressive reduction in treatment-related deaths in Medical Research Council childhood lymphoblastic leukaemia trials from 1980 to 1997 (UKALL VIII, X and XI). Br J Haematol 2001;112;293–9.

Mitchell C, Richards S, Harrison CJ, Eden T. Long-term follow-up of the United Kingdom medical research council protocols for childhood acute lymphoblastic leukaemia, 1980–2001. Leukemia 2010;24;406–18.

Scenario: You are a general paediatrician who regularly treats children with pneumonia (see Table 39.6).

Framed PICO research question: In a pre-school aged child with pneumonia [patient], are oral antibiotics [intervention] as effective as intravenous antibiotics [comparison] for time to resolution of symptoms, rate of hospital admission, length of stay and rate of complications [outcomes]?

Power calculation: You work with a steering group who advise a difference of more than 20% could not be considered clinically equivalent *(magnitude of effect)*.

With a 5% level of significance *(statistical significance)*, 80% power and equivalence defined as no more than a 20% difference *(magnitude of effect)* between treatments of the proportion meeting the primary outcome measure at any time, 98 children would be required in each arm of the trial.

Reference: Atkinson M, Lakhanpaul M, Smyth A, et al. Comparison of oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia in children (PIVOT trial): a multicentre pragmatic randomised controlled equivalence trial. Thorax 2007;62:1102–6.

Table 37.3 UK regulatory authorities from which clinical study approval must be sought

Organization	Mandatory	Remit
National Research Ethics Service (NRES)	For trials involving human subjects/tissues	To review the ethical implications of study recruitment (including patient/parent information sheets), conduct, monitoring and reporting. The principle aim is to protect the rights, safety and well-being of participants and their family. NRES now also has responsibility for the ethical conduct of trials involving genetic or stem cell therapies, previously held by the Gene Therapy Advisory Committee (GTAC). Both of these bodies are now part of the NHS Health Research Authority.
Medicines and Healthcare Regulatory Authority (MHRA)	For studies involving investigational medicinal products or healthcare devices	The MHRA is a governmental agency with responsibility for regulating all medicines and medical devices in the UK. This role includes regulating the design and conduct of clinical trials for medicines and medical devices to ensure acceptable levels of protection for participants.
Administration of Radioactive Substances Advisory Committee (ARSAC)	For studies involving diagnostic or therapeutic radiation	Clinical trials involving the administration of radioactive substances require a certificate from the Department of Health. Applications for certificates are reviewed by members of the ARSAC committee and granted/refused by ministers on their advice.
Trust R&D	Yes	NHS Trusts will require a detailed review of all clinical trial activities to ensure that appropriate ethical, legal and financial considerations have been made, in accordance with the Department of Health guidance, Research Governance Framework for Health and Social Care (RGF).
Human Tissue Authority (HTA)	For studies involving collection, storage and use of human cellular material	The HTA has a statutory duty to regulate the collection, storage and use of human material for research and teaching. Material must be collected with specific consent for storage and research and be handled according to HTA guidance, including rigorous tracking of samples from patient to eventual use/disposal.
Human Fertilisation and Embryology Authority (HFEA)	For studies involving the production and use of human embryos	An independent regulator responsible for oversight of the use of human gametes and embryos for treatment of infertility or research.
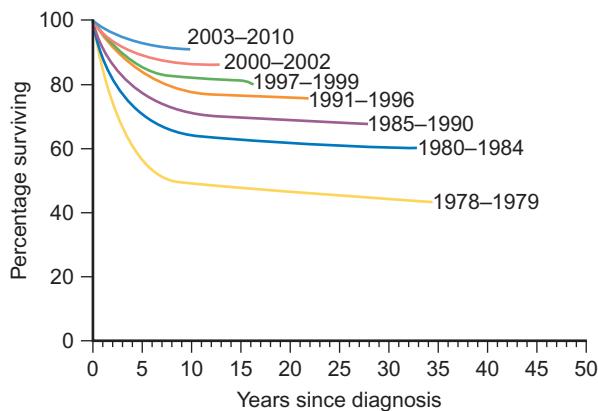
Fig. 37.3 Overall survival in children aged 1–14 years with acute lymphoblastic leukaemia by UKALL trial 1977–2005. *(Adapted from National Registry of Childhood Tumours Progress Report 2012,* www.NCIN.org.uk*.)*

child and the person with parental responsibility with sufficient, understandable information that they are able to make an informed decision about participation. Different amounts and complexities of information will need to be given to children of different ages. A discussion about involvement in a clinical trial must be supplemented with written information for both patient and parent – patient/parent information sheets.

Consent and assent

Consent for a minor (defined by Medicines for Human Use (Clinical Trials) Regulations 2004 as aged less than 16 years) to participate in a clinical trial of a medicinal product (CTIMP) can only be given by a person with parental responsibility. Unlike other areas of clinical practice, consent to participate in a CTIMP is governed solely on age, not competence as assessed according to the Fraser guidelines.

For clinical trials not involving investigational medicinal products, non-CTIMPs, the law in the UK remains untested. Whilst UK law defines a minor as being less than 18 years, many non-CTIMP trials will define a minor as being less than 16 years. Therefore, the individual detail of a trial protocol must be understood by the person taking consent. Having considered the implications of the trial for the child and actively assessed the individual child's capacity to understand the trial, balance the risk and benefits and crucially to understand their right to refuse or withdraw without impact on their care, a researcher may judge a minor to be able to consent to inclusion in a non-CTIMP trial. Good practice would usually involve a parent, or person with parental responsibility, in this process.

Obtaining consent can be challenging when there is disagreement, either between two parties with parental responsibility or between parents and the young person. Best practice would require that, whilst one

Patient well-being

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with good clinical practice (GCP) and the applicable regulatory requirement(s).

2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

Trial design

4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

Trial conduct

6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.

Data handling

10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

Quality assurance

12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

   Reference: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonised tripartite guideline for good clinical practice E6(R1). Current Step 4 version, 10 June 1996. http://www.ich.org

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Clinical trial of investigational medicinal products (CTIMP)

These clinical trials involve the use of a drug which is either new or being used in a new way. Drugs may be **investigational medicinal products** (IMPs) during one part of a trial, e.g. when being used in a new way, but not in another part, e.g. when treatment is the same as current standard of care.

EudraCT number

European Clinical Trials Database (EudraCT – https://eudract.ema.europa.eu/) was established in 2004 to give a unique reference number to all clinical trials in the European Union and wider European Economic Area, involving IMPs. It provides a single point of reference for all regulatory, licensing and scientific bodies to allow identification of clinical trials data being conducted across international borders. It also establishes clear lines of communication allowing timely pharmacovigilance reporting. Finally, it helps ensure strong links between regulatory authorities and trials which include a **paediatric investigation plan** (**PIP**).

Paediatric investigation plan

Pharmaceutical companies applying for a new marketing authorization must demonstrate that they have, where it is reasonable to do so, investigated the specific formulation and use of a new drug for children. Their plan to do so is submitted to the European Medicines Agency as a PIP. Companies registering a PIP are eligible for extended patent rights.

Pharmacovigilance

The process of identifying, reporting and acting on adverse drug reactions seen with drugs used at appropriate doses. Rapid reporting, centralization of data collection and rapid response are critical factors in preventing recurrent toxicity, especially in early phase/first-in-human trials.

parent can consent, it would not be appropriate to enrol a child in a clinical trial if either parent, or the child, did not give their consent or assent, respectively.

Refusal of participation

An important part of the consent process is for the young person and their family to understand that they have the absolute right to refuse to participate in a clinical trial. So as to avoid any coercion, the consent process must include explicit discussion of the fact that refusal will not affect the standard of care a young person receives in any way. Some families will have very valid concerns about trial involvement which must be respected, whether or not the research team agrees with them. The rights of trial subjects remain paramount. Similarly, the right to withdraw from the trial at any point and without needing to explain why must also be explained. Again, it is important that families understand that it will not affect their child's treatment, with the caveat that the child will receive standard care and not any further trial therapies or interventions.

Randomization

The gold standard approach for assessing the benefit of a new investigation or treatment approach is a *randomized controlled trial* (RCT). In this setting, each patient is randomly allocated to receive either standard therapy/placebo or the new treatment. This removes the potential for biasing the outcome by allocating one particular group of patients, e.g. a more severe pattern of disease, to one arm or other. Minimizing bias is considered in Chapter 39, Evidence-based paediatrics.

Difficulties can arise if the randomized intervention begins right at the beginning of the trial. Young people and families can find it hard to agree to give up control of an aspect of their care, especially if the disease is severe or of sudden onset and the new diagnosis accompanied by many other stresses and emotions (Box 37.13). An explanation of the need to randomize as well as the fact that, whilst we hope the new intervention will prove beneficial, we also need to be aware that it might not be as effective or even potentially harmful, is essential. For some families, entry into a

clinical trial is not the right thing at the point of diagnosis and this must be respected.

Biobanking – opportunity for active participation

Many trials will require the collection and storage of tissues for associated biological studies. Young people and families may also be asked whether they would be willing to allow residual diagnostic tissue to be stored prospectively for future studies, in an organized biobank. Biobanking offers young people a safe way to contribute to future research into their condition, something which is frequently welcomed. Biobanking is particularly important in paediatric research, where many conditions are rare and prospective collection forms the only realistic opportunity to acquire sufficient samples for meaningful research.

Monitoring of a trial

Question 37.4

Clinical trials terminology

The following (A–J) is a list of terminology used in clinical trials:

A. Data monitoring committee
B. EudraCT
C. Good clinical practice
D. Institutional Review Board
E. Investigational medicinal product
F. Medicines Healthcare Regulatory Authority
G. Paediatric investigation plan
H. Serious adverse event
I. Sponsor
J. Suspected unexpected serious adverse reaction

Which item of terminology best describes each of the following:

1. The body bearing overall legal and financial responsibility for the design, conduct, analysis and reporting of a clinical trial.
2. A serious untoward event which, from our current knowledge, was not predictable but which is believed to be as a direct consequence of a trial intervention.
3. The body responsible for regular analysis of data from an ongoing trial. Their task is to ensure that the trial has not reached its predefined endpoint in advance of final recruitment and that no unforeseen detrimental effects can be identified.

Answers 37.4

1. I. Sponsor. The sponsor is a pharmaceutical company, funding body or academic institution which bears overall responsibility for a specific trial.
2. J. Suspected unexpected serious adverse reaction (SUSAR). A suspected unexpected serious adverse reaction is defined by the fact that it was unexpected, serious and is suspected as being a direct adverse reaction to an intervention (e.g. a new drug) in contrast to a serious event which may have nothing to do with any intervention within the trial.
3. A. Data monitoring committee (DMC). The DMC is responsible for regular analysis of incoming data returns to ensure that a predetermined treatment effect or unacceptable toxicity has not been seen before the recruitment target is met. This ensures that unexpectedly large treatment effects, both positive and negative, are identified early, minimizing the number of patients given suboptimal treatment.

Safety monitoring

Once a trial protocol has been decided on, the appropriate approvals granted and the first patients recruited, an ongoing process of safety monitoring is required to identify any adverse reactions resulting from the intervention. Clear routes of communication are required to ensure that any severe or unexpected adverse reactions are rapidly reported and acted upon, potentially by suspending the trial or use of the novel intervention. Different types of notifications exist, namely serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs). By their nature, SUSARs cannot be defined but clarification on what constitutes an SAE should be included within the trial protocol.

Serious adverse events

Serious adverse events are experiences related to the trial interventions (either standard or investigational arms) which result in death, serious illness or injury, admission/prolongation of admission to hospital or congenital anomaly/birth defects. They must be reported to the chief investigator within 24 hours. Other serious events should be discussed with the chief investigator in case they qualify for notification.

Framed PICO research question: In premature infants [population], does targeted low (85–89%) [intervention] versus high (91–95%) [control] functional arterial oxygen saturation (SpO$_2$), affect death or severe neurosensory disability on assessment 2 years after the child was due to be born [primary outcomes] or rates of retinopathy, chronic lung disease, weight gain [secondary outcomes]?

Method: Randomized controlled trial. The UK BOOST-II trial aimed to recruit 1200 babies. Four other trials with similar protocols and outcome measures were also run in the US, Canada, Australia and New Zealand. As none of the trials was powered to reliably demonstrate a difference in the primary outcome on its own, a collaboration was agreed between the data monitoring committees to confidentially share interim data to allow a prospective meta-analysis.

Discussion: Unpublished data from the US trial (SUPPORT Trial) showed a marginally significant (p<0.04) reduction in survival in infants whose oxygen saturations targeted the lower 85–89% range. Each of the other DMCs analysed the US data alongside their own national data but found

no evidence to support ending recruitment to the other trials. However, no agreement could be reached about pooling data from all trials. Shortly afterwards, DMCs from the UK, Australia and New Zealand did combine their data and were able to demonstrate a significantly worse mortality at 36 weeks in the group targeting 85–89% saturations. This trial therefore closed early after recruitment of just 973 UK babies, and advised that neonates born at <28 weeks' gestation should not have oxygen saturations targeted to 85–89%.

This example highlights the importance of interim data analysis by independent committees, as well as the importance of international collaboration, both at the trial design and analysis stage. By using all the available data, including unpublished data, a survival benefit was identified earlier, thus accelerating the development of practice and preventing unnecessary recruitment into a trial arm with inferior outcome.

Reference: BOOST II United Kingdom Collaborative Group. Oxygen saturation and outcomes in preterm infants. New Engl J Med 2013:368;2094–104.

Suspected unexpected serious adverse reactions

SUSAR reporting exists to ensure rapid identification of previously unidentified side effects of an intervention. Typically these will be side effects potentially attributable to a new drug or formulation. SUSARs must be notified to the chief investigator within 24 hours and thereafter the chief investigator must notify the MHRA.

Interim analyses and stopping rules

Whilst the trial design, and particularly the power calculation, have estimated the number of children required to achieve a significant result, these estimates are based on the expected magnitude of the effect of the intervention. If the magnitude observed is substantially greater than expected, or an unexpected effect occurs, then a significant result may be achieved before full recruitment is reached. Alternatively, if the trial intervention is associated with an increased toxicity then this must be identified and the trial reviewed and potentially stopped. Commonly, the trial protocol will define the desired level of outcome, as well as any other criteria which, if met, would indicate a need to stop a trial.

In order to monitor for both early successful completion of a trial and adverse outcomes, trials will appoint a data monitoring and ethics committee (DMC/DMEC) who meet at defined intervals to analyse the data received so far. With phase I trials, commonly the committee will meet following administration of a single dose level and decide whether or not to proceed to the next dose level. During this period, enrolment to the trial will usually be suspended. With larger phase III trials, this can be a rolling process which may result in either early closure or amendment of the trial protocol (Box 37.14).

Follow-up and data analysis

Depending on the trial question, as much important information may be collected after the intervention has been completed as during it. For this reason, having a robust mechanism for follow-up is critical. Data can be analysed at specified time points and reported. Whilst there is ongoing data collection and analysis ahead of final publication and development of the next trial, clinicians may need to know whether the current standard treatment remains the gold standard. Commonly a set of *interim guidelines* will be produced defining the perceived new standard therapy based on, for example, interim analyses by the data monitoring committee.

Follow-up

Critical to the success of a trial is achieving as full follow-up of enrolled patients as possible. Loss to follow-up is a major potential source of bias, with patients experiencing unpleasant side effects or perceived poor outcome from their therapy being most likely to drop out. Rigorous attempts to achieve complete follow-up are therefore important, as is consideration of degree of follow-up when assessing the results of published trials. The numbers of patients assessed at each time point, as well as any systematic reasons for lack of assessment must be reported with the trial results to allow accurate interpretation.

As deviations from protocol, withdrawal from trial and loss to follow-up can all introduce bias to a study, all data must be analysed based on the original allocation of a patient. This principle is called analysis on an intention-to-treat basis.

Statistical testing

Statistical analysis of trial data is perhaps the most important yet least well understood area of clinical trial methodology (see Chapter 38, Statistics). Many statistical analyses rely on performing a test of the probability that the result of the trial was achieved by chance alone. They ask the question: 'Is a particular parameter, such as mean or proportion over a threshold, sufficiently different between these samples that the populations from which they are drawn can be assumed to be different also?' The probability is described as the p-value associated with the statistical test performed. A value of $p \leq 0.05$ means that the observed difference between samples could have occurred by chance alone with probability equal to or less than one in twenty, or 5%. Although there are many different statistical tests, only a handful would be applicable to the analysis of a particular data set. The issue to be addressed at this stage of data analysis is: 'What is the most appropriate test to apply to any particular data set?'

Good statistical analyses should start with simple descriptive statistics of the data set which, in reality, represents only a sample of the entire population of children with that condition who might receive a particular intervention. If the data are continuous, the following questions are all pertinent:

- What is the central position of the data (commonly expressed as an average – mean, median, mode)?
- What is the dispersal of the data around the average (standard deviation)?
- How are the data distributed?
- Are the data symmetrical?
- Are there outliers?

If the data are categorical (yes/no data, for example), similar sorts of questions maybe asked. Also, extremely important in the early stages of any analysis is to display the data graphically.

Having described and presented the data graphically, the next critical question is which statistical analysis to perform, e.g. Student's t-test, Mann–Whitney U test, regression analysis, confidence intervals (see Chapter 38, Statistics). Many of the available analyses will only be suitable in a proportion of cases, which may be defined by a number of assumptions. These assumptions must be examined before being able to choose the appropriate test for each analysis. Non-parametric tests make no assumptions as to the nature of the data, making them broadly applicable, but in general they pay the price of having reduced power and therefore being less likely to provide a result which allows the investigator to confidently reject the null hypothesis. Again, considering the appropriate analysis and making an open statement of it in the trial protocol provides confidence in the approach taken and the veracity of the final result.

One final consideration is that of multiple testing. If multiple tests are performed to search out significant differences, then one result in every twenty tests performed will be 'significant' ($p \leq 0.05$) by chance alone. Two approaches are commonly used to avoid such difficulties. Firstly, it is possible to apply statistical corrections to allow for multiple testing. Frequently, however, these rely on increasing the stringency of the test making identification of a true difference more difficult. The second approach is to reduce the number of tests performed by targeting the data analysis towards the primary and limited secondary outcome measures, as clearly stated in the initial protocol. As discussed above, this approach reduces the risk of incorrectly rejecting the null hypothesis (type 1 error, α), whilst maximizing the chance of correctly accepting the alternative hypothesis (thereby avoiding type 2 error, β).

If an appropriate test is applied to accurately obtained data, then it is reasonable to draw conclusions on the basis of a p-value ≤ 0.05. This, however, does not tell you anything about the clinical relevance of the result. A large enough sample size from a tightly dispersed population can provide a statistically significant result for an intervention resulting in minimal change in outcome. The clinical relevance must be assessed by considering the size of the effect and a confidence interval for that effect. The importance of this must then be considered in the setting of side effect profiles, dosing regimen, impact on patient's life, economic cost and so on. This can be considered as the *clinical significance* of a trial result, distinct from the statistical significance.

CONSORT – consolidated standards of reporting trials

This statement encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomized controlled trials. The main product of CONSORT is the CONSORT Statement, which is an evidence-based, minimum set of recommendations for reporting randomized trials. The CONSORT 2010 Statement includes a 25 item checklist to provide guidance for reporting all randomized controlled trials.

Even if you are not planning on undertaking an RCT, the CONSORT Statement makes a useful tool for critically appraising RCTs that you are hoping to implement into your clinical practice.

Further reading: http://www.consort-statement.org

Trial reporting

New findings derived from a clinical trial can only be critiqued and subsequently acted upon if they are widely disseminated. This should include peer-reviewed publication of trials with both positive and negative findings (Box 37.15). Whilst publishing positive findings of well-designed trials should be straightforward, publishing negative findings is more complicated, both because these studies have lower priority for high quality peer-reviewed journals and because there can be reluctance to publish the failure or poor side-effect profile of a new drug. Prospective open access registration of CTIMPs (discussed above), including their stated primary outcome measures, is critical to allow thorough analysis of trial outcome, avoiding poor practice such as reporting only:

- Secondary outcome measures
- Surrogate markers of outcome, not primary outcome measures
- Subgroup analysis not pre-defined in protocol (see discussion on multiple statistical testing, above)
- Event-free survival only, not overall survival (where this would be more appropriate)

Additionally, only by publishing all outcomes can systematic review and meta-analysis of clinical trials be used to answer clinical questions which individual studies are unable to address.

Influence on practice

The clinical significance of trial outcomes is harder to assess than the statistical significance, but is critical to ensuring that appropriate changes to practice are made in response to evidence. Responses may include the development of a subsequent clinical trial, e.g. phase I results being developed into the subsequent phase II trial, or development of the next phase III study based on the new standard of care defined by the preceding trial. In this second example, there may be a period when the initial analysis of the phase III study allows the formation of an interim guidance statement, ahead of the development of the subsequent phase III protocol. Such an approach is commonly used in paediatric haematology/oncology, when a clear survival advantage has been shown in one study arm.

Question 37.5

PICU consortium trial of a new drug

Scenario: A paediatric intensive care (PICU) consortium wants to establish a trial to investigate the role of a new immune-modulating drug in children with sepsis.

Framed PICO (population, intervention, comparison, outcome) research question: In children who present to a PICU with sepsis associated with multiple organ dysfunction [population], is an immune-modulating drug [intervention] compared to standard PICU care [control], effective at reducing mortality and/or hastening recovery [outcomes]?

Discussion: This drug has not been used in this setting in children before and the potential risks of immune stimulation in sepsis are unclear. *In vitro* studies and animal models of sepsis suggest that the drug results in activation of the innate immune system and improved bactericidal activity. Optimal dosing has not been determined in children but early phase trials in adults suggest the drug can be safely administered although an optimal dosing schedule has not yet been determined.

Which of the following statements most accurately describes the position of the consortium?

Select ONE answer only.

A. Additional blood samples should not be taken for associated fundamental science studies.

B. A phase III clinical trial is required to demonstrate superiority over standard PICU care.

C. An early phase I/II clinical trial should be designed to establish safety and appropriate dosing.

D. Children admitted to PICU are too unwell for adequate consent for this clinical trial to be obtained.

E. Collection of a range of demographic and admission-specific data on all patients will allow multivariate analysis to determine which patients are most likely to benefit from the new drug.

The interpretation of clinical significance is reviewed in detail in Chapter 39, Evidence-based paediatrics.

