THIRD EDITION

PRINCIPLES OF Pharmacology for Respiratory Care

Georgine Bills
Christina Rose

THIRD EDITION

PRINCIPLES OF Pharmacology for Respiratory Care

Georgine Bills, MBA, RRT
Emeritus Faculty, Weber State University
Ogden, Utah
Emeritus Faculty, Dixie State University
St. George, Utah

Christina Rose, PharmD, BCCCP
Clinical Professor in Pharmacy Practice
Director, PGY2 Pharmacy Residency in Critical Care
Temple University School of Pharmacy, Philadelphia, PA
Clinical Pharmacy Specialist in Critical Care
Temple University Hospital, Philadelphia, PA

JONES & BARTLETT
LEARNING

World Headquarters
Jones & Bartlett Learning
5 Wall Street
Burlington, MA 01803
978-443-5000
info@jblearning.com
www.jblearning.com

Jones & Bartlett Learning books and products are available through most bookstores and online booksellers. To contact Jones & Bartlett Learning directly, call 800-832-0034, fax 978-443-8000, or visit our website, www.jblearning.com.

Substantial discounts on bulk quantities of Jones & Bartlett Learning publications are available to corporations, professional associations, and other qualified organizations. For details and specific discount information, contact the special sales department at Jones & Bartlett Learning via the above contact information or send an email to specialsales@jblearning.com.

Copyright © 2021 by Jones & Bartlett Learning, LLC, an Ascend Learning Company

All rights reserved. No part of the material protected by this copyright may be reproduced or utilized in any form, electronic or mechanical, including photocopying, recording, or by any information storage and retrieval system, without written permission from the copyright owner.

The content, statements, views, and opinions herein are the sole expression of the respective authors and not that of Jones & Bartlett Learning, LLC. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not constitute or imply its endorsement or recommendation by Jones & Bartlett Learning, LLC and such reference shall not be used for advertising or product endorsement purposes. All trademarks displayed are the trademarks of the parties noted herein. *Principles of Pharmacology for Respiratory Care, Third Edition* is an independent publication and has not been authorized, sponsored, or otherwise approved by the owners of the trademarks or service marks referenced in this product.

There may be images in this book that feature models; these models do not necessarily endorse, represent, or participate in the activities represented in the images. Any screenshots in this product are for educational and instructive purposes only. Any individuals and scenarios featured in the case studies throughout this product may be real or fictitious, but are used for instructional purposes only.

The authors, editor, and publisher have made every effort to provide accurate information. However, they are not responsible for errors, omissions, or for any outcomes related to the use of the contents of this book and take no responsibility for the use of the products and procedures described. Treatments and side effects described in this book may not be applicable to all people; likewise, some people may require a dose or experience a side effect that is not described herein. Drugs and medical devices are discussed that may have limited

availability controlled by the Food and Drug Administration (FDA) for use only in a research study or clinical trial. Research, clinical practice, and government regulations often change the accepted standard in this field. When consideration is being given to use of any drug in the clinical setting, the health care provider or reader is responsible for determining FDA status of the drug, reading the package insert, and reviewing prescribing information for the most up-to-date recommendations on dose, precautions, and contraindications, and determining the appropriate usage for the product. This is especially important in the case of drugs that are new or seldom used.

13990-7

Production Credits
VP, Product Management: Amanda Martin
Director of Product Management: Cathy L. Esperti
Product Specialist: Rachael Souza
Project Specialist: John Fuller
Digital Products Manager: Jordan McKenzie
Digital Products Assistant: Rachel Reyes
Marketing Manager: Michael Sullivan
Production Services Manager: Colleen Lamy
VP, Manufacturing and Inventory Control: Therese Connell
Composition: S4Carlisle Publishing Services

Project Management: S4Carlisle Publishing Services
Cover Design: Scott Moden
Text Design: Kristin E. Parker
Media Development Editor: Troy Liston
Rights Specialist: John Rusk
Cover Image (Title Page, Part Opener, Chapter Opener):
© Winui/Shutterstock
Printing and Binding: LSC Communications
Cover Printing: LSC Communications

Library of Congress Cataloging-in-Publication Data
Names: Bills, Georgine, editor. | Rose, Christina, editor.
Title: Principles of pharmacology for respiratory care/edited by Georgine Bills, Christina Rose, Pharm.D., BCPS, BCCCP, Clinical Professor in Pharmacy Practice, Director, PGY2 Residency in Critical Care, Clinical Pharmacy Specialist in Critical Care, Temple University School of Pharmacy.
Description: Third edition. | Burlington, Massachusetts: Jones & Bartlett Learning, 2019. | Revision of: Principles of pharmacology for respiratory care/Georgine W. Bills, Robert C. Soderberg. 2nd ed. 1997. | Includes bibliographical references and index.
Identifiers: LCCN 2019010991 | ISBN 9781284139792 (pbk.: alk. paper)
eISBN 9781284139808
Subjects: LCSH: Respiratory agents. | Pharmacology. | Respiratory therapists.
Classification: LCC RM388.B55 2019 | DDC 615.7/2--dc23 LC record available at https://lccn.loc.gov/2019010991

6048

Printed in the United States of America
23 22 21 20 19 10 9 8 7 6 5 4 3 2 1

I dedicate this book to my mother, Joyce Wanta, RN, RRT, who was one of the first respiratory therapists in Utah and who developed the first respiratory therapy education program in Utah. She has been the best friend and mentor a daughter could have. I share Christina's dedication to the students and practitioners of our profession.