Future clinical study approaches

Personalized medicine

As we improve our understanding of the molecular subclassification of disease, there is a strong drive to deliver therapies appropriate to an individual patient's disease. Further personalization will include predictions of a patient's handling of a drug or susceptibility to drug toxicity. Indeed, in paediatric oncology, prospective analysis of thiopurine methyltransferase (TPMT) variants and phenotype have been used for many years to guide dosing of 6-mercaptopurine.

Other important components of personalizing medicine can be defined:

- *Stratified medicine*: Subdividing patients according to the genetics or molecular biology of their disease so that appropriate targeted therapies can be given (Box 37.16).
- *Biomarkers*: Described in Box 37.3, biomarkers are features which describe a characteristic of a patient, allowing their disease and subsequent therapy to be stratified. That is to say, a characteristic which allows individualization of their treatment.

Box 37.16 Research approaches to stratified medicine

One consequence of stratifying diseases is that trial subgroups are becoming smaller, often within already rare diseases. Alternative approaches to the classical randomized controlled trial are being taken, both to match the treatment to the 'molecular' disease and to reject ineffective drugs and accommodate potential new drugs without stop/starting the trial. The strategies used are bespoke to each trial and currently most prevalent (although still uncommon) in adult oncology practice, where examples include Focus4 and Stampede trials. As these approaches become better understood, along with the supporting statistical analyses, it seems likely that they will be increasingly applied to paediatric studies too. This will require validated genetic/molecular assays which can be robustly delivered in a clinically relevant time frame.

Further reading:

http://www.focus4trial.org/
http://www.stampedetrial.org/

Box 37.17 Targeted therapies – salbutamol

One of the very first therapies rationally designed to specifically target an active pathway was the widely used asthma medication, salbutamol. Increasingly selective blockade of the β_2 adrenoceptor was achieved by sequential modifications of the adrenaline analogue isoprenaline, resulting in effective relaxation of bronchial smooth muscle tone with reduced cardiovascular side effects.

- *Targeted/precision therapies*: Drugs designed to, usually, inhibit specific molecular pathways which have been demonstrated to be overactive in a particular disease (Box 37.17). Particularly prevalent in modern medical oncology, targeting disease-specific pathways is hoped to provide better disease control with fewer side effects than standard cytotoxic chemotherapy, which broadly 'targets' all dividing cells.

Experimental medicine

Experimental medicine (EM) is an:

Investigation undertaken in humans, relating where appropriate to model systems, to identify mechanisms of pathophysiology or disease, or to demonstrate proof-of-concept evidence of the validity and importance of new discoveries or treatments.

MRC Research Initiatives

Table 37.4 Omics technologies and their uses

Omic study	Analyses	Technologies
Genomics	Genetic sequences – specific targets, coding sequences or whole genome	NGS – large number of platforms
Epigenomics	Chromatin modifications	NGS-based approaches
Methylomics	Example of epigenomics specifically looking at DNA methylation	Array or NGS-based approaches
Transcriptomics	Expression of all genes by measuring mRNA	Array or NGS-based approaches
Proteomics	Protein levels. Can be adapted to measuring activated proteins, e.g. phosphoproteomics	Western blotting, immunohistochemistry, ELISA (analysis of a small number of proteins), mass spectrometry (large scale protein determination)
Metabolomics	Metabolic signature of disease process or treatment effect	Very broad range including chromatography, mass spectrometry and nuclear magnetic resonance spectroscopy

NGS, next-generation sequencing used for massively parallel sequencing of DNA or RNA.

As such, it is performing experiments, in humans, to discover the cause of a disease or to test the validity and importance of new treatments. It is increasingly considered an important element of early phase clinical trial design, feeding back to ongoing pre-clinical studies and informing subsequent later phase trials (see Fig. 37.1).

- EM makes best use of all data available from the most representative model system available, namely early phase clinical trials in humans
- Careful consideration must be given to the clinical and ethical implications of multiple sampling from children
- Comparisons made with pre-clinical models (described above) can highlight differences between model and human and lead to development of improved pre-clinical strategies
- Information on the effectiveness of/resistance to a drug can alter treatment combinations
- The utility of biomarkers can be assessed

Clinical 'omics'

The tools required to dissect the molecular features of both a young person and their disease are becoming increasingly commonplace in fundamental/pre-clinical research and the translation of their use for diagnostic purposes is increasing. Snapshots of the genome made available by next-generation sequencing are complemented by additional 'omic' technologies, which have the power to analyse vast numbers of molecular changes in parallel (Table 37.4). Again, substantial challenges remain in the analysis and interpretation of data, both in populations and also, critically, in individual patients too.

Further reading

Academic Paediatrics Association (APA). <http://www.academicpaediatricsassociation.ac.uk/>; [accessed 10.09.15]. UK association promoting the development of academic paediatrics and child health.

Federation of American Societies for Experimental Biology (FASEB). Funding basic science to revolutionize medicine – 2013 FASEB Stand Up for Science (winner). <www.youtube.com/watch?v=GmhD-RWNL6c>; 2013 [accessed 10.09.15]. Because it is not all about translational and patient-centred research!

General Medical Council (GMC). 0–18 years: guidance for all doctors. <http://www.gmc-uk.org/static/documents/content/0-18_years_-_English_1015.pdf>; 2007 [accessed 10.09.15]. Specifically Paragraphs 36–40 focusing on research.

Medical Research Council (MRC). <http://www.mrc.ac.uk/research/>; [accessed 10.09.15]. Describes some of the major driving initiatives in current clinical research.

Medical Research Council (MRC). Experimental medicine. <http://www.mrc.ac.uk/research/initiatives/experimental-medicine/>; [accessed 10.09.15].

Royal College of Paediatrics and Child Health (RCPCH). Turning the tide: harnessing the power of child health research. <http://www.rcpch.ac.uk/harnessing-the-power-of-child-health-research>; 2014 [accessed 10.09.15]. Describes the Colleges recommendations to develop child health centred research and promote academic training in the UK.

World Health Organization (WHO). International clinical trials registry platform (ICTRP). <http://www.who.int/ictrp/en/>; [accessed 10.09.15].

Miriam Fine-Goulden, Victor Grech

Statistics

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Know about the different ways in which data can be categorized and displayed
- Understand frequency distributions and features of a normal distribution
- Know how to describe different types of data
- Know what confidence intervals and p-values are and how they can be used
- Understand about the application of appropriate statistical tests
- Understand how to interpret statistical results in clinical and epidemiological studies
- Understand the limits of statistical tests

Introduction

Statistics are 'a body of methods for making wise decisions in the face of uncertainty' (W Wallis: *A New Approach*, 1957).

As doctors, it is essential for us to have an understanding of statistical principles and methods so that we can:

- Conduct research
- Interpret data
- Appraise evidence
- Apply and explain results to patients and families.

Other sections in this book describe research, evidence-based medicine and epidemiology. This chapter will cover the fundamentals of statistics that will provide the tools to navigate the world of clinical and epidemiological research and appreciate its scope and limitations.

While all tests are carried out using software packages, readers of journals and researchers need to know which test to implement and understand what the programme is doing and what sort of output to expect.

Types of data

Statistical methods can be applied to *quantitative* data, a set of numbers and values that have been measured. The type and/or method of recording of quantitative data is important since it influences the choice of statistical tests as well as the way in which the data is described and displayed. *Qualitative* data, by comparison, is descriptive and usually represents an expression of thoughts, feelings or experiences. There are resources available which detail appropriate methodologies for analysing qualitative data, but this will not be covered in this chapter.

Quantitative data (also referred to as *variables*, i.e. a characteristic, number or quantity that differs between individuals or items) can be *numeric*, in which a number is recorded, or *categorical* (Fig. 38.1).

Numeric data, in which a number is recorded, can be further subdivided into discrete or continuous datasets:

- *Discrete data* can only be expressed in whole numbers; for example, number of children per family or number of episodes of severe asthma per year.
- *Continuous data*, on the other hand, can take any value in a given range. For example, height, weight or age.

  Categorical data can be:

- *Binary data* – in which there are only two categories; for example, alive/dead or a yes/no response.
- *Ordinal data* – which is in groups that can be ordered; for example, social class 1–5 or grades of bowel cancer.
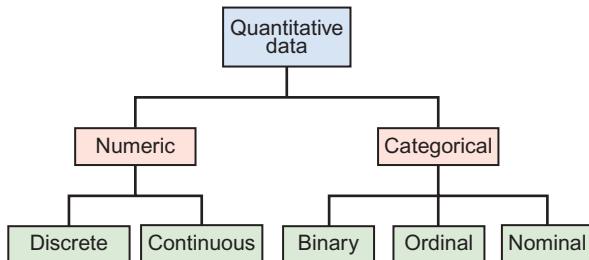
Fig. 38.1 Types of quantitative data.

- *Nominal data* – constitutes a number of groups with no order/hierarchy; for example, blood group or marital status.

Displaying data

The best method for displaying data depends on the type of data and the number of variables and datapoints. A good pictorial presentation of data can be an extremely effective and efficient means of communication. It is also crucial to plot the data:

- In order to ensure that there are no obvious errors, e.g. gross outliers, which may have been due to erroneous data collection or inputting mistakes

Fig. 38.2 Deaths by cause, percentage of total, and numbers, among 5–9-year-olds in the UK, 2010. This chart type gives a simple visual representation allowing the reader to picture all categories at once and compare their relative proportions. *(Adapted from Wolfe I, et al. Why children die: death in infants, children and young people in the UK. May 2014, RCPCH and NCB.)*

Question 38.1

Displaying statistical data

Following is a list of methods of displaying data:
A. Bar chart
B. Box-and-whisker plot
C. Dot diagram
D. Histogram
E. Line diagram
F. Pie chart showing percentages
G. Pie chart showing actual numeric values
H. Scatterplot

For each of the following case scenarios, select the most appropriate graphical depiction method from the list above.

1. A sample of 1000 seven-year-old male schoolchildren undergo BMI testing.
2. Smoking in pregnancy. Results of a survey of mothers: 1 to 3 cigarettes/day = 31; >3/day = 44; do not smoke = 856; unspecified = 44.
3. Analysis of mode of delivery in a group of mothers: 596 normal vaginal deliveries, 318 by caesarean section and 35 by assisted vaginal delivery.

Answers 38.1

1. D. Histogram.
2. A. Bar chart as not a continuous variable.
3. F. Pie chart showing percentages
   See below for details.

- To understand the shape, scope and overall nature of the data
- To identify any interesting patterns.

Tables

Tables are a useful way to summarize and present data and can usually provide more precise numerical data than a graph.

Pie charts

Pie charts are used to demonstrate proportions of a group falling into different categories. A circle is divided into segments, and the angles are proportional to the size of each category (Fig. 38.2).
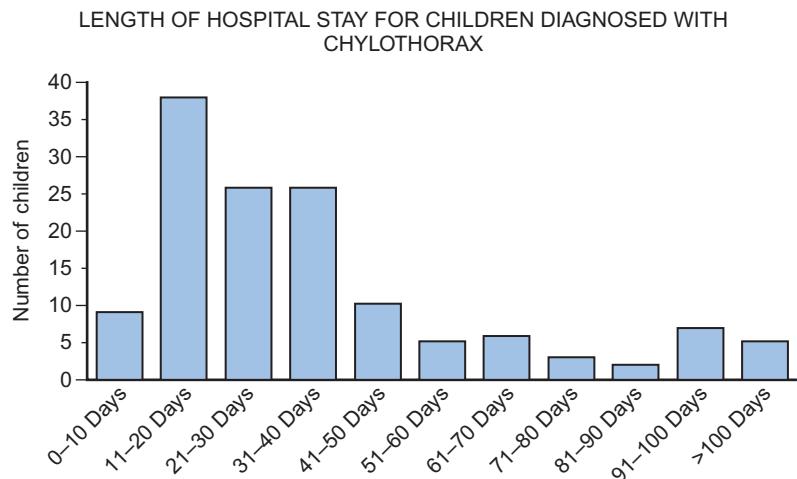
Fig. 38.3 **Length of hospital stay for children diagnosed with chylothorax.** *(Adapted from Haines C, Walsh B, Fletcher M, et al. Chylothorax development in infants and children in the UK. Arch Dis Child 2014;99:724–30.)*
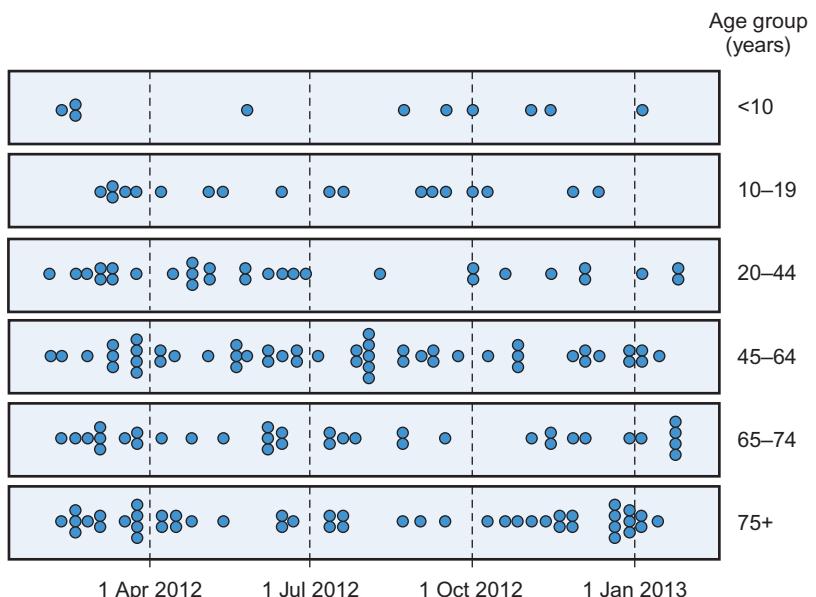
Fig. 38.4 **Asthma deaths over time by age group (n** = **193).** *(From Royal College of Physicians. Why asthma still kills: the National Review of Asthma Deaths (NRAD) Confidential Enquiry report. London: RCP, 2014, with permission.)*

Bar charts

Bar charts (Fig. 38.3) can be used to display a single variable, with the heights of the bars proportional to the frequency. They may also show the relationship between two variables by being grouped or stacked.

Dot diagrams

Dot diagrams (Fig. 38.4) can be used to display continuous numeric data for a variable, for a single group or multiple groups. Each dot represents a single value. It is a simple method of conveying as much information as possible, and it is easy to see outliers and to compare the distribution of results in different groups,

but it may not be practical where there are large numbers of measurements.

Line diagrams

When measurements are repeated at different time points, for example, before and after a certain treatment, lines drawn between paired dots (Fig. 38.5) can illustrate measurements or the effect of intervention/treatment.

Scatterplots

Scatterplots (Fig. 38.6) illustrate the relationship between two continuous variables, represented on

vertical and horizontal axes. Scatterplots may include a line of best fit (see Correlation and regression, below).

Box-and-whisker plots

Typically, the line in the middle of the box represents the median value, the upper and lower horizontal lines of the box represent the upper and lower quartiles and each contain 25% of the values, so the box encompasses 50% of the values. The limits of the whiskers represent the highest and lowest values (i.e. the range) and each whisker encompasses 25% of the values (Fig. 38.7).
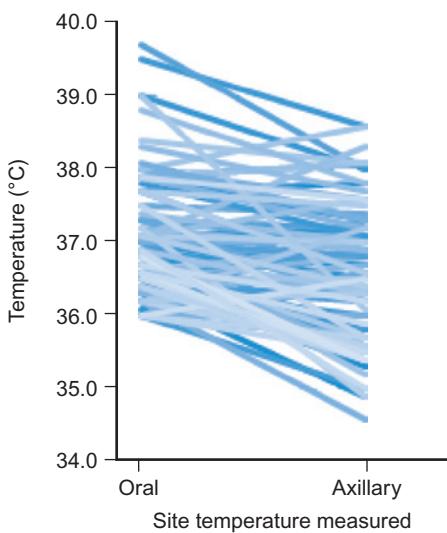
Fig. 38.5 Paired axillary–oral temperatures. Same measurement on each patient. First 100 patients aged 4–14 years. *(Data from Falzon A, Grech V, Caruana B, et al. How reliable is axillary temperature measurement? Acta Paediatr 2003;92:309–13.)*

Describing data

Frequency distributions

The normal distribution is symmetrical and bell-shaped (Fig. 38.8). It is a familiar concept in medicine, as much of the data collected from human subjects is normally distributed, e.g. height and weight.

Data that has a non-normal distribution may be skewed, to the left or to the right. A good example of skewed data in medicine is length of hospital stay: most patients stay for a short period of time, but a small number of patients stay for an extended period, pulling the 'tail' of the distribution to the right.
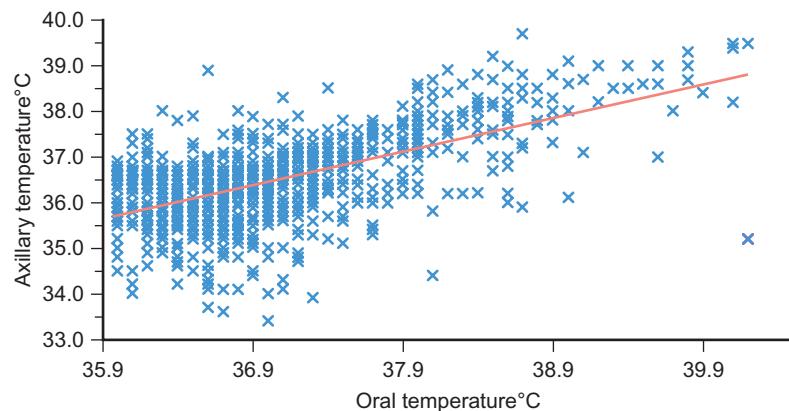
Fig. 38.6 Scatterplot of paired axillary–oral temperatures. Same measurement on each patient. Patients aged 4–14 years. 112 children during the course of their admission to hospital. *(Data from Falzon A, Grech V, Caruana B et al. How reliable is axillary temperature measurement? Acta Paediatr 2003;92:309–13.)*

Tests of normality and data transformation

Whether or not a set of data is normally distributed may be important when it comes to applying statistical tests, as some tests are only valid for normally distributed data. It may be possible to tell if data is normally distributed by 'eyeballing' it in graphical form. There are also mathematical tests that can be applied. These cannot confirm that the data are normally distributed, but can confirm that they are compatible with a normal distribution. In some cases, non-normally distributed data can be 'transformed', for example by logging or squaring, to take on a normal distribution so that certain statistical tests can be applied. The method used is determined by the nature of the data.

Tests that rely on the data being normally distributed are known as *parametric* tests. If datasets are large but not normally distributed, parametric tests may still work well: a property known as *robustness*.

Tests which make no assumptions about the normality of the data distribution are called *non-parametric* tests. These are almost as efficient as parametric tests for normally distributed data and superior for non-normally distributed data.

Mean and median

The *mean* – or average – is a familiar concept. It is calculated by adding up all the values and dividing by the total number of values. For example, the mean time (in minutes) from triage to assessment by a doctor for ten children with fever ≥40°C in an emergency department is the total of all the values divided by ten:

Group 1 mean:

$$\frac{39 + 22 + 48 + 11 + 19 + 33 + 42 + 27 + 28 + 31}{10}$$

$$= 30 \text{ minutes}$$

The mean is a useful measure of the centre where values are normally distributed or close to normally distributed, but it can be affected dramatically by one or two extreme values. For example, in the group

Fig. 38.7 Diagrammatic explanation of box-and-whisker plot.

Labels: Highest value in series; Whisker (25% of values); Upper quartile (25% of values); Median; Lower quartile (25% of values); Whisker (25% of values); Lowest value in series.
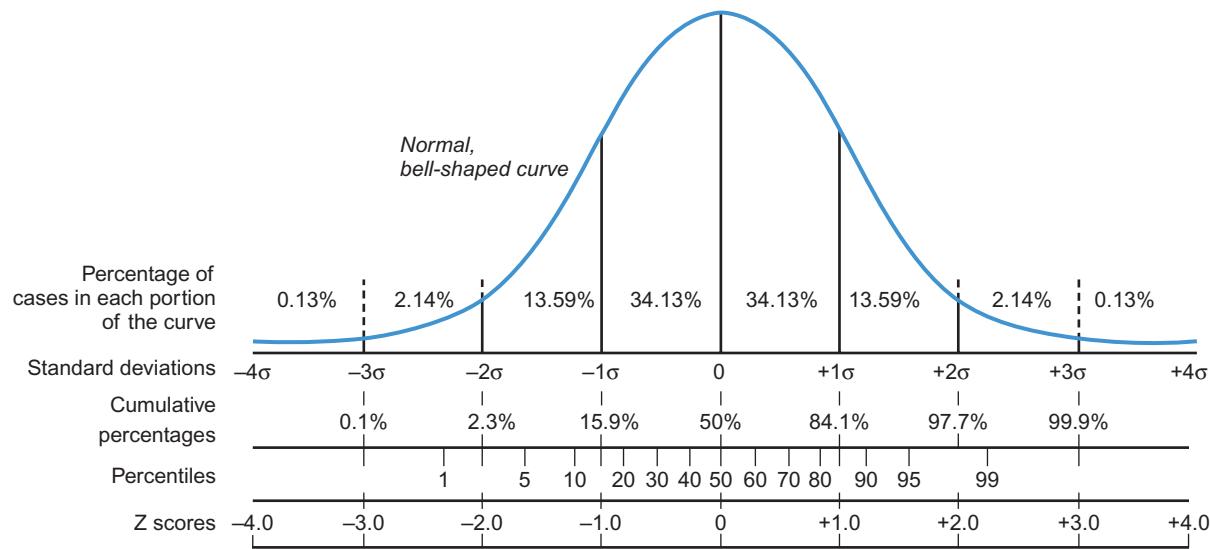
Fig. 38.8 A normal distribution bell-shaped curve with percentage of cases in 8 points of the curve, standard deviations, cumulative percentages, percentile and Z scores. Data that has a non-normal distribution may be skewed, to the left or to the right.