Georgine Bills

I dedicate this book to my husband Tim and my two children, Sabrina and Sam, who are always there to give me infinite love and support. I also dedicate this book to the students and respiratory care professionals who share a passion for learning, challenge me, educate me, and are dedicated to providing excellent care to all their patients.

Christina Rose

Brief Contents

© Anna RubaK/ShutterStock, Inc.

PART 1 General Pharmacologic Principles

Chapter 1 Introduction to Medication Information, Drug Development, and Regulation

Chapter 2 General Pharmacologic Concepts

Chapter 3 Introduction to the Pharmacology of the Autonomic Nervous System

Chapter 4 Dosage Calculations and Problem Solving

PART 2 Respiratory Care Pharmacology

Chapter 5 Administration of Aerosolized and Instilled Medications

Chapter 6 Bronchodilator Therapy

Chapter 7 Anti-inflammatory Drugs Used in Respiratory Disease

Chapter 8 Wetting Agents and Mucoactive Drugs

Chapter 9 Surfactant Agents

Chapter 10 Aerosolized Antimicrobial Therapy

Chapter 11 Agents Used in Special Procedures and of Pulmonary Importance

PART 3 General Pharmacology

Chapter 12 **Critical Care Pharmacotherapy and Advanced Cardiac Life Support**

Chapter 13 **Cardiovascular and Renal Pharmacology**

Chapter 14 **Pharmacology of the Central Nervous System**

Chapter 15 **Pharmacology of the Endocrine System**

Chapter 16 **Antimicrobial Pharmacology**

© Anna RubaK/ShutterStock, Inc.

Preface
How to Use This Book
About the Authors
Acknowledgments

PART 1 General Pharmacologic Principles

Chapter 1 Introduction to Medication Information, Drug Development, and Regulation

Introduction
Understanding Medication Principles
Drug Development
In Vitro and Animal Studies
Phase I
Phase II
Phase III
Phase IV
Abuse of Prescription Drugs
Sources of Drug Information
Review Questions
Posttest
References/Recommended Readings

Chapter 2 General Pharmacologic Concepts

Introduction
Pharmacology
Essential General Principles of Pharmacology
Routes of Administration
Drug Doses
Drug Absorption

Drug Mechanisms
Drug Distribution
Drug Metabolism
Drug Excretion
Factors That Alter Drug Effects
Patient Adherence
Placebo Effect
Pathologic State
Administration with Meals
Gender
Age
Genetic Variations
Drug Interaction
Review Questions
Posttest
References/Recommended Readings

Chapter 3 **Introduction to the Pharmacology of the Autonomic Nervous System**
Introduction
Nervous System
Function and Anatomy of the ANS
Neurotransmitters
General Physiologic Functions Controlled by the ANS
The Sympathetic Nervous System
The Sympathetic Nerve Ending
Sites of Action of Adrenergic Drugs
α-*Adrenergic Drugs*
α-*Blocking Drugs*
β-*Adrenergic Drugs*
β-*Blocking Drugs*
Adrenergic Neuronal Activators and Blockers
Overall Effects of the Parasympathetic Division
The Parasympathetic Nerve Ending
Mechanism of Action of Cholinergic Drugs
Definitions of Cholinergic Drugs
Anticholinesterase Drugs/Cholinesterase Inhibitors
Anticholinergic Drugs
Review Questions
Posttest
References/Recommended Readings

Chapter 4 **Dosage Calculations and Problem Solving**
Introduction

Dosage Units
Systems of Measure
Dosage Frequencies
The Joint Commission–Approved Abbreviations
Problem Solving
Drug Concentration Calculations
Continuous Aerosol Dosages
Other Drug Dosage Calculations
Solution Strengths
Dosage Guidelines for Infants and Children
Review Questions
Posttest
References/Recommended Readings

PART 2 Respiratory Care Pharmacology

Chapter 5 **Administration of Aerosolized and Instilled Medications**
Introduction
Aerosolized Medications
Disadvantages and Limitations of Aerosol Drug Delivery
Adverse Effects of Aerosolized Drug Delivery
Devices Used in Aerosolized Drug Delivery
Liquid Nebulizers
Metered-Dose Inhalers
Spacers and Holding Chambers
Dry Powder Aerosols
Multiple MDI Medications
SVN and MDI During Mechanical Ventilation
SVN During Mechanical Ventilation
MDI During Mechanical Ventilation
Ventilator Parameters During SVN Treatments
Instilled Medications
Disadvantages and Limitations of Drug Delivery by Instillation
Review Questions
Posttest
References/Recommended Readings

Chapter 6 **Bronchodilator Therapy**
Introduction
Mechanisms of Bronchoconstriction and Bronchodilation
Neurochemical Mediators in Bronchoconstriction and Bronchodilation
Relief of Mucosal Edema

Relief of Bronchospasm
Adrenergic (Sympathomimetic) Bronchodilators
Nonselective Sympathomimetics
β_2-Adrenergic Agonists
Sympathomimetic Drug Interactions
Anticholinergic Bronchodilators
Short-Acting Antimuscarinic Agents
Long-Acting Antimuscarinic Agents
Anticholinergic Drug Interactions
Combination Preparations: Adrenergic/Anticholinergic and Adrenergic/Corticosteroid
General Bronchodilator Special Considerations
Methylxanthines and PDE Inhibitors
Mechanism of Methylxanthines and PDE Inhibitors
Therapeutic Use of Methylxanthines
Side Effects of Methylxanthines
Description of Methylxanthines
Methylxanthine Drug Interactions
Magnesium
Mechanism of Bronchodilation Using Magnesium
Review Questions
Posttest
References/Recommended Readings

Chapter 7 **Anti-inflammatory Drugs Used in Respiratory Disease**

Introduction
Bronchoconstriction and Mucosal Edema
Alpha-Adrenergic Sympathomimetic Drugs Used in Mucosal Edema
Asthma
Asthma Management in Adults and Youths ≥12 Years of Age
Asthma Management in Children
Peak Flow Monitoring
Managing an Acute Asthma Episode (Status Asthmaticus)
Corticosteroid Anti-inflammatory Drugs
Advantages and Disadvantages of Aerosolized Corticosteroids
Indications for Inhaled Corticosteroids
Side Effects/Adverse Reactions of Aerosolized Corticosteroids
Antiasthmatic Drugs
Mast-Cell Stabilizers
Leukotriene Modifiers
Immunomodulators
Review Questions
Posttest

References/Recommended Readings

Chapter 8 **Wetting Agents and Mucoactive Drugs**

Introduction
Airway Mucus
Diseases Associated with Mucous Dysfunction
Mucoactive Medications
Bland Aerosols
Mucolytic Agents
Mucokinetic Agents
Expectorants and Bronchorrhea Agents
Guaifenesin
Sodium Bicarbonate
Review Questions
Posttest
References/Recommended Readings

Chapter 9 **Surfactant Agents**

Introduction
Surface Tension
Surfactant
Neonatal RDS
Surfactant Replacement Drugs
Indications for Exogenous Surfactants
Surfactant Replacement Drugs
Review Questions
Posttest
References/Recommended Readings

Chapter 10 **Aerosolized Antimicrobial Therapy**

Introduction
Rationale for Aerosolized Antimicrobial Drugs
Clinical Indications for Aerosolized Antimicrobials
Factors Associated with Efficacy and Safety of Inhaled Antimicrobials
Categories of Antimicrobial Drugs Administered by Aerosol
Antibacterial (Antibiotic) Drugs
Antifungal Drugs
Antiviral Drugs
Antiprotozoal Drugs
Limitations of Aerosolized Antimicrobials
Review Questions
Posttest
References/Recommended Readings

Chapter 11 **Agents Used in Special Procedures and of Pulmonary Importance**

Coauthored by Jennifer Hoh, PharmD
Introduction
Special Procedures
Bronchoscopy
Medications Used for Airway Hyperresponsiveness
Pulmonary Vasodilators
Inhaled Vasodilators in Acute Hypoxemia
Respiratory Stimulants
Apnea of Prematurity
Smoking Cessation
Smoking Cessation Methods
Pharmacologic Therapy for Smoking Cessation
General Considerations of Smoking Cessation
Review Questions
Posttest
References/Recommended Readings

PART 3 General Pharmacology

Chapter 12 **Critical Care Pharmacotherapy and Advanced Cardiac Life Support**

Coauthored by Jennifer Hoh, PharmD
Introduction
Rapid Sequence Intubation
Pretreatment
Induction
Critical Care Pharmacotherapy
Neuromuscular Blockade
ICU Analgesia and Sedation
Shock
ACLS: Adult and Pediatrics
Causes of Cardiac Arrest
Oxygenation
Ventilation and Capnography
Medication Use and Route of Administration
Rhythm-Based Management During Cardiac Arrest
Post–Cardiac Arrest Care
Review Questions
Posttest
References/Recommended Readings