Percentage of cases in each portion of the curve	0.13%	2.14%	13.59%	34.13%	34.13%	13.59%	2.14%	0.13%
Standard deviations	−4σ	−3σ	−2σ	−1σ	0	+1σ	+2σ	+3σ	+4σ
Cumulative percentages		0.1%	2.3%	15.9%	50%	84.1%	97.7%	99.9%	
Percentiles			1 5	10	20 30 40 50 60 70 80	90 95	99		
Z scores	−4.0	−3.0	−2.0	−1.0	0	+1.0	+2.0	+3.0	+4.0

Normal, bell-shaped curve

above, if there was one child who waited for a long time because the doctor was unavailable, this could have a significant effect on the results:

Group 2 mean:

$$\frac{39 + 22 + 48 + 11 + 19 + 33 + 42 + 27 + 28 + 231}{10}$$

= 50 minutes

The *median* value is another measure of the centre, and it is the actual middle value (or the mean of the two middle values if there is an even number of values), so there will be the same number of values above and below it. The median is less influenced by skewed data than the mean. In the example above, the median value will be in between the 5th and 6th values (as there are ten values, an even number – if there were 11, it would be the 6th value).

Group 1 median:

11, 19, 22, 27, **28, 31,** 33, 39, 42, 48 = 29.5 minutes

Group 2 median:

11, 19, 22, 27, **28, 33,** 39, 42, 48, 231 = 30.5 minutes

The single large value that influenced the mean in group 1 did not have as much of an effect on the median.

In data that is normally distributed, the mean and median values will be the same; the greater the skew of the data, the greater the difference between the median and the mean. In non-normally distributed data, the median is therefore usually more representative of the centre than the mean. However, because the median is less sensitive to changes in the data, it may be a less useful summary measure. In a table summarizing data, it may be helpful to display both values.

Data spread

As well as giving an idea of the centre of the data, we also need to know about its spread, or variability, its *dispersion.* The *range* is the difference between the highest and lowest values. It is often given in brackets after the mean or median. For example, using our data for children with fever (above), 'the mean time from triage to assessment was 30 minutes (11–48)', or 'the median time for triage to assessment was 30.5 minutes (11–231)'. One problem with the range is that it is influenced by outliers (extreme values). It can also depend on sample size, as the larger the sample size, the greater the range is likely to be.

A measure of spread that is not sensitive to outliers is the *interquartile range*, as described above under Box-and-whisker plot.

The *standard deviation* is a measure of the spread of data around the mean. In normally distributed data, measurements will be either larger or smaller than the mean. Subtracting the mean from each value gives the difference between that value and the mean. Because the numbers below the mean will be negative (which is not important, because it is the actual difference that matters), all the numbers are squared (to make them all positive), and then added together.

If there is a wide spread about the mean, the values will all be very different from the mean, giving a large number, and conversely, if they are tightly grouped around the mean, the number will be small. The *variance* is the sum of all the squared differences divided by the total number in that sample minus one (so, for example, if there are 100 patient measurements in the sample, you would divide by 99 to get the variance). The square root of the variance is then obtained in order to 'unsquare' the value, and this is called the *standard deviation* (SD).

Therefore:

± 1 SD incorporates 68.2%
± 2 SD incorporates 95.4%
± 3 SD incorporates 99.7%
and
± 1.96 SD incorporates 95%
± 2.58 SD incorporates 99%

Z scores: One of the most frequently used measures for the presentation of results is the Z score (also known as the standard score). They represent the number of standard deviations of an individual data point from the mean. The Z score is calculated from the following equation $Z = (x − \mu) \div \sigma$ where x = the experimental value, μ = the mean and σ = the standard deviation. The calculation of a Z score assumes that the data being analysed is normally distributed, the data points are independent and random and that the sample size is greater than 30.

The mean and standard deviation are good measures of centre and spread in data that is normally distributed with a sufficient sample size. If not, it may be that the median and interquartile range are more appropriate descriptions of the data. The relationship between the normal distribution and a box-and-whisker plot is shown in Figure 38.9.

Confidence intervals

The 'confidence interval' defines the range of values within which the 'true' population mean is likely to lie.

i. *Research question*: Imagine you want to undertake a small research project to describe the serum vitamin
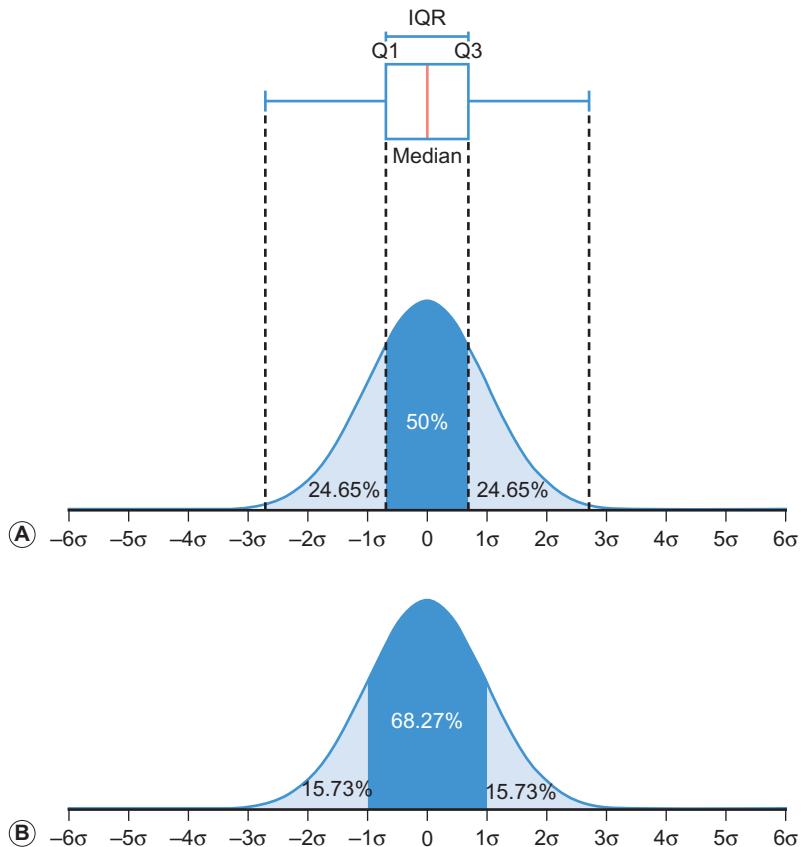
Fig. 38.9 Relationship between the normal distribution and a box-and-whisker plot. A. Median and interquartile range. B. Median ±1 SD and 3 SD.

D levels of urban UK secondary school children. You are aware that it would be impossible to measure the vitamin D level of all UK urban secondary school children and therefore identify one urban school within your county.

ii. *Methods*: There are 1000 children in the school, and your budget does not allow you to measure vitamin D levels in all of them. You therefore select (sample) 100 children at random whom you hope are a representative sample of all children within the school. One hopes that the sample is representative of the whole group (the cohort).

iii. *Results*: You find that the measurements are normally distributed and you therefore calculate a mean value for the vitamin D levels of your 100 selected children. Mean vitamin D = 21.9 ng/mL. You find a standard deviation of 5 ng/mL.

iv. *Discussion*: What if you had collected samples from 100 children who, by chance alone, just happened to have very high or very low vitamin D levels and

Box 38.1 Summary of calculation for SE and CI

Standard error (se) = standard deviation (SD)/
square root of sample size (n)

95% CI = mean − 1.96se, mean + 1.96se

are not actually representative of the whole school population, let alone the whole UK population? How do you know how close your (sample) mean vitamin D value is to the population mean vitamin D value, i.e. the value you would have obtained if you had indeed taken measurements from all 1000 children? This is what confidence intervals help you to estimate.

Confidence intervals are derived using the *standard error* (Box 38.1). The standard error tells you how close a sample estimate (e.g. the sample mean, in our case the mean of our 100 children) is likely to be to the population value (e.g. the population mean, in our

project the mean vitamin D level in all urban UK secondary children).

Using the example above, if we took, theoretically, ten different samples (groups) of 100 children from the school, we would get a range of mean vitamin D values for each group, and these mean values could each be plotted as a histogram with a normal distribution around the ('true') population mean. The degree to which each sample mean is likely to vary from the true population mean is the standard error. As expected, the standard error will be smaller with a larger sample size and where there is less variability of the measurements.

Standard error is calculated:

$$\text{Standard error} = \text{standard deviation (SD)} / \sqrt{\text{sample size (n)}}$$

Therefore, in our case:

$$\text{Standard error} = 5/\sqrt{100} = 5/10 = 0.5$$

This brings us back to confidence intervals, which define the range of values within which the 'true' population mean is 'likely' to lie. Because each of our sample means are normally distributed around the population mean, and in a normal distribution 95% of the values are expected to lie within 1.96 standard errors of the mean, the 95% confidence interval is calculated as follows:

- Lower limit = (mean − 1.96 × standard error)
- Upper limit = (mean + 1.96 × standard error)

The 95% CI is an accepted norm for most research studies, but if, for example, you wanted to calculate the 99% CI, you would have to multiply the standard error by 2.58.

In our example of normal vitamin D levels:

- Standard error = 0.5
- Mean = 21.9
- Therefore the confidence interval (CI) = 20.9–22.9 ng/mL.

The upper and lower limits of the confidence interval define the range within which you would expect to find the population mean 95 times out of 100. That means that 5 times out of 100, the population mean would be expected to fall outside of that range. We can therefore say that we would expect that the true mean of vitamin D levels in our single secondary school will fall between 20.9 and 22.9 ng/mL, 95 out of 100 times.

Regression to the mean

Regression to the mean is the tendency for a variable which is extreme – i.e. far from the average – to be closer to the mean if measured on a second occasion.

Question 38.3

Data analysis

A study aims to compare time trends of a specific illness in childhood.

Methods: A cross-sectional analysis of general practice national health returns from 350 practices during 2005 and 2010.

Results: The age–sex standardized incidence rate of the illness per 1000 patient years in 2005 for children aged 1–5 was 17.2 (95% confidence intervals (CI) 16.6–17.8) and for those aged 6–16 was 8.6 (95% CI 8.3–8.8). In 2010 it was 10.7 (95% CI 10.2–11.2) for children aged 1–5 and 6.3 (95% CI 6.1–6.3) for those aged 6–16. The number of prescriptions issued for the illness per 1000 patients aged 6–16 in 2005 was 357 (95% CI 355–357) and in 2010 was 368 (95% CI 366–370).

Given the data shown above which of the following statements is true? Select ONE answer only.

A. The change in incidence for children aged 1–5 is the same for both sexes.

B. The data can be used to calculate the course of the illness for any affected child.

C. The incidence of the illness studied has decreased in the 6–16 age group between 2005 and 2010.

D. The number of prescriptions issued for the illness has decreased between 2005 and 2010.

E. There has been no decrease in the incidence of the illness in children aged 1–5 between 2005 and 2010.

Answer 38.3

C. The incidence of the illness has decreased in the 6–16 age group between 2005 and 2010. The results show two clearly separated incidence levels and no overlap between the confidence intervals.

A is incorrect because no data is presented which separates the incidence between males and females. B is incorrect because this is a cross-sectional and not a longitudinal study. D is incorrect because the total prescription rates and confidence intervals overlap. E is incorrect because the results show clear separation of the incidence levels and no overlap of the confidence intervals.

p-values

As with confidence intervals, in order to apply evidence from research studies, it is vital to understand what p-values mean and, crucially, what they can and cannot tell us.

Testing for statistical significance involves setting up a *null hypothesis* (see Box 37.7) and measuring the

strength of evidence of the observed data against it. The null hypothesis is usually a statement of the effect of an intervention or of a difference between groups. It is a 'null' hypothesis because it assumes that there is no difference or no effect. For example, 'salbutamol nebulizers given in the emergency department have no effect on admission rates in children with acute asthma', or 'there is no difference in the birth weights between babies born to smoking and non-smoking mothers'.

When conducting studies, researchers set up a null hypothesis to test whether or not the data collected are consistent or not consistent with it. The next step is to choose the *significance level* of the statistical test that will be used (see below for different types of statistical test). A 95% significance level is conventionally selected. After data collection, the p-value is calculated using the appropriate statistical test. If the p-value is at or below the significance level, the null hypothesis is rejected: there is a statistically significant difference. If the p-value is greater than the significance level, the null hypothesis is accepted and there is no statistically significant difference.

A p-value therefore tells us *the probability of obtaining the data we have if the null hypothesis were true.* It helps to quantify the strength of evidence against the null hypothesis. If a p-value is 0.04, for example, if we were to conduct this study 100 times, then we could expect to obtain this result 4 times, or 4% of the time, if the null hypothesis is true, due to chance alone.

The p-value is equivalent to the *type 1 error rate*. A type 1 error occurs when the null hypothesis is rejected when it is in fact true (Box 38.2), i.e. when we conclude that there is an effect or difference where none actually exists, or a 'false positive'.

A *type 2 error*, on the other hand, occurs when the null hypothesis is accepted when in fact it is false (see Box 38.2), i.e. when we conclude that there is no effect or difference where one does in fact exist, or a 'false negative'.

Power and error

The *power* of a test is equivalent to type 1 minus the type 2 error rate. It is the probability that a test will produce a significant difference at a given significance level. For example, where the power of a statistical test is 80, if this statistical test was performed 100 times, it would miss the true difference 20 times out of 100. The power depends on the true difference between the two populations or intervention effects, the sample size and the significance level. For research studies, a power calculation is used to help determine the sample size that would be required to detect a difference at a certain anticipated, assumed or estimated level before a study is carried out.

> **Box 38.2 Examples of type 1 and type 2 errors**
>
> Two teams of researchers are working on answering a similar question: In a pre-school aged child with viral-induced wheeze [patient], is a course of five days of oral prednisolone [intervention] compared to placebo [control] effective at preventing admission [outcome]? The null hypothesis is that there is no difference between the two groups.
>
> Team A undertake their project but only blind the study to subjects and not to the medical staff, allocating the children to the intervention and control arm. Unconscious bias is performed in allocating the patients which results in the treatment arm being statistically significant (p <0.05). If a repeat study with improved methodology finds there is no difference between the groups, this shows that Team A have introduced a type 1 error.
>
> Team B undertake their project but are only able to recruit 200 children to each group, despite a power calculation suggesting they need 350 children in each group. The results show that there is no statistical difference between the two groups. The researchers therefore accept their null hypothesis. If a repeat study with 350 in each group reveals that there is a statistically significant difference between the two groups, then Team B have introduced a type 2 error.

Even when appropriate statistical tests are applied, if a study is underpowered there is a higher chance of making a type 2 error ('false negative'). Underpowered studies are those which have an insufficient sample size given the effect size and group variability. If a study fails to find a statistically significant difference, it may not be that there is truly *no effect*, rather that the study *fails to demonstrate* an effect.

Type 1 errors ('false positives') occur commonly in post-hoc analysis, where data is analysed after it has been collected in a way that was not specified at the start of the study. Researchers may 'fish' through their data, or 'data dredge', applying many different tests until they find a 'significant' result. Post-hoc analyses can be useful and may provide potential avenues of research for future studies, for example, when applied to subgroups of a large population. However, it should be clear which analyses were performed post-hoc, and the results interpreted with this in mind.

Statistical tests

In this section, we aim to summarize the most commonly used statistical tests, explaining which tests are appropriate in different situations, and provide better
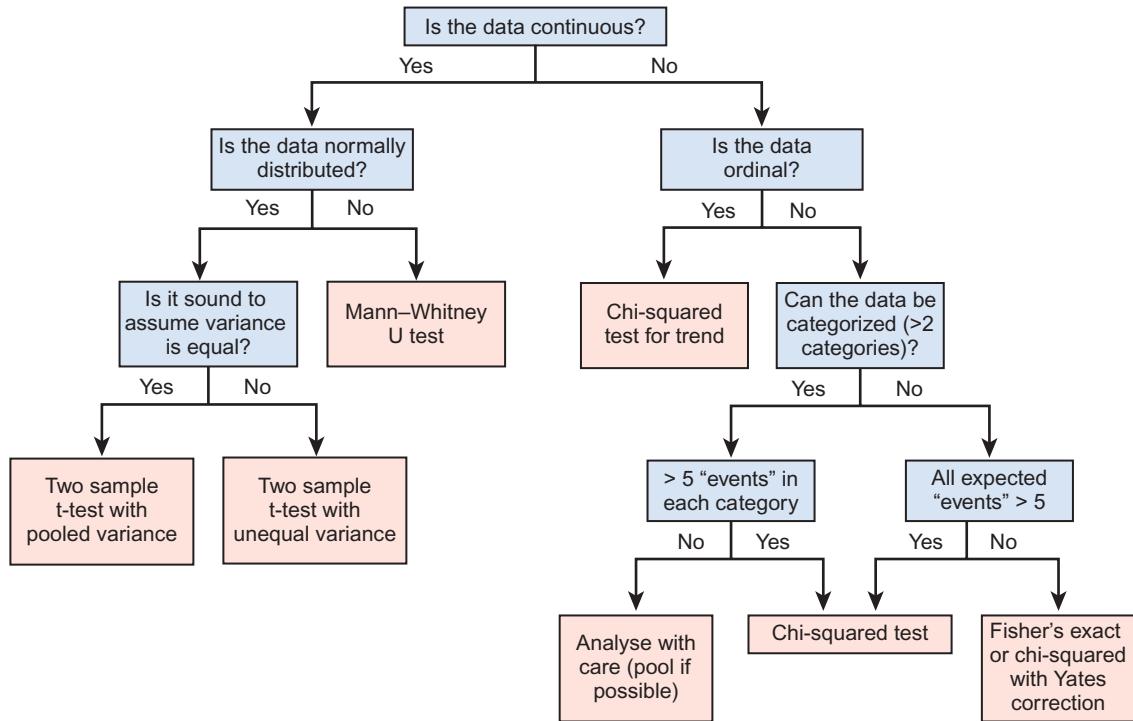
Fig. 38.10 **Statistical tests for comparing two independent groups of data.**

understanding of the statistical methodologies used in the research papers.

The choice of statistical test (Fig. 38.10) will depend on:

- The number and type of variables
- The quantity and distribution of the data.

The test performed is only valid if certain assumptions are met, and these are different for each test. There may be several possible tests that could be applied to any statistical problem; there is often no one 'right' test. However, even if it is valid to apply a certain test in a certain situation, it may not be the most appropriate or powerful. When planning a research study, seeking advice from someone with knowledge and experience of statistics is advisable.

Testing differences between groups

Differences between groups

The following is a list (A–J) of statistical tests:

A. Analysis of variance (ANOVA)
B. Chi-squared test
C. Chi-squared test for trend
D. Kruskall–Wallis ANOVA test
E. Mann–Whitney U test
F. Multiple linear regression
G. Multiple logistic regression
H. Paired t-test
I. Simple linear regression
J. Unpaired t-test

For each of the following case scenarios, select the most appropriate statistical test from the list above.

Each answer may be used once, more than once or not at all:

1. A sample of 1000 seven-year-old male schoolchildren undergo BMI testing. Their BMI is remeasured one year later to make a comparison.

2. A sample of 1000 seven-year-old male schoolchildren undergo BMI testing and are compared with another group of 1000 male children of the same approximate age from a school in another country.

3. A region experiences a large outbreak of invasive meningococcal disease. A retrospective study is carried out in order to identify which factors (e.g. initial platelet count, gender) were associated with survival/death.

Comparison between means, percentages or proportions

For large samples, we can calculate confidence intervals and p-values using standard equations and tables based on mathematical models of the normal distribution, applying the concepts discussed above. In the vast majority of cases, it is appropriate to calculate a *two-sided* p-value, which means that our results could go in either direction – for example, a new drug could be either better or worse than a pre-existing drug. Very rarely (certainly in medical research), a significant difference in one direction may be impossible or the direction of the difference is known with certainty, *a priori*, in which case a one-sided test could be applied, which considers only one tail of the distribution. Using a one-sided test, the null hypothesis is twice as likely to be rejected, so researchers must have very clear grounds for applying it.

T-tests

A t-test (sometimes referred to as 'Student's t-test') can be used in smaller samples with continuous data that is normally distributed, as it includes a modification allowing for the expected increase in chance variation occurring in smaller samples. However, the sample has to be large enough to estimate the population standard deviation.

A *one-sample t-test* is appropriate where a sample is compared to a known value. For example, you want to find out whether there is a difference between the birth weights of babies of UK-born mothers living in the UK and those of babies of UK-born mothers living in the USA. You may already know the mean birth weight of babies born to UK-born mothers living in the UK, and you want to compare the mean from your sample from the USA to see if there is a significant difference.

Two-sample t-tests, on the other hand, compare the sample means of two different populations. For example, the mean number of days of ventilation on PICU for infants with RSV bronchiolitis compared with infants with non-RSV bronchiolitis. In this example, an *unpaired test* would be appropriate, as the two populations are independent, i.e. infants with RSV bronchiolitis and infants with non-RSV bronchiolitis are two separate groups. If you are comparing the same group before and after an intervention, for example, then a *paired test* would be more appropriate. For example, a paired test was used to compare the paired oral and axillary temperatures (see Fig. 38.5), i.e. observations performed simultaneously on the same child.

Analysis of variance (ANOVA)

T-tests can be used when comparing the means of two groups that are normally distributed, but if three or more groups are compared, the appropriate test is an analysis of variance or ANOVA. For example, if you wanted to compare the change in weight from birth to six months of age in four groups of infants fed on different formula milks. Bearing in mind that the null hypothesis is that there is no difference between the means of the groups, a significant p-value derived by using ANOVA tells you that at least one of the groups has a mean that is more extreme (which could be larger or smaller) than would have been expected to have occurred by chance. If the number of groups is small and the data can be easily visualized by graphical display, it may be easy to see which sample mean is different, but if not, further tests – called *multiple comparisons procedures* – may need to be performed.

Non-parametric tests

Where data are not normally distributed, and where transformations cannot be applied in order to meet the requirements for one of the above parametric tests, it is necessary to use a non-parametric test. Parametric refers to the parameters of the distribution – i.e. the mean and the standard deviation of a normally distributed sample. Non-parametric tests do not require any assumptions to be made about the distribution of the data; they compare medians rather than means, but can still provide a measure of precision, usually expressed as a confidence interval. There are many different types of non-parametric test, and only some of the most commonly used ones are described in this section.

Most parametric tests require data to be ranked in order of magnitude. This means that the differences between rank scores do not usually correspond to differences between measurements or observations. For example, using the data above for time from triage to assessment for febrile children in an emergency department, the ranking would be as shown in Table 38.1.