Chapter 13 Cardiovascular and Renal Pharmacology

Coauthored by Michael Barros, PharmD
Introduction
Hypertension
Factors That Control BP
Current Therapeutic Approach to Hypertension
Physiology of the Nephron
Filtration
Tubular Reabsorption
Tubular Secretion
Diuretics and Their Therapeutic Role
Agents for the Treatment of Hypertension
ACE Inhibitors
Angiotensin II Receptor Blockers
Calcium Channel Blockers
Adrenergic Agents
Direct-Acting Vasodilator Drugs
Heart Disease
HF and GDMT
Cardiac Workload
Neurohormonal Activation
ACE Inhibitors
Angiotensin II Receptor Blockers
Angiotensin Receptor-Neprilysin Inhibitor
Beta-Adrenergic Blockers
Aldosterone Antagonists
Hydralazine and Isosorbide Dinitrate
Cardiac Glycosides, Digoxin
Angina and the Effects of Nitrates
Nitrates
Other Categories of Antianginal Drugs
Conduction System of the Heart
Definition and Types of Arrhythmias
Reasons for Converting and Causes of Arrhythmias
Antiarrhythmic Drug Classes
Examples of Antiarrhythmic Drugs
Coagulation Process
Anticoagulant Drugs
Antiplatelet Drugs
Lipids
Drugs Used in Treatment of Hyperlipidemia
Review Questions
Posttest
References/Recommended Reading

Chapter 14 Pharmacology of the Central Nervous System

Introduction
General Anatomy of the CNS
Cerebrum
Diencephalon
Brain Stem
Cerebellum
Effects of Drugs on the CNS
Sedative Hypnotics and Antianxiety Drugs
Barbiturates
Benzodiazepines
Alcohol (Ethanol)
Psychopharmacology and Treatment of Psychiatric Disorders
Categories of Psychopharmacologic Drugs
Antipsychotics
Treatment of Depression
Mood Stabilizers
CNS Stimulants
Epilepsy
Antiepileptic Drugs
Analgesics and Pain Management
Opioid Analgesics
Non-Opioid Analgesics
General Anesthetics
Properties of an Ideal General Anesthetic
Inhaled General Anesthetics
Preanesthetic Medications
Conscious Sedation
Review Questions
Posttest
References/Recommended Reading

Chapter 15 Pharmacology of the Endocrine System

Coauthored by Michael Barros, PharmD
Introduction
Pituitary Gland and Hypothalamus
Control of Hormone Release
Corticosteroids
Glucocorticoids
Mineralocorticoids
Function of the Thyroid Gland
Treatment of Hypothyroidism
Treatment of Hyperthyroidism
Function of the Pancreas

Cystic Fibrosis
Diabetes Mellitus
Treatment of Type 1 Diabetes
Treatment of Type 2 Diabetes
Antigen–Antibody Reactions
Effects of Histamine
Histamine Receptors
Antihistamines and Antiallergic Agent Definitions
Review Questions
Posttest
References/Recommended Reading

Chapter 16 **Antimicrobial Pharmacology 229**
Introduction
Antimicrobial Agents and Definitions
Principles in the Appropriate Use of Antibiotics
Causes of Failure in Antibacterial Therapy
Categories of Antibiotic Drugs
Beta-Lactam Antibiotics
Quinolones
Macrolides
Sulfonamides
Tetracyclines and Glycylcyclines
Aminoglycosides (Amikacin, Gentamicin, Plazomicin, Streptomycin, and Tobramycin)
Glycopeptides
Oxazolidinones
Cyclic Lipopeptides (Daptomycin)
Agents for Anaerobic Infections
Tuberculosis
Drugs Used in the Treatment of TB
Antifungal Drugs
Antifungals Used in Systemic Fungal Infections
Antiviral Agents
Antiviral Drugs
Review Questions
Posttest
References/Recommended Reading

Appendix
Glossary
Index

© Anna RubaK/ShutterStock, Inc.

The respiratory care professional has a broad scope of practice caring for outpatients as well as hospitalized patients with respiratory diseases and assisting with critical care procedures. One invaluable role of the respiratory therapist (RT) is to administer and educate patients on aerosolized and systemic medications used in the treatment of respiratory diseases and other therapies affecting the cardiopulmonary system. RTs will also monitor the effectiveness and recommend alternative therapies for these conditions. It is imperative for these professionals to understand the role of cardiopulmonary-targeted medication therapies and the mechanism of action of the drugs used in the treatment of the conditions they are treating.