The difference between the observations ranked 1 and 2 is eight minutes, whereas the difference between

Table 38.1 Ranking of time from triage to assessment for febrile children in an emergency department

Rank	Observation – group 1 (minutes)
1	11
2	19
3	22
4	27
5	28
6	31
7	33
8	39
9	42
10	48

2 and 3 is only three minutes. Similarly, if the 10th observation was 231 minutes, the difference between that and the 9th observation would be significantly larger than the differences between the others.

For many of the parametric tests, there are equivalent non-parametric tests that can be used in their place. The *Mann–Whitney U test* is the non-parametric equivalent of the two-sample t-test, except where samples are paired, in which case the *Wilcoxon matched paired test* is more suitable. For more than two groups of non-parametric data, the *Kruskall–Wallis* ANOVA test can be used.

Question 38.5

Student's t-test

A number of standard statistical tests are used for the analysis of results in clinical trials. One such test, used to compare two populations, is the Student's t-test.

Which of the following statements about the Student's t-test used to compare two populations is always true? Select ONE answer only.

A. Tables used to calculate p-values are same as those used for chi-squared tests.

B. The data used for each of the two populations studied must be independent of the other group.

C. The t-test can be used for non-parametrically distributed data.

D. The test can only be applied to samples containing 30 or more observations.

E. The t-test can also be used to compare data from 3 or more populations.

Answer 38.5

B. The data used for each of the two populations studied must be independent of the other group.

Student's t-test is only reliable when the data from each population is independent of the other. A is incorrect because different tables for p-values are required for the t-test compared to those used for chi-squared analysis. C is incorrect because the t-test is only applicable to normally distributed data. D is incorrect because the t-test was specifically developed to deal with small sample sizes of fewer than 30 data points. E is incorrect because the appropriate test for three or more populations is the analysis of variance (ANOVA) analysis.

Looking at relationships between groups

Chi-squared test

Chi-squared tests look at the relationship between categorical variables (e.g. yes versus no or eczema versus no eczema). The chi-squared is a test employed for testing if there is an association between variables, unlike the tests above that look at differences between groups. When it is applied, the null hypothesis is that there is no association between the variables. It provides a p-value, which is the probability of obtaining the observed data if the null hypothesis were true (i.e. no association), but does not provide confidence intervals, and so does not give any indication of the magnitude of the association.

Data for chi-squared tests are set up in contingency tables (with binary variables – i.e. yes/no), and the calculations are based on the differences between the observed and the 'expected' values (expected if there was no association between the variables). The contingency tables can be in the classic 2×2 table form, or for more rows, the chi-squared test can be applied to each row. For example, you might want to look at children with peanut allergy at the age of 3 years (i.e. peanut allergy – yes/no), and see if this is associated with weaning at or after six months (i.e. weaned late – yes/no). If you wanted to look at the association of peanut allergy with other factors, you could have more rows in the table, and perform a chi-squared test for association with each, for example, at least one parent with a history of atopy, diagnosis of eczema, presence of family pet, etc.

Where the numbers in one or more cells of a table are small, the chi-squared test is not valid, and the *Fisher's exact test* can be used instead.

Correlation and regression

Chi-squared tests look at the relationship between categorical variables, whereas correlation and regression are methods used to examine the relationship between numeric variables.

The correlation coefficient, r, (sometimes called Pearson's correlation coefficient), provides a measure of linear association in normally distributed data. (If the association between the two variables is not linear, then other tests of correlation can be applied). For example, in examining the correlation between the risk to neonates of developing necrotizing enterocolitis (NEC) and gestation, gestation is the independent variable and number of neonates developing NEC is the dependent variable.

If there is no correlation at all between the variables, then $r = 0$; if there is a perfect positive association (i.e. a positive correlation: as one increases, so does the other), $r = +1$; and a perfect negative association (i.e. a negative correlation: as one increases, the other decreases), $r = -1$.

Scatter diagrams illustrate graphically the relationship between the variables and should always be constructed in the first instance. By convention, the 'independent' variable (e.g. gestation) goes on the x-axis and the 'dependent' variable (e.g. rate of NEC) on the y-axis. The dependent variable is the one that you are interested in seeing change with respect to the independent variable. In our example of NEC, we would expect a negative r value as we would expect rates of NEC to fall as gestational age rises.

The correlation coefficient is calculated using an equation that calculates the 'line of best fit' for all of the data points. The value r^2 measures how successful the fit is in explaining the variation of the data, i.e. how much of the variation in one of the variables is due to its dependence on the other (the rest being due to other known or undetermined causes). It always takes a value between 0 and 1. If it is 0.74, for example in the NEC/gestation example above, then 74% of the variation between the neonates' risk of NEC is accounted for by the gestation, the other 26% being due to other causes (e.g. birth weight, maternal chorioamnionitis, etc.).

If the data is not normally distributed, including if there are significant outliers, or if the independent variables are not continuous, the non-parametric *Spearman rank correlation* method can be applied. In practice, if there are more than 30 datapoints, Pearson correlation can still be used (due to the test's robustness).

Correlation tells us how closely two variables are associated. The *regression* equation provides a measure of how much the value of the dependent variable y changes with a given change in the independent variable x. Since an equation is produced, it can therefore be used for prediction; for example, how much you would expect the risk of NEC to increase with every addition week of prematurity. Confidence intervals can be calculated for the regression line, and these are often displayed graphically. Caution should be used in using the equation to extrapolate values of x beyond those in the data range available. The assumption that the equation holds true beyond the data range in hand is unwarranted.

If there is more than one independent variable, *multiple regression* methods can be applied. For example, taking the sample of neonates and looking at a number of different variables that could be associated with a risk of NEC, e.g. gestation, birth weight, maternal chorioamnionitis, etc. Multiple regression can also be used to adjust for confounding factors. For example, neonates with lower gestations will generally have lower birthweights, so we can use multiple regression to help determine if birthweight is a risk factor for NEC regardless of gestation.

Where the dependent variable is binary rather than continuous, *logistic regression* is used, and where there is more than one independent variable, this is extended to *multiple logistic regression*. For example, you may want to look at the factors that increase the risk of a child with diabetic ketoacidosis (DKA) being admitted to PICU, including, for example, age, pH, blood glucose level, etc. Admission to PICU is the dependent variable, which is binary (i.e. a child is either admitted or not admitted), and the other factors are the independent variables.

Statistics in epidemiology

Many of the terms used in the statistics of epidemiology are covered in other chapters, but some important statistical concepts are covered here.

Receiver operating characteristic curves

In studies of diagnostic tests, *sensitivity* (the true positive rate) and *specificity* (the true negative rate) are key concepts (see Chapter 2, Epidemiology and public health). The sensitivity of a test is the proportion of people who have a disease who will test positive (i.e. how useful a test is at ruling people in), and specificity is the proportion of people without the disease who test negative (i.e. how useful a test is at ruling people out). The perfect test would have 100% sensitivity and 100% specificity (or 1, on a scale of 0–1). However, this is rarely the case. As you 'modify' the cut-off of a test, you may choose to have lots of 'false positives' (low specificity) in order to ensure that you do not miss any cases (high sensitivity) and vice versa.

Receiver operating characteristic (ROC) curves plot sensitivity (the 'true positive rate') against 1 minus sensitivity (the 'false positive rate'). The closer the area under the curve (AUC) is to 1.0, the closer the diagnostic test is to being 100% sensitive and 100% specific (Fig. 38.11).
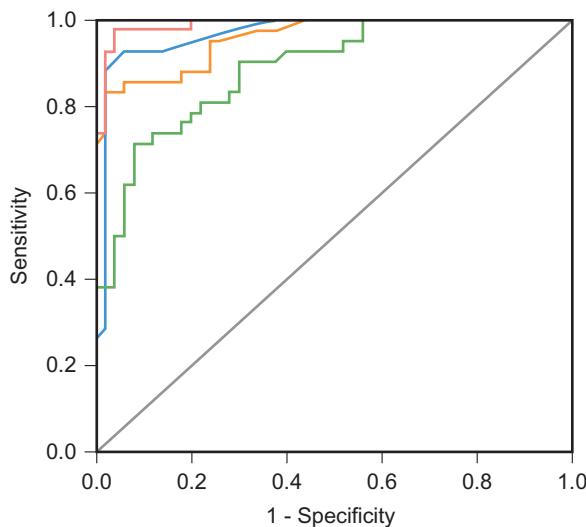
Fig. 38.11 Receiver operating characteristic analysis. This example shows the receiver operating curves for basophil activation test (red), skin prick test (blue) and other tests (orange and green) to discriminate between allergy and tolerance in peanut-sensitized children. It shows how closely the test is 100% sensitive and 100% specific. *(Adapted from Santos AF, et al. 2014 Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children. doi:10.1016/j.jaci.2014.04.039. Published under a creative commons license.)*
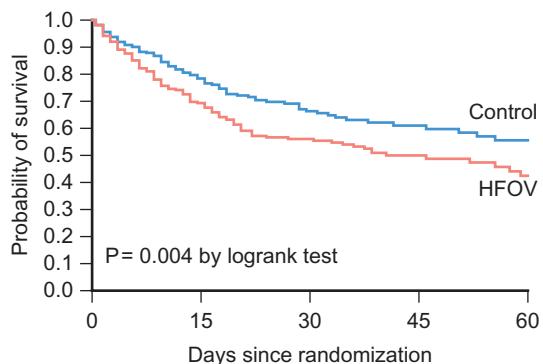
Fig. 38.12 Use of logrank test to show reduced probability of survival of adults ventilated using high frequency oscillation (HFOV) in early acute respiratory distress syndrome compared to control of low tidal volume and high positive end-expiratory pressure ventilation. The trial was stopped early. *(Adapted from Ferguson ND, et al. High frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 2013;368:795–805.)*

Answer 38.6

C. Kaplan–Meier curve.
   See below for explanation.

ROCs can also be used to help determine a useful cut-off point for a diagnostic test, as this will usually mean a trade-off between sensitivity and specificity. Figure 38.11 is taken from a study of children with suspected peanut allergy. We can see that in these children different tests have differing AUCs.

Survival analysis

Question 38.6

Representation of data

A group of 200 babies whose mothers intend to breastfeed are followed up from birth to one year of age in order to determine at what age breastfeeding was terminated. How would such data best be depicted? Select ONE answer only.

A. Dot diagram.

B. Histogram of number of babies still breastfeeding with time.

C. Kaplan–Meier curve.

D. Scattergram of age at termination of breastfeeding by age.

E. Scattergram of age at termination of breastfeeding by age with line of best fit.

Survival analyses are used where the outcome being compared between groups is the time to a specified event, such as death (hence the term 'survival', though it need not be death, it could be any event, e.g. pregnancy, time to end of exclusive breastfeeding, failure of a transplanted organ, etc.). Although 'time to event' is a continuous variable, standard statistical analyses cannot be applied, because the times are not likely to be normally distributed and because by the time the data is analysed, events will not necessarily have occurred to all of the people in the study. These are called *censored observations*, and include those known to be still alive (or not yet having the event occurring), those known to have been alive previously but now lost to follow-up, and those who are known to have died, but of some unrelated cause.

Kaplan–Meier curves display survival data graphically, showing cumulative survival at each time-point. Censored observations may be marked on the graph with short horizontal lines. The *logrank test*, so-called because it uses logarithms of the ranks of the data, can be used to compare the survival curves of different groups (Fig. 38.12).

An extension of the logrank test is *Cox regression*, also known as the proportional hazards model, which can be used to analyse the effects of more than one risk factor on the outcome (e.g. survival).

Understanding the limits of statistics

The well-known quote, attributed by the writer Mark Twain to the British Prime Minister, Benjamin Disraeli, 'There are three kinds of lies: lies, damned lies and statistics', is often employed in jest. However, one must be aware of the limits of statistics and appreciate that a 'statistically significant' result does not equate with 'the truth'.

Validity of the study

Irrespective of the statistical methods used, a study may be subject to bias and confounding, both of which will affect its validity. It could also be a well conducted, valid study but performed in a population very different from your own, limiting its applicability. These considerations are discussed in more detail in Chapter 39, Evidence-based paediatrics and Chapter 37, Clinical research.

Appropriate application of statistical tests

Statistical tests are based on mathematical models with in-built assumptions, and applying them to data inappropriately will provide spurious or incorrect analyses. In practice, this is most likely to occur when researchers fail to understand the underlying mathematical reasoning behind the tests they are using. When planning a research study, it is vital to seek advice on statistical methods before starting to collect data.

Association and causation

Statistics can give us an idea of how closely two factors are associated or correlated, but that does not mean that one necessarily causes the other. For example, sales of barbecues may be inversely correlated with rates of admission to hospital with bronchiolitis, but that does not mean that lots of people buying barbecues prevents infants being admitted to hospital with bronchiolitis.

Clinical and statistical significance

A difference that is statistically significant may illustrate a genuine difference but not one that is clinically relevant or important. For example, a new type of preventative inhaler for asthma that reduces admissions by 0.7%.

Further reading

Bland M. An introduction to medical statistics. Oxford: Oxford University Press; 2000.

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Bob Phillips, Peter Cartledge

Evidence-based paediatrics

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Understand basic principles of evidence-based medicine in order to implement it into clinical practice
- Be able to formulate a clinical question
- Be able to undertake a hierarchical search strategy using online search databases
- Be able to critically appraise a randomized controlled trial (RCT)
- Be able to interpret the commonly used measures of treatment efficacy
- Be able to give an evidence-based presentation

Introduction

Evidence-based medicine (EBM) has now established itself as a key principle at the heart of modern clinical life. But what is it? In this chapter we will look at the principles of evidence-based medicine and how to practise it.

When we make a clinical decision (e.g. should I give this wheezy child a nebulized or spaced β_2 agonist?), we need to think about the patient and the overall outcome. There could be beneficial outcomes, but these should be weighed against the possibility of negative effects. As clinicians, we instinctively assess the chances of these outcomes, weigh them, and conclude on a course of action. If we are treating a child with an acute exacerbation of asthma, we may want to know what is the best mode of delivery for a β_2 agonist? But what does best mean? Patient satisfaction? Ease of delivery? Fewer symptoms? Fewest side effects? Fewer admissions? Most cost-effective? Least expensive?

For the clinician, the process of practising EBM can be difficult, time consuming, and (dare we say it) boring. In this chapter, these barriers will be tackled with examples of EBM in practice, revealing that the five minutes spent thinking this through may have saved you hours of work whilst improving the care provided to your patients.

What is EBM?

EBM was defined by one of the founders of the EBM movement, David Sackett, as 'the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients'. But what does that mean in real terms? EBM is a short-hand term for five linked ideas:

1. Our practice should be a meeting of (Fig. 39.1):
   – Our clinical skills (including history, examination and diagnosis building)
   – Our patient's own values, preferences and beliefs
   – The best available evidence
2. Seeking information/evidence is key to learning and should mostly be 'just in time' (see below), determined by an individual patient or population's problem.
3. The care we offer should integrate quality clinical research with clinical experience, rather than relying on habit, dogma or tradition.
4. Searching and appraising evidence is only meaningful if it is applied to decisions and actions that benefit patients.
5. Clinicians, including those in training, should continuously evaluate their performance.

Some misconceptions about EBM are listed in Box 39.1.
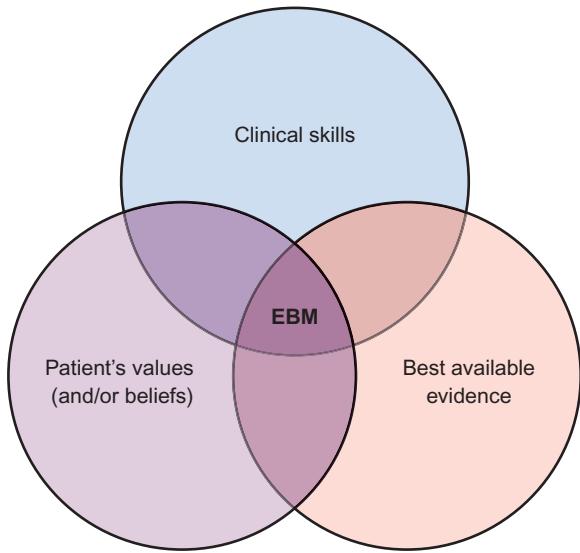
Fig. 39.1 **Key components of EBM. Evidence-based medicine is the convergence of clinical skills (including history, examination and diagnosis building), the patient's values, preferences and beliefs and the best available evidence.**

Box 39.1 Misconceptions of EBM

There are a series of misconceptions regarding EBM which should to be dismissed as untrue:

- EBM belittles or removes clinical expertise
- EBM ignores patients' values, preferences and beliefs
- EBM promotes 'cookbook' medicine
- EBM is simply a cost-cutting tool
- EBM is only for tertiary hospital clinicians/specialists
- EBM is exclusively limited to undertaking research rather than using research findings
- EBM leads to the renunciation of therapies when there is an absence of evidence from RCTs
- EBM is performed by statisticians sitting in offices and not by clinicians working in wards, clinics or operating theatres.

Why practise EBM?

Altruistic reasons for practising EBM

Practicing EBM improves patient care. There really should be no other incentive. Considering this in terms of the four pillars of medical ethics can be helpful:

1. *Autonomy*: All patients have the right to make decisions about their own care. This is central to EBM. Their values, preferences and beliefs should always be taken into account when making decisions.

2. *Beneficence*: When starting therapies you need the best available evidence to be certain that they have a meaningful benefit to the patient.

3. *Non-maleficence*: If a therapy or test has no meaningful benefit but is harming the patient (e.g. through side effects) then it should be stopped or not used in the first place.

4. *Justice*: Scarce resources must be fairly distributed. When rationing provisions, there must be good evidence that they are effective. If they are not, this resource could have been used elsewhere.

Personal reasons for practising EBM

There are also selfish reasons for wanting to practise EBM:

1. *Personal development/examinations*: EBM is included in the RCPCH Curriculum for Paediatric Training, which states that: 'In addition to a detailed knowledge and understanding of diseases in children and young people, paediatricians must ensure they are up-to-date, conform with highest standards of practice, aim to promote evidence-based medicine where possible and audit practice (assessment standards 18–20).'

2. *Self-preservation*: Clinicians are presented with huge volumes of research evidence. Without the time to read all this information, skills are required to filter out the good from the bad.

3. Reduced workload: Practising EBM will hopefully help patients to be diagnosed more effectively and get better quicker, therefore reducing workload.

Meeting our information needs

There are 11 new systematic reviews and 75 new trials published every day (Bastian 2010). It is impossible to keep up-to-date with all medical advancements, so long-term professional strategies are required to meet our learning and information needs.

'Just in case' information

Reading this book is an example of just in case information: packing in a range of general nuggets to provide a good underlying understanding of paediatrics in order to be good clinicians. When taken to the extreme, it is the diligent, regular reading of a series of journals 'just in case' a particular case was to present. This is inefficient and induces guilt when you cannot manage it.

'Just in time' information

This is a lifelong skill – the acquisition of information 'just' as you need it, e.g. reading a patient's clinic notes before they arrive. In the EBM context, it is identifying information that will help us best manage our patients

Table 39.1 Steps of EBM

Step	Skills required	Barriers	Consequences of inadequate implementation
Step 1: Asking a question	• Good clinical skills • Inquisitive nature • Specific PICO questions	• Time to formulate questions • Excessive reliance on senior colleagues	• Out-of-date practice • Dangerous practice
Step 2: Acquiring information/evidence	• Literature searching and storage	• Lack of good quality research evidence • Inadequate database searching skills	• Biased evidence found and inappropriate practice
Step 3: Appraising the information/evidence	• Systematic appraisal techniques • Critical mind-set	• Lack of an appraisal tool (i.e. DIY appraisal)	• Biased evidence applied to wrong patients
Step 4: Applying the evidence to your patient	• Sensitivity • Good communication	• Understanding study methods, statistics and applying research to individual patients • Perceptions of curtailing clinical freedom • Conflict of opinion	• Out-of-date practice • Dangerous practice
Step 5: Assessing your performance	• Self-awareness	• Lack of time to reflect on learning or practice change (e.g. 'audit')	• Missed opportunities to focus personal development

by seeking rapid answers to specific queries. Research has shown that a doctor in training will have two unanswered questions for every three patients they consult (Green et al 2000). An inquisitive clinician could have many more questions. As our clinical experience improves, this number is unlikely to change, but the content may become more focused.

The five steps of EBM

The practice of EBM is a multi-step process. Each of these steps (Table 39.1) requires individual skills and practice, though some resources will allow us to short-cut some of these steps. Throughout this chapter, there are examples of the 'five steps' in practice (see also Tables 39.3, 39.4, 39.6 and 39.9).

Step 1: Asking a question

It is all too easy to practise medicine without asking questions, as asking questions exposes potentially embarrassing gaps in our knowledge. The first step of EBM is to address this challenge and admit ignorance or uncertainty, then convert our information needs into answerable questions. This means having an inquisitive mind. Looking at the anatomy of enquiry, ask initially 'What sort of question am I asking?' If it is a clinical question then it can be grossly categorized as 'foreground' or 'background'. Background questions are broad, and are often 'what is' or 'what causes' type questions, e.g. 'What causes asthma in childhood?' Foreground questions are specific and pointed, and can be fitted into a 'PICO' framework (patient-problem, intervention, comparison, outcome). This art is known as 'framing a clear question' and is an

> **Box 39.2 Top tips for putting EBM into practice (framing questions)**
>
> • Search at the point of care.
> • If you are too busy to search immediately, write your questions down (e.g. a notebook, smartphone or portfolio).
> • Present your questions to your colleagues for feedback.
> • Write educational prescriptions on ward rounds (http://www.cebm.net/wp-content/uploads/2014/04/educational_prescription_1.pdf)

essential skill. A well-framed question must be directly related to the patient and structured in order to search for a relevant and precise answer.

Framing a clear question: PICO questions

A popular method for framing a clinical question is the PICO method (Box 39.2):

- **P** – *Patient, Pathology, Problem or Population*: What are the key features that describe the patient or population? Be specific.
- **I** – *Intervention or Interest*: Be specific about the intervention, test or risk factor you are considering.
- **C** – *Control or Comparison*: What would be appropriate alternatives? This may be placebo or more often currently used treatments.
- **O** – *Outcomes*: Consider patient-oriented short-term and long-term outcomes; remember negative effects too. Avoid surrogate markers (e.g. improved CRP).

Choosing the right outcomes to search is incredibly important. If you have a strong opinion on a topic, it is likely to be drawn from experience, e.g. always giving inhaled salbutamol to wheezy children in A&E. But what do we actually want to know about our intervention? Will it stop the patient dying? Will it keep them out of hospital for longer? Will they feel better? These are all important questions.

Step 2: Acquiring information/evidence

The aim of this step is the acquisition of good quality information/evidence to answer your skilfully constructed question. This can be difficult, but with practice and a few tips on where to look, it gets easier. The process therefore follows three steps:

1. Converting your PICO question into searchable terms
2. Searching for secondary sources (e.g. guidelines, Cochrane/DARE, etc.)
3. Finding primary sources if secondary sources are not available (e.g. PubMed). (See http://www.youtube.com – search for 'PubMed Advanced Search Builder' in YouTube for a 3-minute tutorial on how to search in PubMed.).

Getting your search right is both an art and a science. A good search is both sensitive and specific. A sensitive search will not miss any relevant papers, a specific search will not have too many irrelevant articles.

Converting PICO questions into searchable terms

Once you have written a sound PICO question you must convert the question into searchable terms.

To form a search strategy:

1. Convert each arm of your PICO into search terms (including alternate spellings, synonyms, and truncations).
2. Search for the correct MeSH term (if you are using a database that does not automatically map). 'MeSH' is essentially the National Institute of Health (NIH) thesaurus of medical terms that guides towards the 'correct medical term'. This means a searching clinician is able to find the relevant research, including when the papers' authors have not used the 'preferred' medical term). (See http://www.nlm.nih.gov/mesh/; Tutorial: http://www.nlm.nih.gov/bsd/viewlet/mesh/searching/mesh1.html).
3. Combine the search terms using the correct Boolean operators (Table 39.2).

Table 39.2 Boolean operators

Term	Search description
OR	(Infant OR child) will find all articles/documents containing at least one of these keywords
NOT	(Infant NOT child) will find articles/documents containing the keyword infant but exclude those also including the keyword child
AND	(Infant AND child) will find articles/documents containing both of these keywords
* (Truncation)	Infant* will find articles/documents containing the keywords infant OR infants OR infantile OR infancy, etc.

Where to search

There is probably no correct answer to the question, 'where is best to search?' You are likely to find databases which you are more comfortable using. Trip®, the Cochrane library® or PubMed® are good databases to be familiar with (Box 39.3).

Hierarchical searches

A hierarchical search aims to look for the best quality evidence first, and then work downwards if insufficient research is discovered (Fig. 39.2). If you are searching in a clinical environment, a database such as Trip® will often find results quickly (Table 39.3) and present them in evidence type. If this fails, the Cochrane library and DARE website should be searched (Table 39.4). If this does not yield any results, then PubMed's 'Clinical Queries' is the next best port of call followed by a search for primary resources in PubMed.
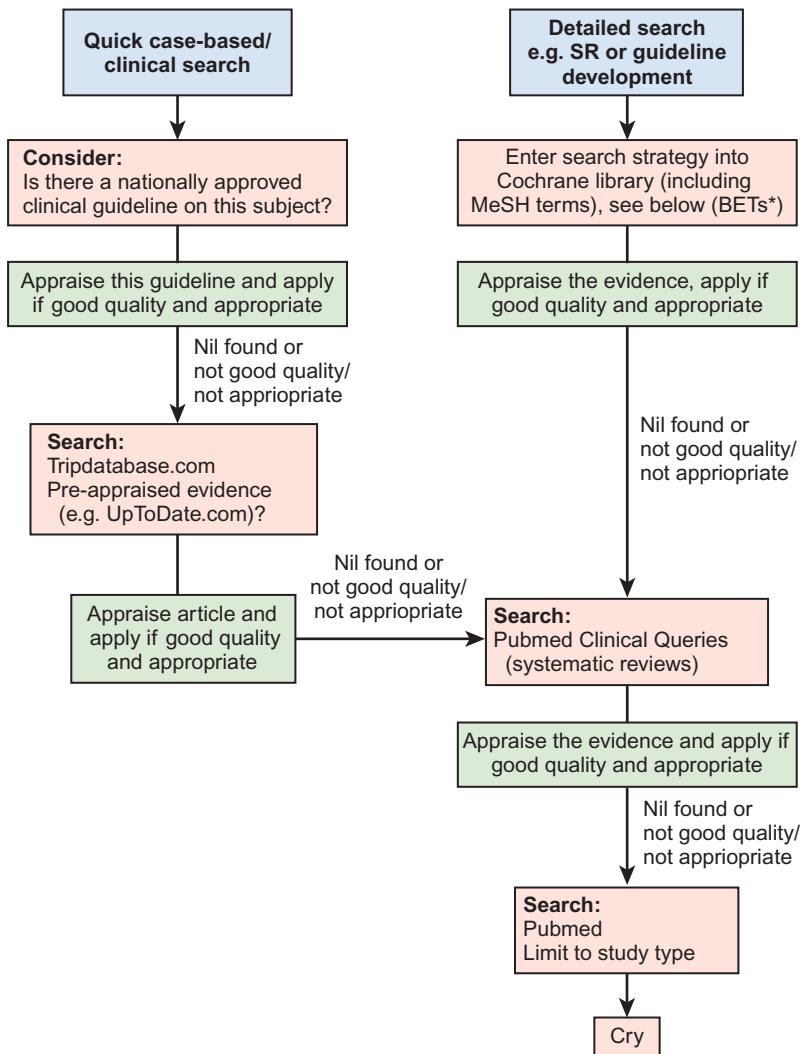
Fig. 39.2 Hierarchical search strategy. (*BET = Best Evidence Topic.)

If performing a more detailed search (e.g. for guideline development) then an extensive search should be undertaken, preferably with the help of an information specialist at your local library.

Boolean operators
Almost all database search engines use Boolean operators (see Table 39.2) to combine search concept.

Search filters
When searching PubMed, a search filter can be used to find evidence relating to different areas of practice (e.g. therapy or diagnosis); these are handily available via the PubMed 'Clinical Queries' page. This can quickly make the search more sensitive and specific.

What is 'current best evidence'?
A common misconception regarding EBM is that only RCTs or systematic reviews constitute the 'evidence' in

EBM. Though double-blinded RCTs are often considered the 'gold standard' for establishing treatment effects, they will not be the best at answering questions about diagnosis, prognosis and/or harm. Secondly, there may not be RCTs available to answer certain treatment questions. There are barriers to research in child health and this often means that good quality information is unavailable (see Box 37.1). If no literature is available to answer your question, then an email/discussion with an expert may be the 'current best evidence' for your clinical question. Do not negate the importance of qualitative research, which significantly adds to the wealth of evidence available on particular subjects.

Levels of evidence
An understanding of 'levels of evidence' will enable you to search for the 'current best evidence'. Evidence hierarchies are often used to describe the relative

Table 39.3 Best evidence topic (BET) – treatment

Treatment – acute exacerbation of asthma

Scenario: A 6-year-old child is admitted with a moderate exacerbation of asthma. He has been given a nebulizer of salbutamol in the A&E department and needs admission for a trial of inhaler and holding chamber (spacer). You wonder if he could have been given the inhaler in the A&E and the child sent home sooner?

Step 1: Asking a question (PICO): In a child with a moderate exacerbation of asthma [patient], is inhaled, spaced, salbutamol [intervention] as effective as nebulized [comparison] β_2 agonist in terms of time to resolution of symptoms, likelihood of admission and deterioration [outcomes]?

Step 2: Acquiring evidence:

Search terms: Asthma AND spacer AND nebulizer.

Databases: Trip database – 110 results. Best result – Cochrane review.

Step 3: Appraising the evidence:

Study group	Intervention	Study type	Outcomes	Key results	Comments
2295 children in 27 trials from emergency and community setting.	Any β_2 agonist given by any nebulizer versus the same β_2 agonist given by metered-dose inhaler with any spacer.	Cochrane systematic review. Only RCTs considered for review.	**Primary outcomes:** Admission to hospital or duration of stay. **Secondary outcomes:** Duration in emergency department, change in respiratory rate, blood gases, pulse rate, tremor, symptom score, lung function, use of steroids, relapse rates.	Meta-analysis of probably heterogeneous results. Spacer versus nebulizer relative risk of admission was 0.72 (95% CI: 0.47 to 1.09). In children, length of stay in the emergency department was shorter with spacer, mean difference of –0.53 hours (95% CI: –0.62 to –0.44 hours).	Clear primary and secondary outcome measures. Particular emphasis on the allocation concealment, which in general appears poor in most papers.

Commentary:

Acute exacerbation of asthma is common in both hospital and primary care. The airways are narrowed due to mucosal oedema, hypersecretion and bronchospasm. β_2 agonists have been used successfully to relieve the bronchospasm. This paper included RCTs including adults and children. It can be argued that adults and children differ in their ability to use the devices being tested. Therefore, the results for adults and children were separated for each outcome.

In this systematic review it was found that the method of delivery of β_2 agonist did not appear to affect hospital admission rates but did significantly reduce the duration of stay in the emergency department.

Step 4: Applying the evidence (the clinical bottom line):

1. No outcomes were significantly worse with spacers, and in most cases spacers can be substituted for nebulizers to deliver β_2 agonists in acute asthma (excluding life-threatening asthma).
2. Spacers offer a significant advantage in terms of time spent in emergency department, oxygenation and side effects.
3. Spacers should be routinely used instead of nebulizers to administer β_2 agonists for acute asthma in children and young people. (Strong recommendation, high quality evidence.)

Reference:

Cates CJ, et al. Holding chambers (spacers) versus nebulizers for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev 2006;(2):CD000052.

authority of various types of medical research. There is no individual, universally accepted hierarchy, and a tiny, very poorly conducted RCT will be less use than a well-constructed cohort study.

A simple hierarchy has been described by Professor Greenhalgh in *How to read a paper*:

1. Systematic reviews and meta-analyses
2. Randomized controlled trials with definitive results
3. Randomized controlled trials with non-definitive results
4. Cohort studies
5. Case-control studies
6. Cross-sectional surveys
7. Case reports

GRADE

A better approach to 'levels of evidence' might be to describe how convincing the totality of evidence is

which underpins a management decision. This concept is what underpins the 'grades of recommendation' found in guidelines. A large number of methods for describing the quality of evidence behind recommendations have been created. Most systems have the same principles at their heart. The guideline developers are first asked to assess the methodological quality of the studies, then developers are asked to evaluate the whole of the evidence and how it applies to the recommendation at hand: this gives the 'grade (or strength) of recommendation'. The systems vary in how the study quality is assigned, which factors are included in assessing 'a strength' of recommendation, and if different axes are used for different types of question (for example, therapeutic, diagnostic, and prognostic).

The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) system has been developed by the international GRADE Working

Table 39.4 Best evidence topic (BET) – diagnosis

Diagnosis – cyanotic heart disease

Scenario: You start at a new hospital where you undertake 'postnatal checks' on newborn infants. You notice that in this hospital you do not need to perform post-ductal pulse oximetry testing. You discuss this with your consultant, who asks you to find out more exact details on the benefits of this.

Step 1: Asking a question (PICO): In an asymptomatic newborn infant [patient], does post-ductal pulse oximetry [intervention] increase the number of infants correctly identified with congenital heart disease or reduce mortality rates [outcomes]?

Step 2: Acquiring evidence:

Search terms: (Infant, newborn OR infant* OR newborn OR 'newborn infant' OR neonat*) AND (heart defects, congenital OR congenital heart defect* OR Defect*, congenital heart OR heart, malformation of OR heart abnormalit* OR congenital heart disease OR cyanotic heart disease OR cyanotic heart defect OR congenital heart malformation) AND (oximetry OR oximetry, pulse OR blood gas monitoring, transcutaneous OR oximetry, transcutaneous OR oximetry, transcutaneous OR saturation*, oxygen OR oxygen saturation*)

Databases: Cochrane: 164 results, 4 non-Cochrane reviews including below meta-analysis.

Step 3: Appraising the evidence:

Study group	Intervention	Study type	Outcomes	Key results	Comments
13 eligible studies with data for 229,421 asymptomatic newborn babies. 118 infants with critical congenital heart defects. 748 false positives. 33 false negatives.	Pulse oximetry. 60% of studies used foot alone (postductal).	Systematic review and meta-analysis of 12 cohort and 1 case-control study.	Detection of critical congenital heart defects.	Sensitivity 76.5% (95% CI 67.7–83.5), specificity was 99.9% (99.7–99.9), false positive rate 0.14 (0.06–0.33). Likelihood ratio positive 549 (238–1195), likelihood ratio negative 0.24 (0.17–0.33). Lower false positive rate if oximetry >24 hours (p=0.0017), but no effect on sensitivity.	Clear description of search strategy. No statistical description of heterogeneity. Significant publication bias was reported.

Commentary:

Screening for critical congenital heart defects in newborn babies can aid early recognition, with the prospect of improved outcome. In this case, the new doctor was not interested in an individual patient but a population. As the search had the potential to lead to widespread change in the clinical assessment of all newborns, the search for evidence needed to identify the most relevant and highest quality available. The search was therefore very comprehensive.

Though this systematic review found that pulse oximetry is highly specific for critical congenital heart disease, it does not look at broader outcomes. For example, do infants who have their diagnosis made earlier using screening have better long-term outcomes (e.g. mortality)? This would be an important consideration when balancing the cost (equipment, time, etc.) of implementing such a screening tool.

Step 4: Applying the evidence (the clinical bottom line):

1. Pulse oximetry is a non-invasive test that is easy to perform with high accuracy and could identify other disorders such as septicaemia or symptomatic pulmonary hypertension.
2. The false-positive rate for detection of defects was significantly lower when pulse oximetry was done after 24 hours
3. 'In view of the many babies that have now been tested with pulse oximetry, further research in this area is unlikely to produce substantially different findings'
4. Routine pulse oximetry should be undertaken on neonates prior to discharge, ideally after 24 hours. (Strong recommendation, moderate quality evidence.)

NB: The * in the search terms is referring to search truncations to ensure optimum sensitivity of the search (see Table 39.2).

Reference:

Thangaratinam S, et al. Pulse oximetry screening for critical congenital heart defects in asymptomatic newborn babies: a systematic review and meta-analysis. Lancet 2012;379(9835):2459–64.

Group. GRADE is a transparent, structured process for developing and presenting summaries of evidence and is integrated into Cochrane reviews and NICE guidelines. The GRADE system classifies quality of evidence as high, moderate, low, and very low (Table 39.5).

Grade of recommendations

The GRADE system goes on to combine this quality of evidence with a judgement about the balance of risks and benefits to produce strong or weak recommendations. When the benefits of an intervention clearly outweigh its risks and burden, or clearly do not, a strong recommendation is produced. When the trade-off between benefits and risks is less certain, either because of low-quality evidence or because high-quality evidence suggests that benefits and risks are closely balanced, weak recommendations are made. (For further details, see GRADE working group: http://www.gradeworkinggroup.org)

'But more research is needed'

How can we decide if questions really do 'need' more research? It may be worth thinking of how likely benefits and harms may be, what the importance of these outcomes is and, finally, how much would you consider reasonable to pay for the answer? For example,

Table 39.5 GRADE quality of evidence (with definitions)

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low	Any estimate of effect is very uncertain

> **Box 39.4 Top tips for putting EBM into practice (searching)**
>
> - Search at the point of care.
> - Use search engines that you are comfortable with.
> - Ask a hospital librarian to sporadically check your searches.
> - Register (i.e. create an account) with your favourite search engine to allow you save searches for later review.

'Do antihistamines reduce itch in chickenpox?' versus 'Are oral antibiotics as effective as intravenous antibiotics in children with neurodisability and pneumonia?' Do we really need more research to prove the use of antihistamines in chickenpox? If you compare this with the implications of ineffective management of a significant lung infection in a disabled child? Such value judgements are important; they will have different answers from different perspectives; they will be subject to political influences from pressure groups; being aware of them might stop us from frequently expounding 'more research is needed'. Conversely, there are times when a 'lack of significance' can be falsely interpreted that an intervention is not effective, when in reality the methods employed have not been powerful enough to find the truth to the question posed. In this case more research *is* needed.

> **Key point – Is it possible for health professionals in developing countries to access journal articles?**
>
> Yes. HINARI provides free or very low cost online access to the major medical journals to local, not-for-profit institutions in developing countries (www.who.int/hinari/en/).

What to do when you find no evidence?

The problem of 'not enough evidence' is a common one we face as paediatricians and one that will frequently frustrate our attempt to implement evidence into practice. It is a big problem, so what do we do in this situation? The issues depend on:

- What is the goal of treatment?
- What are the potential benefits and harms?
- The uncertainty about our estimates of these
- The 'regret' associated with getting the decision wrong.

If you have a potentially toxic drug that you are using in an asymptomatic population to prevent a fatal disease, you need strong evidence to recommend

its use. If you are aiming to moderately improve someone's well-being with a side-effect free intervention, the evidence can be much weaker.

A summary of top tips for searching for evidence is shown in Box 39.4.

Step 3: Appraising the information/evidence

Once you have acquired your information/evidence, you must critically appraise it for its importance and validity. The skills of appraisal, like all skills, take time to learn and improve. To continue to develop your skills, it needs to be integrated into what you do on a regular basis. Appraisal is not the overzealous criticism of research to prove that it is flawed and therefore not applicable. It is rather the process of teasing out important details which will have a bearing on whether you use a test, treatment, etc., and just how useful they are likely to be based on this research.

There are four main considerations when appraising any evidence:

1. Relevance
2. Validity
3. Importance
4. Applicability.

An appraisal checklist is shown in Box 39.5 and an example of appraising the evidence in Table 39.4.

1. Relevance

This stage is largely intuitive. Using your PICO question will enable you to focus your attention and quickly decide whether the study is assessing the relevant intervention in the appropriate patients and reporting the important outcomes. In Table 39.6, we can see quickly that the paper identified is relevant to our clinical scenario and the question that the patient's mother has asked of us.

2. Validity

Can you believe the results presented? This question delves into the biases that may be produced by

Table 39.6 Best evidence topic (BET) – treatment

Treatment – pneumonia

Scenario: A previously well 4-year-old child presents with fever and signs of respiratory distress. Community-acquired pneumonia (CAP) is confirmed radiologically. He is mildly tachypnoeic but has no oxygen requirement. His mother asks you if it is really necessary for him to stay in hospital for intravenous antibiotics?

Step 1: Asking a question (PICO): In a pre-school aged child with pneumonia [patient], are oral antibiotics [intervention] as effective as intravenous antibiotics [comparison] for time to resolution of symptoms, rate of hospital admission, length of stay and rate of complications [outcomes]?

Step 2: Acquiring evidence:

Search terms: (child, preschool OR pre-school child* OR preschool child*) AND (Pneumonia OR lower respiratory tract infection OR LRTI) AND (antibiotic OR anti-bacterial agents) AND (oral OR administration, oral) AND (intravenous OR administration, intravenous). Databases: Cochrane – no results. PubMed (Limit: randomized controlled trial) – 15 results.

Step 3: Appraising the evidence:

Study group	Intervention	Study type	Outcomes	Key results	Comments
246 children (1.5–5.4 years) with CAP admitted to eight hospitals in UK	Oral amoxicillin versus intravenous benzylpenicillin	Multicentre randomized-controlled equivalence study	1. Time for temperature to decrease to <38°C for 24 hours 2. Cessation of O_2 requirement 3. Length of stay 4. Complications	No significant difference in temperature resolution, O_2 requirement or complications Length of hospital stay was shorter in the oral group (1.77 versus 2.1 days, p=0.001).	Equivalent demographics between groups. Clear inclusion criteria. Concealment of allocation. Intention to treat. Non-blinded.

Commentary:

Pre-school children admitted with CAP are often commenced on intravenous antibiotics. This treatment carries the risk of harm such as painful cannulation, extravasation, thrombophlebitis, and prolonged hospital stay. If oral antibiotics were found to be equally effective, these harms could be avoided.

When searching for papers to answer this PICO question, the outcomes would be very important, e.g. a significant outcome would be 'development of empyema'. Speed of radiological resolution (with no clinical measures) would not be a significant outcome (it is a surrogate marker).

In this paper: children admitted to both tertiary and district general hospitals were included. Complications and treatment failure were similar in both groups. Of the 246 children, three developed empyema, all were in the intravenous arm of the study. We can therefore give this mother the advice that her child can be safely treated at home with oral antibiotics. She should be counselled that if her son's respiratory difficulties were to deteriorate, she should return immediately to the hospital.

Step 4: Applying the evidence (the clinical bottom line):

1. Oral antibiotics are as effective as intravenous antibiotics in the treatment of CAP in pre-school aged children. (Strong recommendation, high quality evidence)
2. In all but the sickest of children, oral antibiotics should be the first line treatment for CAP (in combination with observation of tolerance and symptoms) (Strong recommendation, high quality evidence).

NB: The * in the search terms is referring to search truncations to ensure optimum sensitivity of the search (see Table 39.2).
Reference:
Atkinson M, et al. Comparison of oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia in children (PIVOT trial): a multicentre pragmatic randomised controlled equivalence trial. Thorax 2007;62:1102–6.

Box 39.6 Cochrane reviews

Cochrane reviews are systematic reviews of primary research in health. They investigate the effects of interventions for prevention, treatment and rehabilitation and the accuracy of diagnostic tests. These reviews are unparalleled in terms of quality, volume and scope. What also sets Cochrane reviews apart is the continuous effort to update them.

The logo of the Cochrane Collaboration (see above, Copyright © The Cochrane Collaboration) provides an excellent example of how systematic reviews can change the widescale practice of clinicians. It is based around the 1989 Cochrane review, which asked the questions: "In a pregnant woman presenting in premature labour [patient],

does a short course of a corticosteroid [intervention] compared with placebo [control] reduce respiratory morbidity and mortality in the premature infant? A question now rarely asked on neonatal units around the world.

The 'forest-plot' at the centre of the logo reveals the results of the seven RCTs, each being represented by a horizontal line. The diamond represents their combined results. If a horizontal line crosses the vertical line, it indicates that that particular study found no difference between intervention (steroids) and control (placebo). The position of the diamond to the left of the vertical line indicates that the treatment studied is beneficial. Conversely, a diamond to the right would reveal a treatment that did more harm than good. This review brought home the message of the huge gap between available evidence and clinicians' awareness of its existence.

Because no systematic review of these trials had been published until 1989, most obstetricians had not realized that the treatment was so effective. As a result, tens of thousands of premature babies had probably suffered and/or died unnecessarily. This is just one of many examples of the human costs resulting from the failure to perform systematic, up-to-date reviews of RCTs and to apply them to clinical practice.