Pharmacology is the study of how a drug interacts with the human body to cause an effect or desired therapeutic action. An RT is responsible for administering, monitoring, and recommending appropriate treatments for many cardiopulmonary conditions. It is important to understand the proper use, how a drug works in the body as well as the time to anticipate a drug effect, duration of action, and any adverse effects or side effects of the administered drug. The role of the RT continues to evolve, and with health care changing, they will care for more patients with various disease states. This text will not only focus on medication therapy used in the treatment of pulmonary conditions but also review other commonly used classes of medications an RT may encounter when caring for patients with multiple comorbidities. An RT may be required to discuss the importance of adherence to respiratory as well as other medication therapies to patients and need to be able to identify the adverse effect of medications that may interfere or influence the patient's cardiopulmonary system.

Section-by-Section Overview

Part 1 General Pharmacologic Principles

The layout of this text is divided into three distinct sections. The first section includes general pharmacologic principles required to understand the medication therapies, terminology, and drug mechanisms discussed in later chapters of the text. Illustrations, tables, and figures are provided to emphasize important information to the learner and highlight key points or complex concepts.

Chapters 1, 2, and 3 include an introduction to medical information, drug development, and general pharmacologic concepts, respectively. Common medication terms, definitions, and an introduction to terms used when discussing drugs with abuse potential are introduced in Chapter 1. This chapter also briefly reviews the drug development process and lists common

sources of drug information that can be valuable to an RT when seeking an answer to a drug-related question. Chapter 2 introduces general principles of pharmacology that are required to understand more in-depth descriptions of drug mechanism of action in drug therapy–specific chapters. The chapter starts by reviewing different routes of administration and the pros and cons of each. The term “pharmacokinetics” is introduced in this chapter and the factors involved in how a drug is absorbed, distributed, and cleared from the body are discussed. Chapter 3 reviews the role of the autonomic nervous system (ANS). The ANS includes the sympathetic and parasympathetic nervous system. There is a focus on how these systems influence body systems including the cardiopulmonary system. Drugs that affect each of these systems are reviewed in this chapter, with more detail of the therapies used in pulmonary disease discussed in Chapter 6.

Chapter 4 is a problem-based chapter focusing on drug calculations. The chapter starts with reviewing conversions between metric and household units. The calculations are concentrated on calculating doses from prepared solutions, converting between units of measure, and calculating doses for aerosolized medication therapy in volume and weight. Each problem is reviewed in a step-by-step format to ensure the learner can follow each step required to perform the calculation.

Part 2 Respiratory Care Pharmacology

The second section of the book is concentrated on drug therapies specific in respiratory care. Chapter 5 is a review of proper administration of aerosolized medications given by various devices and dosage forms. Figures and photographs illustrate the important principles. Chapters 6–11 review best practices in treating pulmonary diseases with targeted aerosolized and systemic therapies. Guideline recommendations for using bronchodilators and inhaled corticosteroids in the treatment of asthma and chronic obstructive pulmonary disease are discussed in Chapters 6 and 7. The optimal use of short-acting and long-acting bronchodilators and anti-inflammatory agents is emphasized as well as adverse effects to monitor when using these agents in patients and important patient education points. This section also discusses the mechanism of action and the use of mucolytics, surfactant use in neonates, and available aerosolized antimicrobials. Chapter 11 discusses the pharmacology and the use of agents in the assessment of pulmonary conditions and drugs used during bronchoscopy. This chapter also reviews other agents of pulmonary importance that are either administered or recommended by RTs including inhaled pulmonary vasodilators and medications used in smoking cessation therapy.

Part 3 General Pharmacology

The third section of the text is a review of the general pharmacology of common drug classes and therapies used in common medical conditions unrelated to the pulmonary system. Any effects these drug classes may have on the pulmonary system are emphasized. Chapter 12 addresses common medication therapies encountered in a critical care patient population. RTs are critical in the management of intensive care unit patients on mechanical ventilation. Understanding medications used in the treatment of shock, sedation, and pain management is important for RTs to be able to assess if a patient’s condition or medication therapy can be inhibiting their ability to wean from mechanical ventilation. Understanding the available treatment option to calm a patient asynchronous with the ventilator is necessary to care for mechanically ventilated intensive care unit patients. Medication therapies used during pediatric and adult cardiac life support are also reviewed. The American Heart Association recommendations and algorithms for the treatment of arrhythmias in cardiac arrest are also

included in this section. Chapters 13–16 review the mechanism of action, common uses and side effects of medications used to treat common cardiac diseases, drugs that affect the central nervous system and endocrine system, and common antimicrobial agents.

What's Unique

This text is a comprehensive reference on drug therapies used in the treatment of respiratory as well as other medical conditions.