References: www.cochrane.org; www.thecochranelibrary.com

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different elements of study design. Despite all the best intentions, a research study might not produce results that are 'based upon truth'. A good understanding of research methods (see Chapter 37, Clinical research) is required to fully appraise the validity of any evidence you have found and apply it appropriately to your patient.

Assessing validity involves asking critical questions of the way the research was performed. For example, if appraising an RCT, you may need to ask critical questions such as:

- Was the assignment of patients to treatments appropriately randomized?
- Were all of the patients who entered the trial properly accounted for at its conclusion?
- Were patients, health workers and study personnel 'blind' to treatment?
- Were the groups similar at the start of the trial?
- Aside from the experimental intervention, were the groups treated equally?

Different study designs will have different critical questions to ask. Hence the importance of using appraisal tools (see Box 39.5).

Validity of common trial designs

A number of different quantitative trial designs exist – systematic review and meta-analyses (Box 39.6), randomized controlled trial (RCT), cohort, case-control, cross-sectional surveys. Whilst the double-blinded randomized controlled trial is frequently seen as the gold standard approach for investigating a new treatment intervention, each study design can be the most appropriate choice for a given clinical setting (see Table 37.2). Each trial design has individual limitations and biases which must be borne in mind when interpreting the results and applying them to your patient.

Reducing bias

When appraising a paper, one should assess if the researchers have used common techniques to reduce bias where possible. Common techniques are:

- *Allocation concealment*: This refers to the security of the randomization. Before a patient is offered a place on a trial, there should be no way of the investigator knowing which treatment the patient will receive. Why conceal? A 'subconsciously' biased investigator keen on intravenous antibiotics (see Table 39.6) may put sicker

children into the IV group as he wants these children to get better faster, which might make intravenous antibiotics look ineffective in the research project.

- *Intention to treat analysis*: For whatever reason, the patients' data should always be analysed according to the group allocated at randomization. Randomization is the point in the study when patient characteristics (and confounding variables) are matched. There may be a systematic reason (connected to the treatment) why certain patients cannot comply with the protocol. In Table 39.6, if children on oral antibiotics deteriorated and were changed onto intravenous antibiotics, then they should be analysed in the 'oral' arm of the study, not the intravenous arm.
- *Blinding* (or masking): The process of obscuring to patient, observer, or both the treatment to which they are allocated. It relies on two therapies having no clearly discernible effects to 'unmask' the allocation. In Table 39.6, it would be impossible to blind the patients to which treatment they were going to receive as one requires cannulation.

3. Importance

Are the results likely to result in an important improvement/harm/correct diagnosis? A good understanding of statistics (see Chapter 38, Statistics) is required to fully appraise the significance of any evidence you have found and apply it appropriately to your patient. When appraising the 'significance' of the results, you will need to ask critical questions, such as:

- How large was the treatment effect?
- How precise was the estimate of the treatment effect? (i.e. What are its confidence limits?)

Similar to validity, different study designs will need different critical questions regarding significance.

Measurements of efficacy

If a dichotomous outcome is present (e.g. having cerebral palsy or not having cerebral palsy; Table 39.7), then a variety of measures can be generated. Of these, those that give information of the risk reduction (relative, absolute, or its inverse, the number needed to treat) are useful. We have used the groundbreaking TOBY study described in Chapter 37, Clinical research, to demonstrate these terms (Table 39.7). Table 39.8 gives the definitions of some of the common measurements of efficacy derived from dichotomous results of RCTs.

Question 39.1

Treatment of eczema herpeticum

A 7-year-old child with chronic atopic eczema is admitted with eczema herpeticum. You want to start acyclovir in combination with an antibacterial agent. His mother is concerned about the number of courses of antibiotics he has had and wants to know if this is really necessary. You find a multicenter retrospective cohort study of 2000 children ages 2 months to 17 years admitted with eczema herpeticum which reveals the following:

	Acyclovir with oral antibiotics	Acyclovir without oral antibiotics
Hospitalization	40	60
No hospitalization	960	940

What is the number needed to treat (NNT) to prevent hospitalization? Select ONE answer only.

A. 20

B. 30

C. 40

D. 50

E. 60

Answer 39.1

D. 50

The NNT = 1/Absolute Risk Reduction (ARR) (see Table 39.8). Therefore, to work out the NNT first of all you need to calculate the absolute risk reduction: 60/(940 + 60) − 40/(960 + 40) = 0.02 (20 per 1000 children). Therefore the NNT in this case = 1/0.02 = 50.

Table 39.7 Presentation of dichotomous results (TOBY study, cerebral palsy in cooled survivors of hypoxic–ischaemic encephalopathy; see Box 37.13)

	Event (Cerebral palsy)	No Event (No cerebral palsy)	Totals
Intervention group	a	b	a + b
(Moderate cooling)	(33)	(87)	(120)
Control group	c	d	c + d
(Standard care)	(48)	(69)	(117)
Total	a + c	b + d	a + b + c + d
	(81)	(156)	(237)

(Data from Azzopardi DV et al, New England Journal of Medicine 2009:361;1349–58.)

Table 39.8 Key statistical terms (using the example of cerebral palsy in survivors of hypoxic–ischaemic encephalopathy (HIE) who were cooled or not; see Table 39.7)

Term	Calculation	Explanation	TOBY example	In lay terns
Risk	Risk (in intervention group) = a/(a+b) Risk (in control group) = c/(c+d)	Number of 'events' compared to all the 'events and no events' together.	Risk (in cooling group) = a/(a+b) = 33/120 = 0.275 Risk (in control group) = c/(c+d) = 48/117 = 0.41	In all the infants who were cooled the risk of cerebral palsy is 28%, whereas the risk for all those who are not cooled it is 41%
Relative risk (RR) (risks ratio)	$RR = \dfrac{a/(a+b)}{c/(c+d)}$	How many times more likely it is that an event will occur in the treatment group relative to the control group: RR < 1 Effective RR = 1 Ineffective RR > 1 Harmful	RR following cooling = 0.275/0.41 = 0.67 (67%)	Infants who were cooled had two-thirds of the chance of developing cerebral palsy.
p-values	Dependent upon the statistical test employed.	How likely it is that the result you found is due to chance.	The relative risk of cerebral palsy in survivors of HIE is 0.67 (p=0.03)	'I am 97% sure that cooling an infant will reduce the chance of them developing cerebral palsy. There is a 3 in 100 possibility that these findings occurred completely by chance' (if p=0.03)
Confidence intervals	Dependent upon the statistical test employed.	The range within the true effect is 'likely' to fall. The likelihood is described using p-value.	RR confidence interval = 0.47–0.96 (p=0.03)	If this research project were repeated 100 times, 97 of the studies would give a relative risk within the range of 0.47–0.96. 'I am 97% confident that the true effect size lies in this range.'
Odds	Odds (in intervention group) = a/b Odds (in control group) = c/d	Number of 'events' compared to 'no events' in one of the groups.	Odds (in cooling group) = a/b = 0.38 (38:100) Odds (in control group) = c/d = 0.70 (70:100)	In the infants who were cooled, for every 38 infants who developed cerebral palsy there were 100 infants who did not develop cerebral palsy. In the infants who were not cooled, for every 70 infants who developed cerebral palsy there were 100 infants who did not develop cerebral palsy.
Odds ratio (OR)	$OR = \dfrac{a}{b} \Big/ \dfrac{c}{d} = \dfrac{a \cdot d}{b \cdot c}$	The ratio of the odds of an event in the intervention group to the odds of an event in the control group OR < 1 Effective OR = 1 Ineffective OR > 1 Harmful	OR following cooling = 0.38/0.70 = 0.54	There is a 46% reduction in the likelihood of developing cerebral palsy in those who were cooled compared to those who were not.
Absolute risk reduction (ARR)	$ARR = c/(c+d) - a/(a+b)$	The absolute difference in the rates of events between the two groups. The ARR gives an indication of the baseline risk and treatment effect: ARR > 0 Effective ARR < 0 Harmful	ARR = 0.410 – 0.275 = 0.135 (14%)	Cooling an infant following HIE reduces the risk of cerebral palsy by 14%
Control event rate (CER)	$= \dfrac{c}{(c+d)}$	Same as risk (control group)	CER = c/(c+d) = 48/117 = 0.41	Same as risk (control group)
Relative risk reduction (RRR)	Relative Risk Reduction = $\dfrac{\text{Absolute Risk Reduction}}{\text{CER}}$	The reduction in rate of the outcome in the intervention group relative to the control group	RRR = 0.135/0.41 = 0.33 (33%)	If you cool your newborn baby having suffered HIE, you reduce their risk of cerebral palsy by 33%.
Number needed to treat	$NNT_B = \dfrac{1}{ARR}$	Number of patients needed to treat in order to prevent one adverse event: NNT ≥ 1 Effective NNT ≤ –1 Harmful	NNT = 1/0.135 = 7.4	For every seven infants who we cool after HIE, we will prevent one case of cerebral palsy

Antenatal steroids for preterm birth

You are asked to speak to a pregnant woman who is in preterm labour. She is very hesitant to receive steroids as she wants a 'natural birth'. She wants to know just how beneficial steroids will be to her infant. You know that a Cochrane review was performed on this and so refresh yourself on the data. Treatment with antenatal corticosteroids was associated with a reduction in death.

	Antenatal steroid	No steroid	Total
Death	261	341	602
Survival	1552	1473	3025
Total	1813	1814	3627

Risk steroid = 0.143

Risk no steroid = 0.188

Question 39.2

Which of the following is the true absolute risk reduction for death? Select ONE answer only.

A. 4.5%

B. 24.0%

C. 31.5%

D. 73%

E. 76%

Question 39.3

Which of the following is the true relative risk reduction for death? Select ONE answer only.

A. 4.5%

B. 24.0%

C. 31.5%

D. 73%

E. 76%

Question 39.4

Which of the following is the number needed to treat to prevent one death? Select ONE answer only.

A. 1.3

B. 1.4

C. 3.2

D. 4

E. 22

Question 39.2

A. 4.5%.

Question 39.3

B. 24.0%.

Question 39.4

E. 22.

Refer to Table 39.8 for method for calculations.

4. Applicability

Can I apply the results so that my patients receive similar benefits to the study participants?

The question of applicability is the natural bridge into Step 4: Applying the evidence to your patient, and involves asking questions such as:

- Is my patient similar to the patients studied?
- Were all clinically important outcomes considered?
- Do the potential harms of treatment/investigating outweigh the benefits?
- Can I offer the treatment/test?

Step 4: Applying the evidence to your patient

The evidence must next be applied to the individual patient taking into account the patient's and family's own values, preferences or beliefs. Part of our appraisal process (Step 3) is critically analysing the paper in the context of our own patient. We should ask ourselves several critical questions, which are considered below.

Is my patient similar to those patients studied?

In most cases, the treatments we use have not been tested in trials where the populations matched ours exactly. In paediatrics, often the evidence is translated from adult studies. The outcomes recorded may only be surrogates, rather than clinically important changes. In order to use the best evidence in practice, we must consider how they apply to our patients. To do this we should:

- Ask if there are biological differences between the populations. In terms of febrile seizures (Table 39.9), does your patient have developmental delay that would make him/her distinctly different from the population studied?
- Consider whether differences in psychology, social setting, or economy will stop the data being applicable. If there are significant differences in economic or social setting, it may strongly affect the results. For example, a child with a previous febrile seizure, who attends nursery, may have a

Table 39.9 Best evidence topic – prognosis

Prognosis – febrile seizure (FS)

Scenario: A developmentally normal 18-month-old infant with no family history of febrile seizures presents with a febrile seizure (FS) during an upper respiratory tract infection and fever of 38.5°C. His mother is very anxious about what has happened and would like to know if it is likely to happen again.

Step 1: Asking a question: In a child with a first febrile seizure [patient] without complex features [interesting thing], what is the risk of future febrile seizures [outcomes]?

Step 2: Acquiring evidence:

Search terms: (Seizures, febrile OR febrile Convulsion* OR Febrile Fit) AND (Child OR child* OR infant*). Databases: Cochrane library – nil. PubMed Clinical Queries (Prognosis, Systematic Reviews) – 72 results.

Step 3: Appraising the evidence:

Study group	Interesting thing	Study type	Outcomes	Key results	Comments
2496 children with 1410 episodes of recurrent FS.	Seizure occurring with fever (≥38°C). Excluded children with neurologic abnormality (including developmental delay) or who had received prophylactic antiepileptic medication.	Pooled analysis of five cohort studies (two population-based, three clinic-based). All had same definition of FS.	Risk factors: 1. Family history (FH) of seizure in a 1st degree relative. 2. Initial FS type (e.g. >1 in 24 hours, partial, prolonged (>15 mins). 3. Temperature at time of FS. 4. Number and type of FS recurrence. 5. Complex seizure recurrence.	30% of children will have a recurrence after a first FS. 7% will have a complex seizure recurrence. 47% of these will have a further recurrence. Hazard (number of recurrences per child/month): • Age (12m) = 0.03 • Age (24m) = 0.25 • Age (>36m) = <0.005 Hazard ratios: • FH = 1.42 • Fever <40.0°C = 1.54	Hazard ratio described for temperature above or below 40°C, but this is not clinically useful In day-to-day practice the temperature is not always taken at time of seizure.

Commentary:

FS is a common acute presentation to general paediatric units. There are theories that children have a genetically determined (FH) threshold of seizures during a certain age period. This is consistent with these results. A pooled analysis is in essence a form of meta-analysis. It pools the raw data rather than the published data. This has the advantage that some errors in the data or analysis can be partially eliminated. These are therefore very expensive and time-consuming to conduct but result in higher-quality evidence.

This mother can therefore be counselled that recurrence rate is 30% but for her child it is slightly lower as there is no FH of note and because of his age. His low fever of 38.5°C (i.e. it was <40°C) does increase his risk of recurrence.

Step 4: Applying the evidence (the clinical bottom line)

1. Recurrence hazard declines with time and is highest in the first 6 months after the initial seizure.
2. Children aged <18 months at onset have a higher recurrence hazard.
3. Temperature (<40.0°C) and FH are the only other risks associated with recurrent seizure. (Weak recommendations, moderate quality evidence.)

NB: The * in the search terms is referring to search truncations to ensure optimum sensitivity of the search (see Table 39.2).

Reference:

Offringa M, et al. Risk factors for seizure recurrence in children with febrile seizures: a pooled analysis of individual patient data from five studies. J Pediatr 1994;124(4):574–84.

higher risk of fever episodes and therefore a higher risk of febrile seizure. Social circumstances may mean that one family will opt for ambulatory care with the possibility of readmission, where another requires in-patient facilities.

Were all clinically important outcomes considered?

Did the researchers consider all the outcomes that are important to your patient? What is the information on side effects? Is there any information about adverse events in children? Are the outcomes described directly relevant to our patients (e.g. length of time in hospital) or surrogate outcomes (resolution of chest radiograph findings in Table 39.6)? As with everything in EBM, these guides do not give you the rules to act on, but tools to think through.

Benefits and harms

When applying the results of a clinical trial, it is often difficult to tangibly understand the balance that should be struck between the beneficial and adverse effects of a treatment. If, hypothetically, intravenous antibiotics had been found to reduce hospital stay in every three treated (NNT = 3) but resulted in 1 in 50 having a significant episode of MRSA bacteraemia (number needed to harm (NNH) = 50), then is it worth using the treatment?

There is a coarse way to approach this: say 'Yes, of course it is' and give the drug. Then there is a purely qualitative way: 'How would you like this drug that might be good at getting you home quickly but might make you very sick?' And then there is another way which seeks to quantify the differences by asking: 'How much worse is MRSA bacteraemia versus being in hospital?' If the patient says 'It's 25 times as bad', use it to adjust the estimates like this: NNT for good thing versus NNH for bad thing/relative importance:

NNT = 3 vs weighted-NNH = 50/25

NNT = 3 vs wNNH = 2.

This means it would be rational for this person to take oral medication as the chance of benefit from intravenous antibiotics (one in three) is outweighed by the adjusted chance of adverse effects (one in two). This method of adjusting NNTs provides a way of conceptualizing in a rational, individual, way.

Feasibility

Is the treatment, test, etc., available within your clinical environment? Do I have the facilities and resources (e.g. time, money) to ensure the treatment is administered safely?

When considering if you can go 'beyond the evidence', look at biological and psychological differences, consider the inherent risk and co-morbidities, examine all the outcomes closely, and assess if the action is possible. Then you will have a better idea of how far you can apply 'best evidence' to your practice.

Presenting statistics to patients

How we present research results to patients is important. We could say:

- 'For every ten people I give this drug to, one will benefit' or
- 'Taking the drug improves success rates by 10%' or
- 'Taking the drug will double your chances of success.'

The above statements all refer to the same underlying difference of treatment success in 20% of patients versus 10% in the comparison group. The statements refer to the NNT, the 'absolute risk reduction' and the relative risk, respectively. Examples of how to present statistics to patients are given in Table 39.8.

What to do when the evidence you find contradicts practice

Why do we find it so difficult to break our clinical practice habits? It may be just something deeply entrenched in our human psychological make-up.

Two people can look at the same data but come to opposite conclusions.

It can seem daunting to try to change our own practice, let alone the practice of senior clinicians. It very much depends on personalities and relationships, but it is often a refreshing change to have new evidence presented, or an enquiring mind focusing on improving what is undertaken. Some bosses are like oil tankers in the time and effort it takes to change direction, but many are not and will happily modify practice if it is going to improve the care of their patients. The right approach can help: assume wisdom and helpfulness and ask something like 'Could you find some time to look at this research I came across? It seems at odds with what we do, and might be important to discuss.' However, before changing the practice of others, it is good to learn how to alter the way you behave yourself. We do not usually change rapidly but we need to become aware, then accept, then learn the 'how to', and then finally take the plunge.

Step 5: Assessing your performance

e-portfolio

The RCPCH e-portfolio is used by trainees in the UK. Trainees in paediatrics are expected to log two clinical questions each month in order to meet their competencies of training. Use these cases as an opportunity to direct a case-based discussion (CbD). In this respect, not only will your clinical skills be appraised but also your EBM skills.

Giving an evidence-based presentation

Case-based journal clubs

Sadly many journal clubs continue to run along the lines of 'I found this interesting article in last month's edition of Archives, let's have a look at it.' This is an example of 'just in case' information and therefore will waste one hour of time for each of the busy clinicians attending.

An evidence-based journal club should focus around a case and a relevant paper. Appraisal should consider 'how good is the study?' rather than 'how poor is the study?' Such a journal club can be split into three sections, cycled between subsequent weeks:

1. A question is devised, based around a real patient recently seen in the department.
2. A search performed and the best paper(s) found.
3. An analysis of the best paper(s) and how the results can be applied to the patient.

Question 39.5

Statistical terms

Following is a list of statistical terms:

A. Absolute risk reduction

B. Confidence interval

C. Control event rate

D. Number needed to harm

E. Number needed to treat

F. Odds

G. Odds ratio

H. p-value

I. Relative risk

J. Relative risk reduction

K. Risk

Which of the following is best described by the lay descriptions of statistical terms above? Select ONE answer only for each question. Each answer may be used once, more than once, or not at all.

1. You are treating a pre-school aged child with an acute exacerbation of asthma. On discharge you want to start an inhaled steroid. His mother is worried about side effects and whether it is worth starting the medicine. You find a randomized controlled trial that is applicable to the patient. You are able to tell the mother that 41 children of this age would need to be given the treatment to prevent one exacerbation requiring oral-steroid.

2. You are treating a pre-school aged child with an acute exacerbation of asthma. On discharge you want to start an inhaled steroid. His mother is worried about side effects and whether it is worth starting the medicine. You find a systematic review that is applicable to the patient. You are able to tell the mother that from this paper you are 95% certain that steroids do reduce the number of children who have further exacerbations.

3. You are treating a pre-school aged child with an acute exacerbation of asthma. On discharge you want to start an inhaled steroid. His mother is worried about side effects and whether it is worth starting the medicine. You find a randomized controlled trial that is applicable to the patient. The results of this study show that inhaled steroid reduced the risk of exacerbations requiring oral steroids by 27% from 15% to 11%.

Answer 39.5

1. E. Number needed to treat
2. B. Confidence interval
3. J. Relative risk reduction

These steps may need to be dissected so that they can be performed over subsequent meetings.

The problems you are likely to face when doing this include:

- Lack of answers to the questions asked.
- Research nihilism – no paper is perfect so no answer can be given.
- Lack of access to papers.
- Staff changes and constantly revisiting the basics.

Evidence-based presentations

1. When you are asked to give a presentation – whether a case, an audit or a research project – you can use the framework of EBM to guide your work. Outline the 'patient's dilemma' and the clinical question.
2. Refer to how you found the information you are presenting (you do not need to screenshot your searches for this).
3. Appraise the information; tell your audience about its strengths and weaknesses.
4. Synthesize this and come up with an action and learning points.
5. Ask – perhaps beforehand – for feedback you can place in your e-portfolio.

Depending on what you are focusing on, the proportion devoted to discussion will vary. For example, if you have a research project/paper to describe, then still set the background using the EBM framework and how you found the information or paper, but your own appraisal will take up most of the presentation..

Practising in an evidence-based way

EBM: 'doing' or 'using'

The doing mode of EBM is the purest form and involves at least the first four steps of EBM (see Table 39.1). This allows tailor made searches for evidence for individual patient needs. The using mode of EBM involves searching sources where evidence has already been searched and appraised by a secondary party. This allows rapid and efficient acquisition of evidence that has already been searched and appraised, a limiting factor being that the evidence may not be as highly relevant to your patient's needs. Neither of these is

more 'correct' than the other and most practitioners of EBM will move between the two.

Guidelines

A common definition of a guideline is 'a systematically developed statement to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances'. Some guidelines are excellent sources of information, and the authors have usually done the job of collating and appraising all relevant evidence into a clinically relevant document. Well-produced guidelines are an excellent way of providing both 'just in time' and 'just in case' information.

When is it appropriate to work outside of guidelines?

Guidelines are guides, not cages. They summarize and rationalize the management pathways for the vast majority of children, young people and families with medical problems. Sometimes, though, the guideline is not appropriate for the patient in front of you, and learning when to deviate from guidelines is a high-level skill that needs to be mastered to be a truly competent clinician.