- The mechanisms of action of the drug classes included are described in easy-to-understand language and difficult concepts are further clarified with figures or illustrations.
- Need to Know boxes highlight important information for students to remember.
- Case Studies are included in each chapter in Sections 2 and 3 of the text to allow students to apply the material discussed in the chapter.
- Open-ended review questions and posttest questions are included at the end of each chapter to allow the students to test their knowledge of the material covered in each chapter.
- Eight of the 16 chapters focus on dosage calculations and medication therapy specific for the assessment and treatment of pulmonary conditions.
- A critical care chapter highlights therapies that may influence patient compliance with or weaning from mechanical ventilation.
- Evidence-based guidelines for the use of the medication therapies discussed in this text are referred to and emphasized using tables and treatment algorithms.

How to Use This Book

© Anna RubaK/ShutterStock, Inc.

Chapter Features

- Each chapter of the book begins with a list of **Key Terms** and **Learning Objectives** to help you focus on the most important concepts in that chapter.
- Each chapter contains **Tables** that highlight important information, such as **Table 3-2 Effects of Parasympathetic and Sympathetic Divisions**

TABLE 3-2
Effects of Parasympathetic and Sympathetic Divisions

Neuroeffector Site	Sympathetic Effect (Norepinephrine)	Parasympathetic Effect (Acetylcholine)
Arteries	Vasoconstriction (*exception*: coronary and skeletal arteries are dilated)	Most are not affected
Heart	Increased rate and force of contraction	Decreased rate and force of contraction
Intestines and gastrointestinal activity	Decreased	Increased
Pupil of eye	Dilation (mydriasis)	Constriction (miosis)
Respiratory tract	Bronchodilation	Bronchoconstriction
Urinary bladder	Relaxation	Contraction
Urinary sphincter	Constriction	Relaxation

- This text is **illustrated** with diagrams and photos demonstrating a variety of concepts, including **Figure 14-1 Structures of the brain**

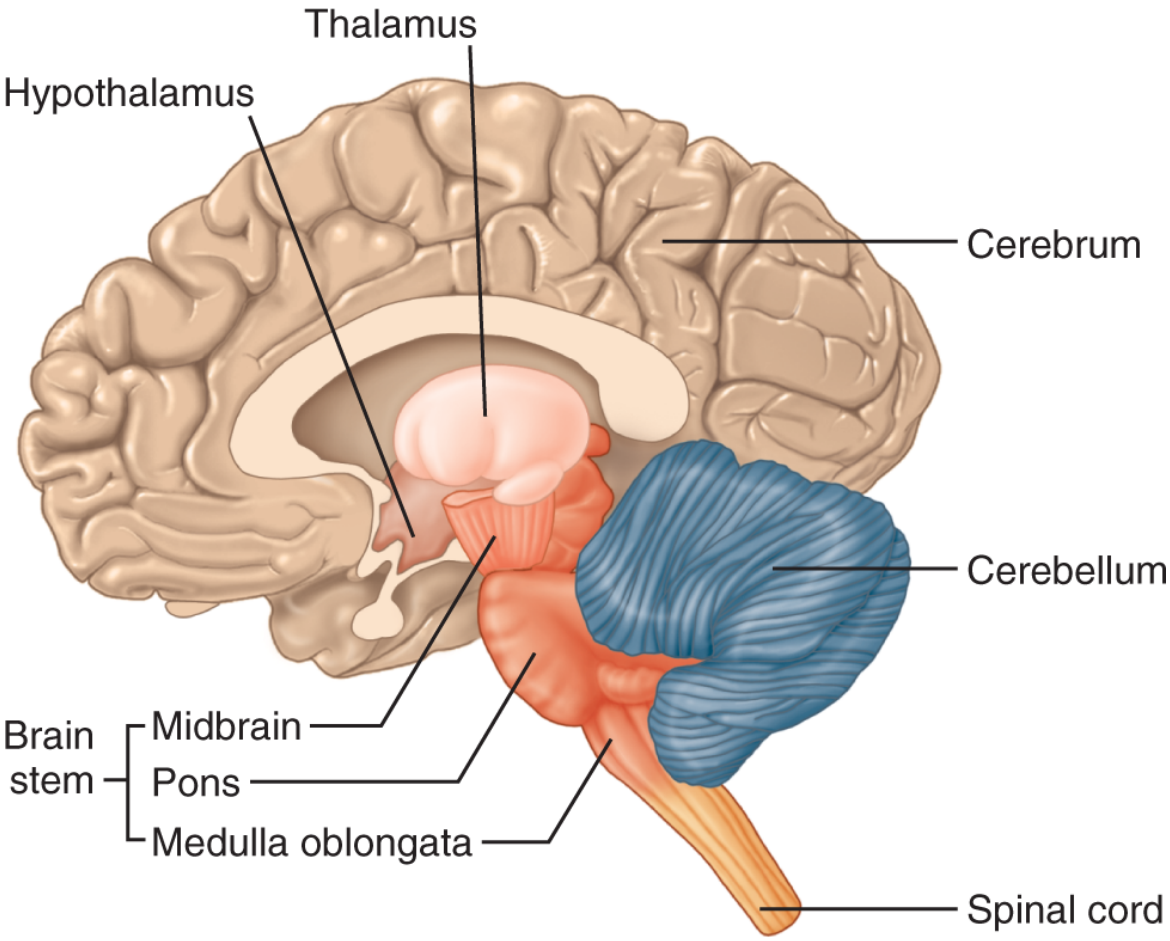


FIGURE 14-1 Structures of the brain.

- **Need to Know** boxes highlight important concepts for students.

NEED TO KNOW
Barbiturates, such as methohexital or phenobarbital, are CNS depressants and can cause respiratory depression at high doses.

- **Case Studies** are included so as to help the reader review and put into practice what they have learned.
- **Review** and **Posttest questions** test students on the important information from each chapter.

Instructor Resources

Qualified instructors will receive a full suite of instructor resources, including the following:

For the Instructor

- A comprehensive chapter-by-chapter PowerPoint deck
- A test bank containing more than 300 questions on a chapter-by-chapter basis
- 10 additional dosage calculation problems with answers

Case Study 14-1

A 76-year-old man is brought into the emergency department by ambulance. The patient's son found him minimally response when he went to check on him this morning and found an empty bottle of vodka on his nightstand. As the respiratory care practitioner (RCP), you are asked to put a non-rebreather mask and 12 L/min of oxygen and potentially be prepared for endotracheal intubation.

History: Insomnia, alcoholic cirrhosis, hypertension, and diabetes.

Vital signs: Heart rate, 118 beats/min; blood pressure (BP), 95/55 mm Hg; respiratory rate, 10 breaths/min; and O_2 saturation 93% on room air.

Home medications: Diazepam 20 mg HS for sleep (new prescription), propranolol 20 mg PO twice daily, and insulin glargine 20 units at bedtime.

Questions

1. Explain why or why not you believe diazepam is an appropriate benzodiazepine being used for sleep in this patient?
2. What were the factors that contributed to this patient's change in mental status and respiratory depression?
3. What drug can be used to reverse the effects of diazepam in this patient and what are the precautions for its use?

About the Authors

© Anna RubaK/ShutterStock, Inc.

Georgine Bills, MBA, RRT earned an A.S. (Respiratory Therapy, 1973) and B.S. (Health Administrative Services, 1985) from Weber State University and an MBA (Health Administrative Services emphasis, 1991) from the University of Utah. She practiced clinically at the University of Utah Medical Center (1970–1973) and Cottonwood Hospital (1973–1987), both in Salt Lake City, UT. She was the Respiratory Therapy Program Director at Weber State University for 17 years and retired as Emeritus Faculty in 2008. She then developed and was the initial program director for the Respiratory Therapy program at Dixie State University in St. George, UT, until her retirement in 2013.

She served on the AARC Board of Directors (1985–1988), was a site-reviewer for JRCRTE from 1988 to 2010, and was a member of several NBRC Cut-Score Committees. In addition to this textbook, she has authored several journal articles and a textbook chapter regarding pharmacology and the administration of medications by RCPs.

Christina Rose, PharmD, BCCCP, is a Clinical Professor in Pharmacy Practice at Temple University School of Pharmacy and a Clinical Pharmacy Specialist in pulmonary and critical care at Temple University Hospital in Philadelphia, PA. Christina earned her PharmD degree from the University of the Sciences in Philadelphia and completed a PGY-1 Pharmacy Residency at Virginia Commonwealth University Health-System in Richmond, VA and a PGY-2 Pharmacy Residency in Critical Care through the University of the Sciences in Philadelphia, PA. Christina is a member of the Respiratory and Clinical Pharmacy sections of the Society of Critical Care Medicine. She is also an active member of the American College of Clinical Pharmacy's Critical Care Practice Research Network. She has authored several book chapters and presented over 30 abstracts related to the pharmacotherapy of critically ill patients and pulmonary pharmacotherapy. Christina has been educating pharmacy and other healthcare professional students for more than 15 years. She is an active member of the multidisciplinary team caring for patients in the medical respiratory intensive care unit at Temple University Hospital.

Acknowledgments

© Anna RubaK/ShutterStock, Inc.

The authors acknowledge the contributions of Robert C. Soderberg, DDS, MS (Pharmacology) for his work on the first edition of this textbook. The authors also acknowledge the contributions of University of Kansas Medical Center faculty Bethene Gregg, MS, RRT; Barbara Ludwig, MA, RRT; Judith Mathewson, MS, RRT; Terri Dobey, MEd, RRT; and Paul Matthews EdS, RRT, FCCM for their work on the patient case studies in the first two editions of the text. Case studies for this edition of the textbook were revised and developed by Weber State University faculty Janelle Gardiner, MS, RRT and Lisa Trujillo, DHCc, RRT.

Part 1
General Pharmacologic Principles

© Anna RubaK/ShutterStock, Inc.