There are some things that are obvious: if a child has had an anaphylactic reaction to penicillin, the guideline-advised piperacillin-tazobactam will be dangerously inappropriate. There are some less obvious: occasionally the crackly, wheezy, bluish child in front of you does demand a chest radiograph to detect the mediastinal mass that is causing the problem. Learning where the balance of clinical experience, research-based data and patient/family characteristics come together is the art of EBM.

Just in case EBM

There is still a need to have a trickle of new information entering your life, not just the reactive 'pull' of clinically relevant answers. The best ways of getting it

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Box 39.7 Good sources of 'using' EBM information

Your sources of 'just in case' information should be highly filtered – along EBM lines:

- Set up an 'Evidence update' account with BMJ McMaster and have relevant evidence sent to you, for free (http://plus.mcmaster.ca/EvidenceUpdates/)
- Archimedes section of Archives of Disease in Childhood (http://adc.bmj.com)
- Journal of Paediatrics: Current Best Evidence (http://www.jpeds.com/content/societyCollectionCBE)
- UpToDate (www.uptodate.com)
- Evidence-Based Child Health: A Cochrane Review Journal
- Bandolier
- Clinical Knowledge Summaries

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vary, but require you to source a digestible, personally acceptable form of highly-EBM filtered news (Box 39.7).

Further reading

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Peter I Lachman, Ellie Day, Lynette M Linkson, Jane Runnacles

Quality improvement and the clinician

LEARNING OBJECTIVES

By the end of this chapter the reader should:

- Be aware of the main quality issues relating to paediatric care
- Understand the concepts of quality improvement
- Be able to describe basic improvement tools
- Be able to provide examples of quality improvement in child health

The concept of quality in healthcare and the understanding of its relevance and role have evolved over the past twenty years. Our aim as paediatricians is to improve the quality of care and outcomes for children. Our challenge is to work with children and families to understand the issues they face, to jointly define the potential solutions and then develop improvement programmes to implement them. We now understand that advances in medical science achieved in the last century are insufficient to guarantee good clinical outcomes. The UK reviews following the paediatric cardiac surgery clinical crisis at Bristol and high profile child protection cases confirm that we need more than our knowledge about clinical medicine and guidelines to achieve good clinical outcomes. These seminal events led first to the development of clinical governance and clinical audit, and subsequently raised the profile of the patient safety agenda and the concept of quality improvement.

Question 40.1

Quality improvement and patient safety concepts

Following is a list of patient safety and quality improvement terminology:

A. Effectiveness

B. Healthcare-associated harm

C. Natural variation

D. Medication error

E. Patient safety

F. Reliable healthcare

G. Risk management

H. Unwarranted variation

Which of the above terms is the most appropriate description for each of the following scenarios? Select ONE answer for each question:

1. Children presenting in status epilepticus receive treatment according to the NICE guideline when they present to the emergency department at their local hospital.

2. A child on the PICU dies as a result of a central line associated bacteraemia and review reveals that the central line care bundle has not been followed.

3. Discharge plans for asthmatic children in the paediatric department are different depending on which consultant is on call.

Quality improvement in healthcare is 'the combined and unceasing efforts of everyone, i.e. healthcare professionals, patients and their families, researchers, commissioners, planners and educators, to make the changes that will lead to better patient outcomes (health), better system performance (care) and better professional development (learning)'. This implies that we all are responsible for the quality of care we deliver and that quality improvement should be part of our job as clinicians and other healthcare providers.

The purpose of quality improvement in paediatrics and child health is to ensure that children receive *the care needed and wanted the first time, every time*. This requires safe, effective, care that is reliably and consistently delivered and the consideration of its value. The latter is defined from the viewpoint of the child and their family, i.e. what do they value in terms of the care that is delivered, both in terms of value for money but more importantly the value in achieving the child's desired outcome? There is a definite gap between what we know to be best practice from research and the care that is delivered to children. Quality improvement provides the framework to close this gap.

Major quality issues facing the health services in general

The Institute of Medicine identified six dimensions to quality care:

- Patient or person centeredness: ensures that patient values guide all clinical decisions.
- Equity: aims to provide care that does not vary in quality because of personal circumstances including geographic location, ethnicity and socio-economic status.
- Patient safety: intends to avoid harm from the care that is intended to help.
- Effectiveness: the provision of evidence-based care based on the need of the patient.
- Timely care: aims at ensuring access when and where care is needed.
- Efficiency: refers to the need to decrease waste, duplication and improve the performance of healthcare.

The above principles can be translated into practical standards, which form a useful framework for an approach to quality improvement:

- Governance for safety and quality in health service organizations, which incorporates clinical governance and the structures required for quality and safety.
- Partnering with patients to develop services and how services are delivered.
- Preventing and controlling healthcare-associated infections.
- Ensuring medication safety from prescribing to dispensing to administration and reconciliation.
- Patient identification and procedure matching at all times.
- Reliable clinical handover at all interactions.
- Blood and blood products safety.
- Preventing and managing pressure injuries.
- Recognizing and responding to clinical deterioration in acute settings.
- Preventing falls and harm from falls.
- Ensuring that the access to and the flow of patients through the system is timely and efficient.

Question 40.2

Variation in healthcare

A review of services at your local hospital reveals that there is a significant variation in the management of children admitted with asthma. This is most likely to suggest:

A. A lack of evidence on which treatment decisions for individual children can be based.

B. A well-constructed local guideline is in place, which identifies areas where the evidence base is inconclusive.

C. An incomplete understanding of the pathophysiology and natural history of the condition in childhood.

D. Outcomes are generally better for children when didactic algorithms are not in place.

E. Outcomes for asthma care in this centre are likely to be worse than expected.

Answer 40.2

E. Outcomes for asthma care in this centre are likely to be worse than expected.
 See below for discussion.

Quality problems facing children

Most of the above are adult focused but also apply to children. However, in paediatric and child health practice, children are subject to multiple and complex additional issues either in hospital or in the community. Any paediatric improvement programme either at national or local level needs to take account of and address these specific challenges.

Variations in service provision

As in adult care, variation in service provision is a key problem. An analysis of the way health services for children are organized has revealed that there are wide disparities in service provision across Europe (Wolfe et al 2013). A more consistent approach to the way we design and integrate services and how we address the totality of children's needs would result in the development of equivalent outcomes. On a system or policy level (known as the macro level), it has been recommended that in order to improve outcomes, one needs to look at the whole healthcare system and consider reconfiguration of the different elements of care in health as well as in social care and education. It is estimated that approximately 1500 preventable deaths occur in paediatric departments in the UK each year, while many more children live with preventable disabilities, chronic pain and unequal access to the services they need. Across the UK, variation in how care is delivered in different areas has a major impact on local outcomes.

There are three key components to variation in service provision: variation in how services are designed, variation in the choice of care interventions, and variation in the delivery of effective care.

1. Variation in how services are designed

The design of services and what can be provided is a major factor in the standard of care that children receive, and on their resultant outcomes. Variation is to be expected in all that we do and in all processes we undertake. This may be in the way we set up the systems and processes of care, or in the way we treat individual children. An example of systems variation is the difference in the way emergencies are managed within the working day, overnight and over weekends or bank holidays. The processes are clearly different; there is variation in the clinical expertise available and in the outcomes that are achieved. Another example is in emergency care provided when a major accident increases the number and rate of arrival of patients above the normal predicted range. This in turn can lead to problems in access and equity of delivery. Some areas may have long waiting times and others are seen promptly, depending on how the service is designed. Where a child lives determines the quality of the care they will receive. The Royal College of Paediatrics and Child Health (RCPCH) has highlighted this problem as one of the challenges that the NHS must address. Reports on disease-specific outcomes, e.g. on epilepsy, have demonstrated the impact variation can have on clinical outcomes.

2. Variation in choice of care interventions

In the past, the evidence base in paediatrics was not as robust as it is today. Many aspects of what we do now is well evidenced and the development of guidelines has provided a basis for what works and what does not. Parents will often defer to the opinion of the clinician, believing that it is based on the best evidence available. In cases where robust evidence does not yet exist, there needs to be local consensus on how to manage certain conditions in order to minimize variation.

3. Variation in the delivery of effective care

Where there is a clear evidence base and a gold standard of care for a specific disease or patient group, every child with that condition should receive the same care. Variation from standardized protocols, not dictated by the clinical needs of the child, may be unwarranted and harmful. Variation is to be expected in all clinical activity and is an inevitable consequence of differences between systems, i.e. different hospitals, different clinicians, different patients, etc. Unwarranted variation in care is that which is not explained by the clinical need or the choice of the parent and child. Unwarranted variation in care is widespread and occurs when clinicians:

- Overuse treatments or procedures that do not help patients get better
- Underuse interventions that can work
- Misuse interventions that can harm patients.

Variation in clinical care derives from decisions that clinicians make regarding diagnosis and treatment interventions and is the responsibility of clinicians. Resource and service design are less likely to be under the clinician's control. Trainees are aware of the different preferences of their consultants in the treatment of children where they work. Guidelines are often not followed and variation can be confusing for both staff and families and ultimately has a detrimental impact

on outcomes. Despite short-term clinical placements, trainees are well placed to undertake small tests of change and lead team-based improvement projects. Trainees have an opportunity to highlight and then address local variation through the use of improvement methodology.

To understand variation further, one also needs an understanding of the individuals who work in healthcare, i.e. their beliefs and attitudes, which form the culture of their work environment. Doctors are taught to be professionally autonomous and this influences their ability to work in teams. Changes in working patterns due to policies such as the European Working Time Directive require new ways to work together. These require a shift in culture and a change in previously held beliefs. Particular attention needs to be placed on the interaction of different professional groups within multidisciplinary teams; and across primary, secondary and social care boundaries. An understanding of the culture of the different professions, different clinical teams and the organization as a whole is essential to achieve improvement. Improvement and data collection needs to be seen primarily as a means to improve care rather than to judge how well individuals are doing or score performance.

Higher risk of harm

Patient safety is defined as freedom from healthcare-associated, preventable harm. Patient safety in children is different from adults, as they are vulnerable, dependent on adults and may lack a voice. Children rely on adults, and adult-trained clinicians frequently provide their healthcare in adult-oriented facilities.

Children vary in size, posing problems in interventions such as medication, e.g. weight-dependent drug dosing increases the risk of medication errors. Children are also more vulnerable from the failure of health professionals to recognize abnormal vital signs, such as heart rate, which vary with age.

A patient safety incident is any healthcare-related event that was unintended, unexpected and undesired and which could have caused or did cause harm to patients. Serious patient safety incidents are usually caused by multiple systems failures, rarely simply by frontline staff error. Errors may occur many times without any consequence; however, they only need to align once to cause a serious harm event. Patient safety projects need to consider a wider perspective and address the process of care rather than the individual care provider.

Risk management is the process by which one identifies factors that prevent the provision of safe, efficient and effective care. Traditional ways of detecting adverse events in paediatrics have relied on voluntary reporting.

Approximately 10–20% of errors are reported, and of those many do not cause harm. The measurement of harm is complex and requires a number of perspectives. Harm is best defined as 'anything that one would not like to happen to oneself, one's own child or a member of one's family'. Using a broad definition that is personal at the same time helps one understand how pervasive harm can be. The key is that in patient safety one wants to reduce harm to the minimum possible.

For children, the key challenges for safety are:

- The healthcare system is not child-focused, e.g. seeing children in an adult hospital.
- The environment may not be child-centred or designed around the needs of the child.
- The equipment may not be appropriate for all the children of different ages and needs.
- All the staff may not be trained in paediatrics or child health, or be fully aware of the nuances of child health and development.
- The children themselves cover a wide range of disease presentations as they vary in age from neonates to adolescents and young adults.
- The tasks may not be appropriate for the level of training or experience of the clinicians.

Specific problems include:

- Delayed and missed diagnosis of conditions such as sepsis, juvenile idiopathic arthritis, brain tumours and sepsis, to name a few.
- Failure to recognize clinical deterioration resulting in collapse and death.
- Medication harm due to prescribing errors, administration mistakes and poor reconciliation of prescriptions across healthcare settings.
- Infections of different types, especially peripheral and central line infections.
- Tissue viability due to cannulation.

An increasing number of patient safety tools are emerging to reduce medication harm (such as drug calculator apps and zero tolerance prescribing) and healthcare-associated infections (including care bundles to reduce central line infections), and to improve both the identification and management of the deteriorating child (Paediatric Early Warning Score (PEWS)) and communication between healthcare professionals (Situation, Background, Assessment, Recommendation (SBAR)).

Clinical care bundles are collections of processes required to effectively and safely deliver care for patients undergoing particular treatments with inherent risks. A bundle is a grouping of several *scientifically grounded elements* essential to improving clinical outcomes. Several interventions are bundled together and significantly improve patient care outcome. A patient gets a 'Yes' when all elements are achieved every

time and a 'No' even if one element is left out. One must achieve 100% compliance of all elements of the bundle. An example is the central line bundle, for which the key components are hand hygiene, barrier precautions on insertion, chlorhexidine skin cleaning, optimal catheter site selection and daily review of the line.

Coordination of care for chronic conditions

Perhaps the most challenging part of healthcare for children and their families is the coordination of care between the different healthcare providers, and across agencies such as social care and education. The many complex chronic paediatric conditions managed by multiple agencies make it difficult to deliver an integrated model of care which places the child at the centre of the process. It has also been hard to measure quality and outcomes. This is compounded by the lack of a single unifying IT infrastructure to support integrated care. Key problem areas include:

- Safeguarding of children, where there have been periodic catastrophic failures in protective services, with communication often being the underlying problem.
- Child mental health, with problems of children with behavioural problems not having access to services.
- Transition into adult care. In the UK, at least 20% of children are living with a chronic illness. These numbers are likely to increase with improved survival in disabling childhood conditions and UK data suggests that 26% of those with a chronic condition have multiple diagnoses. The commonest chronic diseases are arthritis, heart disease, respiratory problems, skin disorders and mental health conditions.

Lack of child-centred care

Healthcare services for children are traditionally designed around the healthcare professional, and are often attached to adult services, with poor integration of community and hospital care. For example, children may wait in adult emergency departments or use adult-focused community-based primary care. There is growing recognition of the need to adapt working practices to ensure high quality care is provided to children at all times. The National Service Framework for Children in England set national standards for children's health and social care, but there are still inequalities in children's health outcomes. Healthcare professionals need to consider whether the individual care provided to a child/young person is patient-centred and whether

the service and wider system is designed to meet the needs of children. Clinicians need to ask about the users' experience of healthcare and to enlist parents and children to co-design services in order to improve quality of care.

Improving healthcare

The translation of research findings into practice is problematic. Implementation science refers to the study of the methods used to translate and implement the findings of clinical research into clinical practice. This often involves the study of human behaviour and the way clinicians apply new knowledge.

Improvement science is grounded in testing and learning cycles to ensure that change results in measurable improvement. It requires an understanding of statistics and psychology, and is grounded in a 'learning cycle'. Just as one would design an experiment to test a hypothesis in a scientific experiment, a QI project involves identifying a problem that needs improvement, assessing the factors that may cause the problem, introducing an anticipated improvement, followed by data collection to show if this change has led to the anticipated improvement. Box 40.1 summarizes some examples of paediatric improvement interventions.

Achieving improvement is not easy. Simply asking people to improve by working harder has not been effective. Improvement requires leadership, a clear vision, an understanding of ways to test changes followed by spreading and sustaining the improvement. Most of the theories behind the methods currently used were derived by statisticians or psychologists.

Healthcare organizations have adopted a number of approaches to improvement, ranging from comprehensive organization-wide methods which aim to change the total culture (Box 40.2), to simple techniques, described below, which an individual clinician or clinical team can apply.

Whichever method is used, the evidence suggests certain conditions need to be in place for successful implementation. This includes resources and training, clinical engagement, managerial participation, and organization-wide coordination and use of data. Healthcare can be a challenging environment for quality improvement, especially for trainee doctors. Success depends on fitting the chosen method with the local context and this may include adapting the approach to circumstance. When outcomes of an improvement project are less than optimal, it is rarely to do with the chosen method and more likely to do with the way individuals interact within the clinical team (this is termed the clinical micro system).

In most health systems, the method that has been recommended for the individual clinician or the

Box 40.1 Examples of paediatric quality improvement interventions

Case 1

Safety: How can the recognition of deterioration of seriously ill children be improved?

Background: A review of serious safety events (SSEs) and ward-to-ICU transfers identified five risk factors: family concerns, high-risk therapies, presence of an elevated early warning score, watcher/clinician gut feeling and communication concerns.

Intervention: Unit-based huddles (structured safety briefings) and 3-times-daily inpatient huddles were developed to identify patients at increased risk. Nurses reported any patient with a risk factor to the charge nurse every 4 hours; allowing escalation of concerns.

Results: UNSAFE (unrecognized situation awareness failures events) were measured. The rate of UNSAFE transfers per 10,000 non-ICU inpatient days was significantly reduced from 4.4 to 2.4. The days between inpatient serious safety events (SSEs) increased significantly (Brady PW, et al. Pediatrics 2013;131:e298–e308).

Case 2

Medications: Reducing medication errors in PICU by changing the prescribing system.

Background: Prescribing errors account for a large number of paediatric medication errors on intensive care units but voluntary reporting tends to underestimate the error rates.

Intervention: A zero tolerance prescribing policy, a dedicated prescribing area to reduce distractions and a formal set of rules for all was introduced. Nursing staff were asked to refuse to administer inadequate prescriptions and daily verbal feedback of prescribing errors was given. A monthly bulletin providing anonymous feedback of errors was published.

Results: There was a significant reduction in prescribing errors from 892 errors per 1000 PICU occupied bed days to 447 (an absolute risk reduction of 44%) (Booth R, et al. Intensive Care Med. DOI 10.1007/s00134-012-2660-7).

Case 3

Efficiency: Improving paediatric discharge/length of stay without increasing readmissions.

Background: Inefficient discharge impacts patient flow through the hospital and studies suggest that 1 in 4 paediatric patients experience unnecessarily long admissions.

Intervention: Improvement science was used to standardize discharge criteria for common conditions and plan for discharge proactively to reduce delays. Changes were tested using a series of PDSA cycles and statistical process control (SPC) charts (see Box 40.6) assessed the impacts of interventions over time.

Results: Within 18 months, the percentage of patients discharged within 2 hours of being medically fit had improved significantly (42% to 80%). This was associated with decreased median length of stay. There was no increase in readmission rates or decrease in patient satisfaction (White CM, et al. BMJ Qual Saf 2014;23:428–36).

Box 40.2 Lean six sigma methodology

Lean is a concept that was developed in Toyota motor manufacturing to describe the way in which production processes are organized. It is basically about getting the right things to the right place, at the right time, in the right quantities, while minimizing waste and being flexible and open to change.

Lean thinking focuses on what the customer values: any activity that is not valued is waste. If you remove the waste, the customer receives a more value-added service, which in healthcare could mean any activity that helps patients manage their symptoms or get better. The 5 principles of *Lean* are:

1. Specify value by involving patients in your work: map their 'journey' through your organization to allow staff to see what the patient sees.
2. Identify and visualize the value stream, i.e. what makes the patient journey worthwhile. Mapping the different stages of the process helps to understand how a patient receives care.
3. Analyse the steps to see the obstacles that prevent free flow of the patient on their journey, or the unnecessary steps that are not of benefit to them.
4. Pulling patients along their journey may be more effective than 'pushing' patients from one queue to another. This is more important for those patients with more than one problem.
5. Perfection aims to continually improve the patient journey through ongoing development of these principles.

In healthcare, *Lean* has a strong focus on reducing waiting times, since time spent waiting is not value-added. For example, Hereford Hospital has applied *Lean* to improve turnaround times in pathology and pharmacy. They have adopted rapid improvement events where staff identify waste using a form, and then decide on the areas to focus their improvements. They have run similar projects focused on the entire patient journey. (See Further reading for more examples.)
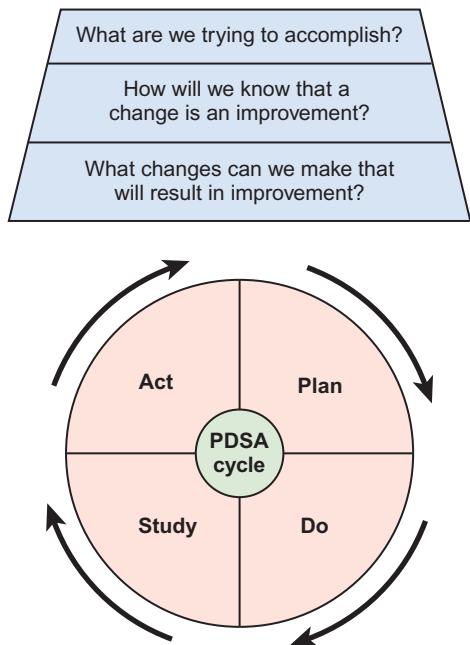
Fig. 40.1 **The Model for Improvement.** *(From Langley GJ, et al. The improvement guide, 2nd ed. San Francisco: Jossey-Bass; 2009, with permission.)*
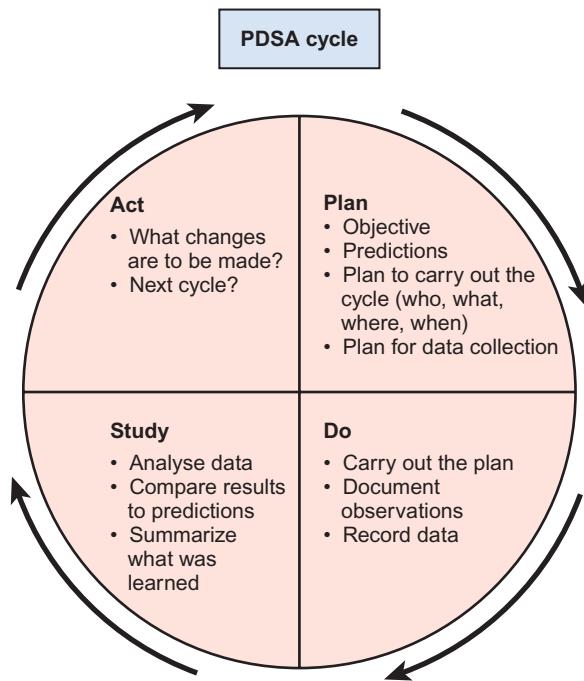
Fig. 40.2 **Plan Do Study Act (PDSA) cycle.** *(From Langley GJ, et al. The improvement guide, 2nd ed. San Francisco: Jossey-Bass; 2009, with permission.)*

Box 40.3 Clinical example of use of the Model for Improvement

Problem

A 5-year-old child is noticed not to be interacting all the time in class at school. There is no past medical history and no family history of note. There is no past illness and the child is otherwise well with a normal examination. The ECG is normal and the EEG indicated a pattern suggestive of petit mal epilepsy.

Aim (What are we trying to accomplish?)

To decrease the episodes of absence seizures from 10 per day to zero.

Measure (How will we know that a change is an improvement?)

The parents of the child and the nursery school teacher will record the number of absence seizures per day.

Parents will provide an assessment of the other reactions to the medication, e.g. behaviour, sleep concentration, etc.

Change or intervention (What changes can we make which will result in improvement?)

The child will be commenced on the lowest dose of the recommended anticonvulsant.

PDSA

PLAN: Discuss with parents the intervention, side effects and how to measure the number of absence seizures.

DO: The parents implement the recommended treatment.

STUDY: At the one month review, the effects of the intervention are assessed using the measures as well as other responses to the medication (behaviour, sleep, etc.).

ACT: A decision is made either to increase the dose or remain on the same dose.

And the cycle restarts.

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clinical team is the Model for Improvement (Fig. 40.1), also called 'a small test of change'. This is a method that is very similar to what we use in our day-to-day clinical practice (Box 40.3).

The methodology allows one to combine thinking and action through small-scale cycles of testing change (e.g. starting with one clinician and one patient). The process involves making a plan and predicting what will happen, implementing the small test of change, and then studying what happened before retesting (Fig. 40.2).

A clear aim statement and a set of defined measures to capture impact is the first step to a successful improvement project either on a small or large scale. Interventions, or ideas for change, can then be

Table 40.1 Changes to consider in healthcare

Domain	Example
Safety	• Decrease in prescribing errors • Prevention of unexpected clinical deterioration • Improvement of handover between clinical teams • Decrease in healthcare-associated infections (HAI)
Effectiveness	• Implementation of protocols • Developing 'reliability' in service provision, which means that the child receives the right care in the right place every time by ensuring that guidelines are followed all the time, or that staff changes do not mean a change in the quality of the service provided • Coordination of transitions • Improve communication between service providers using defined tools
Child-centredness	• Decreasing starving of children pre-operations • Environment in emergency waiting rooms • Integrated care with community services
Efficiency	• Starting clinics or operating lists on time • Decrease in repeat of blood tests • Decrease DNAs in clinic
Equity	• Change in services to improve utilization by disadvantaged children • Reduction of unwarranted variation in care (e.g. access to services, such as epilepsy specialist nurses, in different regions)
Timeliness	• Decrease waits for appointments • Timely review of new admissions by a consultant • Laboratory results returned for quick diagnosis

generated. Some will need to be aimed at the macro level; but changes should be made and measured by the front-line teams, so that improvement addresses local patient and clinical concerns. Empowering clinicians to lead change and make a difference to patient care adds value to patients and to the front-line clinician who has a duty to continually improve. The first step is to look for possible areas to develop a project. Table 40.1 suggests potential areas for improvement, which can be approached using the Model for Improvement framework outlined above.

A driver diagram (Fig. 40.3) can help determine how you approach your improvement project. It breaks the project aim into the key factors or components/drivers, which impact in the aim. The primary drivers are the fundamental requirements, the secondary drivers enable the primary driver to be achieved and these are followed by the changes to be tested.

The example below looks at the overall problem of deteriorating children, one of the key reasons there is a higher mortality rate in the UK than in other European countries. The outcome of cardiac arrest in children is poor, but the majority of arrests are preventable. Analysis of medical/nursing notes in the period prior to arrest may reveal documented changes in physiological parameters or variations in management/investigations that may have predicted or even prevented the arrest.

A quick review of the medical and nursing notes may be all that is required to identify valuable lessons for dissemination amongst relevant teams. This analysis should develop ownership from the clinicians themselves to encourage a no-blame safety culture.

The framework below has been successful, with anticipation and awareness being the major intervention.

Once a problem has been identified, it is important to define the aim for the project – what does one want to improve, by how much, where, on which group of patients and by when? This is demonstrated in Box 40.4.

Measurement for improvement

Question 40.3

Measurement of improvement

You have designed an improvement project aiming to decrease emergency admission rates for your patients with epilepsy. A colleague, who has read the relevant NICE guidelines, suggests that you measure the number of patients who have been reviewed in outpatient clinics within the last 12 months. She feels that infrequent review is contributing to poor control of epilepsy in some children. As part of your project, this measure would be classed as a:

A. Balancing measure

B. Outcome measure

C. Process measure

D. Standard measure

E. Structural measure

Answer 40.3

C. Process measure.

Data is the basis for all research, clinical interventions and decision-making, and also for improvement. Data for improvement is used to drive change. Data for research is used to develop new knowledge; and data for judgement is what one does in clinical audit – assess whether the set standards have been met. In the process of improvement, one needs data to understand the baseline (initial audit), develop an improvement plan, test changes and implement further change. A set of measures are defined to allow assessment of impact of each small change and sequential progress toward the overall aim. Once the aim has been achieved, measurement helps to ensure the improvement is sustained and the new process is part of normal working.

This approach differs from a randomized controlled trial in which the hypothesis and prediction is fixed throughout the process. With improvement projects, the aim is constant but the predictions and methods change depending on the results of small tests of change. The measurements obtained still have significance (p-values can be calculated), but the

approach is different to the scientific teaching of medical research.

There are four main types of measures:

- *Outcome measures,* which tell us what actually happens to the child – what are we ultimately trying to achieve? (e.g. for a paediatric diabetes service: average HbA1c level).
- *Process measures*, which tell us about how the system works – are we doing the right things to get there? (E.g. percentage of patients with HbA1c level measured twice in the past year.)
- *Balancing measures* – are the changes we are making to one part of the system causing problems in other parts of the system? (E.g. rates of hypoglycaemic episodes – to make sure they are not increasing with better glycaemic control.)
- *Structural measures* – do we have the right tools and resources (human, physical, financial) at our disposal? (E.g. percentage of patients who have access to a diabetes nurse specialist.)

In addition, one needs to consider the cost of the improvement and the value (quality over cost) it derives. The most important measures to collect are outcome measures that have been shown to improve care for patients. Outcomes are more challenging to
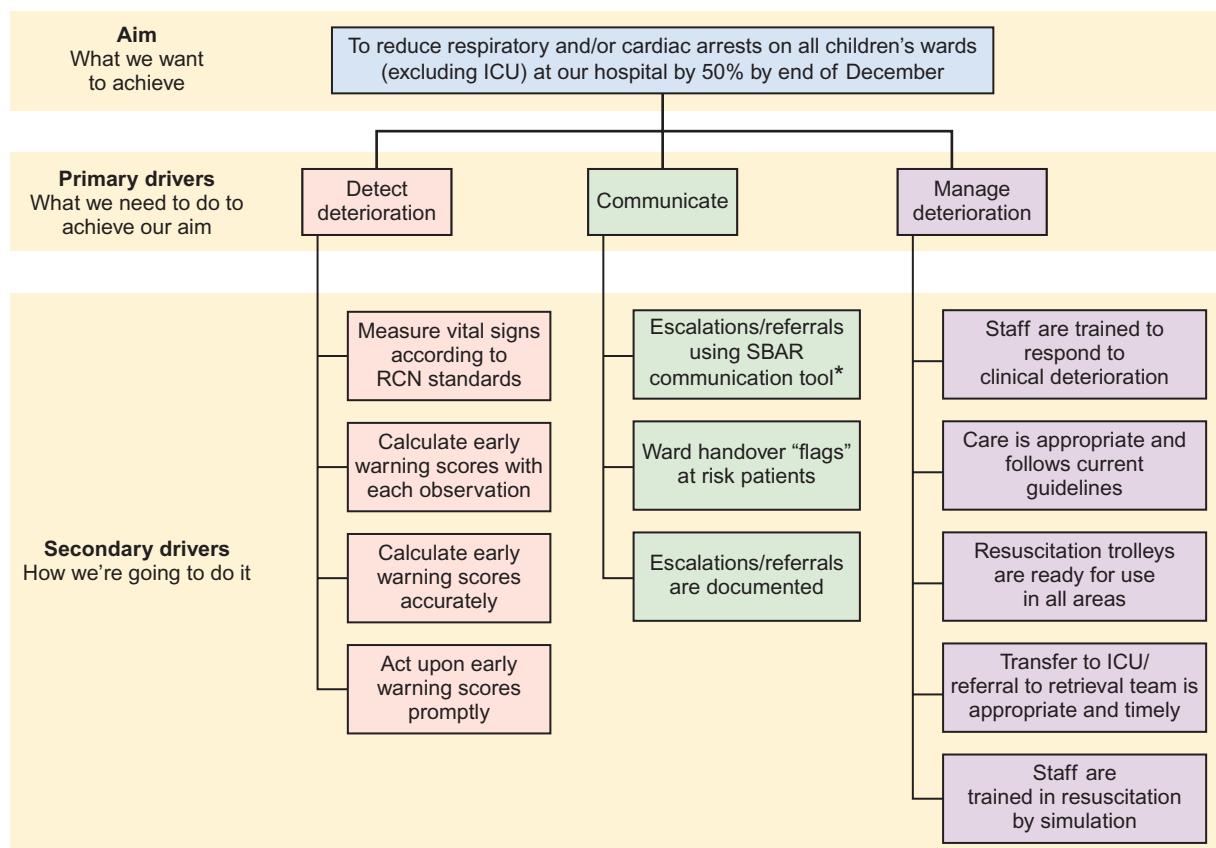
Fig. 40.3 Driver diagram. *SBAR, Situation, Background, Assessment, Recommendation. (From Runnacles J, Moult B, Lachman P. Developing future clinical leaders for quality improvement: experience from a London children's hospital. BMJ Quality and Safety, November 2013, with permission.)*

Problem

Failure to detect the clinical deterioration of children has been one of the challenges all front-line clinicians need to face. The early identification of the deteriorating child has been facilitated by the introduction of Paediatric Early Warning Scores (PEWS). These are used to convert the data from a combination of clinical and vital signs into a composite single score which can identify children at risk of sudden deterioration. There are different versions, but early warning scores consist of a combination of scores from a selection of routine observations of patients, e.g. pulse, respiratory rate, respiratory distress, and conscious level. If a child deteriorates, the score increases and gives an indication that the child needs to be assessed. However, they may not be the only factor which needs to be assessed and other signs may be present. The introduction of the score is difficult, as it requires a change in attitudes and behaviour.

Aim

To ensure that every child on the ward has an early warning score that is recorded and acted upon by the end of the year.

Plan

Meet with colleagues and other stakeholders to brainstorm ideas for implementing PEWS. Choose an idea that the team support, for example a new observations chart with PEWS. Develop the chart (the task) and then test it. Predict what will happen – will anyone use it, will the chart be appropriate, will it pick up the ill children? Can you measure the change?

Do

Do a trial (the small test of change) with this new chart for 10 patients on the ward for one day.

Study

Look at chart completion rates and get feedback from nurses about ease of use. You may also wish to study escalations to the medical team.

Act

Ensure staff members have access to results of the study phase. Consider next steps, for example redesign of charts if needed, posters and staff awareness/training activities. Each of these could form a new PDSA cycle.

Box 40.5 Using run charts to measure change

When collecting data, one needs to use measures that occur frequently, e.g. daily or weekly, so that learning accrues quickly. When identifying the chosen measure, one needs to consider how data will be collected, who will collect the data and how it will be analysed. First, measure the process for a short while, e.g. one week if frequent, and then plot the baseline. Extend the median and begin the test and annotate where you begin. Continue to plot as the data changes. There are rules as to when a significant change has occurred and once that has been proven, the median can be redrawn. Four of these rules are:

- If there are eight or more consecutive points on one side of the median excluding points on the

median, this indicates that a *special cause* has influenced the process, i.e. if a change has been made, and there are eight points on the positive side of the median, then the improvement is significant (see Fig. 40.4A).
- A *trend* is when five consecutive points occur in the same direction and this indicates that a special cause has occurred (see Fig. 40.4B).
- If you see a pattern that recurs eight or more times in a row, it is a good idea to look for a special cause (see Fig. 40.4C).
- If there is one data point far outside the mean, look for a special cause (see Fig. 40.4D).

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measure than processes, and therefore process measures can be used as a proxy in the short term, particularly if they are based on good evidence.

How to use run charts to study variation and demonstrate improvement

In quality improvement projects, we use run charts (Box 40.5, Fig. 40.4) and statistical process control

(SPC) charts (Box 40.6) to demonstrate continual improvement. These are a form of time series analysis, where data is plotted against time; statistical process control (SPC) charts are the simplest way to show the variation in a system. They allow for identification of variation that is normal, or variation due to extenuating factors that need to be investigated. These charts also help to assess whether an improvement has been made. There are numerous rules for the interpretation of run charts that allow for statistical significance to be inferred.

Question 40.4

Quality improvement projects

This is a list of possible steps in a quality improvement project:

A. Apply lean six sigma methodology

B. Audit the previous 12 months' data

C. Decide on your first PDSA (Plan, Do, Study, Act) cycle

D. Devise a driver diagram

E. Engage the multi-professional team

F. Invite patient input

G. Organize a process mapping session

H. Present to the senior management team

I. Record data using a run chart

J. Write a SMART (Specific, Measurable, Achievable, Realistic and Time-bound) aim

Which of the above is the most appropriate next step for each of these projects? Select ONE answer for each.

1. You have been tasked to improve the flow of new admissions from the emergency department (ED) to the ward (to reduce delays, ensure observations are recorded and improve completion of nursing admission documents).

You have already engaged the Emergency Department and paediatric multidisciplinary teams, who seem to have differing opinions regarding the correct sequence of actions when admitting a patient, so you need to clarify this.

2. Due to a number of complaints, your team plans to improve patient experience in the outpatient department to ensure it is more child-friendly. You have already engaged the play specialists and outpatient nursing team, who are keen to redesign the waiting area.

3. You are concerned about the large number of medication errors highlighted in a recent audit and have formed a team to improve this. The team have written a specific aim and planned the first PDSA cycle to see if a pharmacist present on ward rounds can reduce the number of errors.

Answers 40.4

1. G. Organize a process mapping session.
2. F. Invite patient input.
3. I. Record data using a run chart.

Box 40.7 provides eleven top tips to getting started with an improvement project.
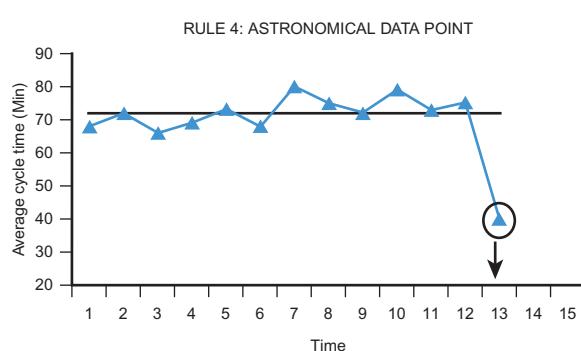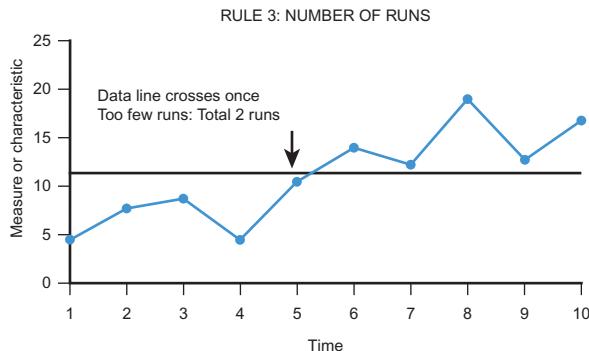
Fig. 40.4 Examples of run charts. See Box 40.5 for explanation. *(From Perla RJ, Provost LP, Murray SK. The run chart: a simple analytical tool for learning from variation in healthcare processes. BMJ Quality & Safety 2011;20(1):46–51, with permission.)*

Box 40.6 Use of a statistical process control (SPC) chart

A paediatric medical team is struggling to get their ward discharge summaries completed within the trust target of 24 hours post discharge. An incident has occurred where a patient has missed a treatment appointment due to a delayed discharge summary.

Aim: To reduce the number of days taken to complete discharge summaries and increase the percentage completed within 24 hours within 12 months.

Measure: Actual time taken (average number of days) and percentage completed within 24 hours (trust target). There are two measures for this project as they provide different information. A reduction in the average number of days taken to complete summaries is not demonstrated by the percentage measure. The baseline data showed the average number of days taken to complete summaries was around 5 days. It was important to track a reduction in the measure as this was likely to happen before an improvement in the number completed within 24 hours.

Change or intervention: There are meetings with all ward team members to discuss the issues. The team maps out the current process for the completion of discharge summaries. This identifies a number of issues and ideas. The team then identifies their first test of change to improve the process. Discharge summaries will be allocated to a specific doctor of the team at the main weekly ward round. Naming the person responsible for the summaries' completion will prevent confusion and ensure the work is fairly distributed amongst the team.

PLAN: All doctors in post-graduate training and consultants are informed of the plan and are asked to allocate a doctor to each patient on the Tuesday ward round. This is recorded on the handover sheet.

DO: The consultant allocates the name and the clinician's assistant records it on the handover sheet.

STUDY: After two weeks, the team meets to discuss how the tests have gone. The implementation of the new system is variable and not all the consultants are adopting the change. Trainees who have been allocated a discharge summary are still struggling to complete them within 24 hours because of their other clinical commitments.

ACT: The team discusses the issues and questions that have arisen and clarifies the confusion regarding the content and structure of discharge summaries. The team identifies a need for training and education to ensure there is a standardized content for discharge summaries. The next PDSA cycle will look at ensuring all consultants allocate names on the ward round.
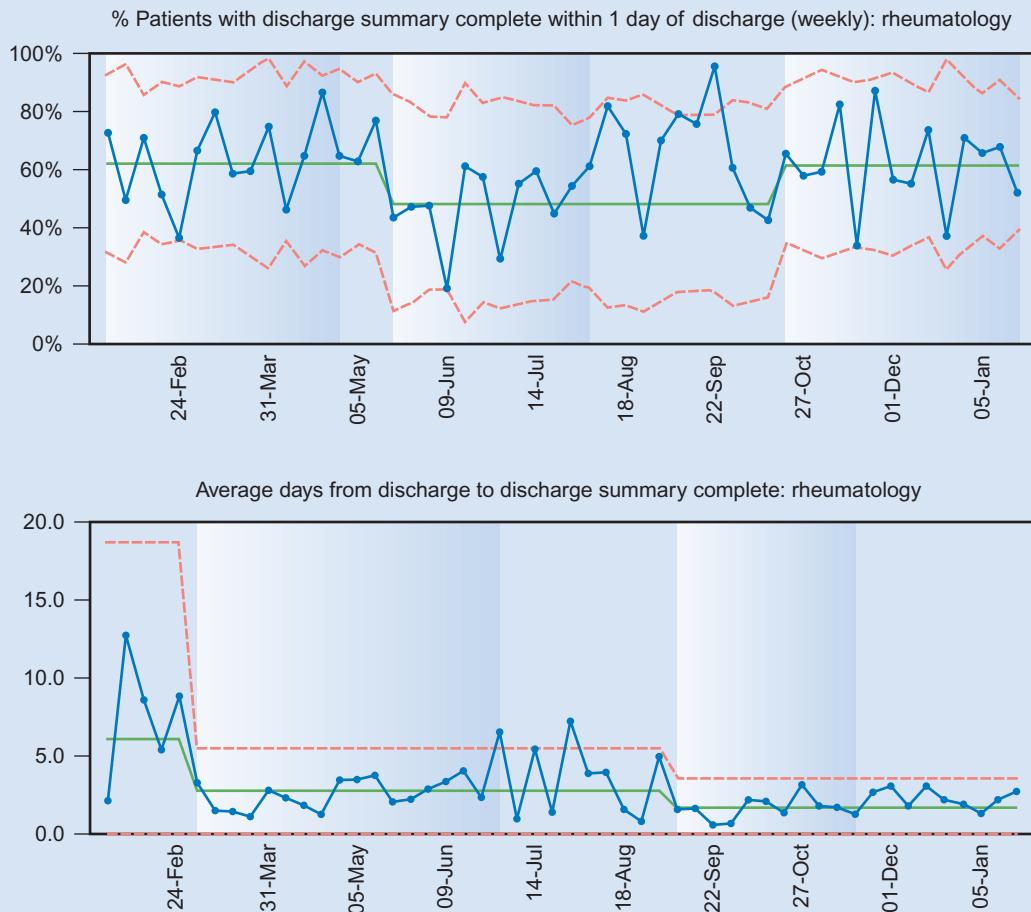
Fig. 40.5 A. Example showing percentage of patients with discharge summary completed within one day of discharge. B. Average number of days between discharge and completion of discharge summary. *(Courtesy of Great Ormond Street Hospital NHS Foundation Trust.)*

is paramount to provide good and high-quality care. However, these are not sufficient to provide continual improvement of patient outcomes and care that is safe and effective. Don Berwick outlined the challenge for all clinicians when he stated: 'Mastery of quality and patient safety sciences and practices should be part of initial preparation and lifelong education of all health care professionals, including managers and executives.'

The delivery of quality care is a shared responsibility; all of us working in paediatrics and child health have a responsibility to address concerns of variation, harm, care coordination and experience to improve the quality of care we provide to children and families. The start of a project begins with defining the problem – what do you want to improve?

Further reading

Institute for Healthcare Improvement. <www.ihi.org>; [accessed 12.09.15]. Provides information and tools and reviews on quality improvement and patient safety.

Panasar S, Carson-Stevens A, Salvilla S, Sheikh A. Patient safety and healthcare improvement at a glance. Chichester: Wiley-Blackwell; 2014.

Special edition on Quality Improvement and Patient Safety. Curr Treat Options Pediatr 2005;1(4). <http://link.springer.com/journal/40746/1/4/page/1>; [accessed 18.12.15].

The Health Foundation. <www.health.org.uk>; [accessed 12.09.15]. Provides evidence scans and up-to-date reviews of quality improvement.

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Conclusion

In any clinical practice, a good grounding in subject matter knowledge, technical skills and understanding of the pathophysiology, psychology and medical issues

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