© Anna RubaK/ShutterStock, Inc.

OUTLINE

Introduction
  Understanding Medication Principles
Drug Development
  In Vitro and Animal Studies
  Phase I
  Phase II
  Phase III
  Phase IV
Abuse of Prescription Drugs
Sources of Drug Information

OBJECTIVES

After completion of this chapter and its learning activities, you will be able to:

1. Describe a drug's trade name, generic name, therapeutic dose, therapeutic effect, and side effects; and determine whether it is a teratogen or carcinogen, when provided with the drug's information.
2. Describe the four phases of drug development.
3. Describe some aspects of governmental control of abuse of prescription drugs and review the five schedules of drugs as defined by the Federal Comprehensive Drug Abuse Prevention and Control Act of 1970.
4. List the sources from where detailed and up-to-date information about drugs can be obtained.

KEY TERMS

Adverse reaction
Allergy
Carcinogen
Drug
Drug dependence
Generic name
Idiosyncratic reaction
Off-label
Placebo
Tachyphylaxis
Teratogen
Therapeutic effect
Tolerance
Trade name

Introduction

Respiratory therapists have access to many different categories of drugs that are used to treat multiple diseases. Understanding commonly used terminology related to drugs and knowing how they were tested for safety and efficacy and how they are controlled are essential for any practitioner administering medications. When a prescribed medication is unfamiliar to any therapist, it is essential to know where to find information about the drug to determine its intended effect and to monitor its potential side effects.

Understanding Medication Principles

The following terms are important in the study of medication use, and to understand the concepts discussed throughout this text, they will need to be mastered.

Drug

A **drug** is a biologically active substance or chemical that modifies cellular function or produces a physiologic effect when introduced to the body.

Placebo

A **placebo** is a substance, chemical or otherwise, that contains no active ingredient but can cause modification of effects in either a positive or negative manner, purely on the basis of suggestion.

Drug Nomenclature

Every drug has three different names, which often makes the study of pharmacology confusing. The β_2-agonist albuterol is an example. The chemical name α_1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α, α′-

diol sulfate refers to the chemical structure of the drug; the **generic name** (nonproprietary) is albuterol, and the **trade names**/brand (proprietary) include ProAir®, Ventolin®, and Proventil®, under which the drug is marketed and sold by the company.

Therapeutic Effect

The **therapeutic effect** is the intended effect of a drug (e.g., pain relief from morphine or sedation from midazolam).

Tolerance

Tolerance is a phenomenon, occurring after a period of use of some drugs, that necessitates an increase in dosage to maintain an effect.

Tachyphylaxis

Tachyphylaxis is the rapid development of tolerance to a drug, making it less effective.

NEED TO KNOW

Tolerance means a patient requires increasing dosages of a drug to achieve the desired effect. Tachyphylaxis is a rapidly developing tolerance, sometimes seen in bronchodilators.

Allergy

Allergy is an adverse reaction caused by triggering the immune system that results from an exposure to a drug, food, or chemical. An allergy may also occur after exposure to a drug, food, or chemical that is similar to another one a patient was exposed to in the past. Common reactions that occur as a result of an allergy include anaphylactoid-type reactions, rash, urticaria, or changes in blood pressure.

Adverse Reaction

Adverse reactions or side effects are a response to a drug that is harmful, excessive, and unintended. Every drug has some side effects; they may be very harmful and require discontinuation or therapy change and may be just a nuisance. Some adverse reactions can occur with prescribed doses of a drug, for example, diarrhea with antibiotics, and some occur because of an overdose or a dose higher than that prescribed, as in the case of respiratory depression with high doses of morphine.

Idiosyncratic Reaction

An **idiosyncratic reaction** is a type of adverse drug reaction. It is an unexplained or unpredictable reaction to a drug and can be manifested as an accelerated, toxic, or inappropriate response to the usual therapeutic dose.

Teratogens

Teratogens are drugs or substances that are known to cause birth defects.

Carcinogens

Carcinogens are drugs or substances that cause malignant neoplasms or cancers.

Drug Dependence

Drug dependence occurs when a person requires a drug or substance to function normally. When the substance or drug is removed or withheld, it will result in physical or psychological symptoms. Withdrawal symptoms may be due to an altered physiologic state that occurs, such as tremors, sweating, and hallucinations, as a result of alcohol withdrawal, or a psychological need such as craving the rush of smoking or the hand-to-mouth connection that smoking a cigarette requires.

Drug Development

A drug takes many years to develop, from the time its chemical structure is identified until it is determined to be effective and safe to use and market to the general population. The Food and Drug Administration (FDA) must first approve all new drugs before they can be marketed in the United States. This process is expensive and has been estimated to cost anywhere from $800 million to $2.6 billion. The multiple stages of drug development are described in **Figure 1-1**.

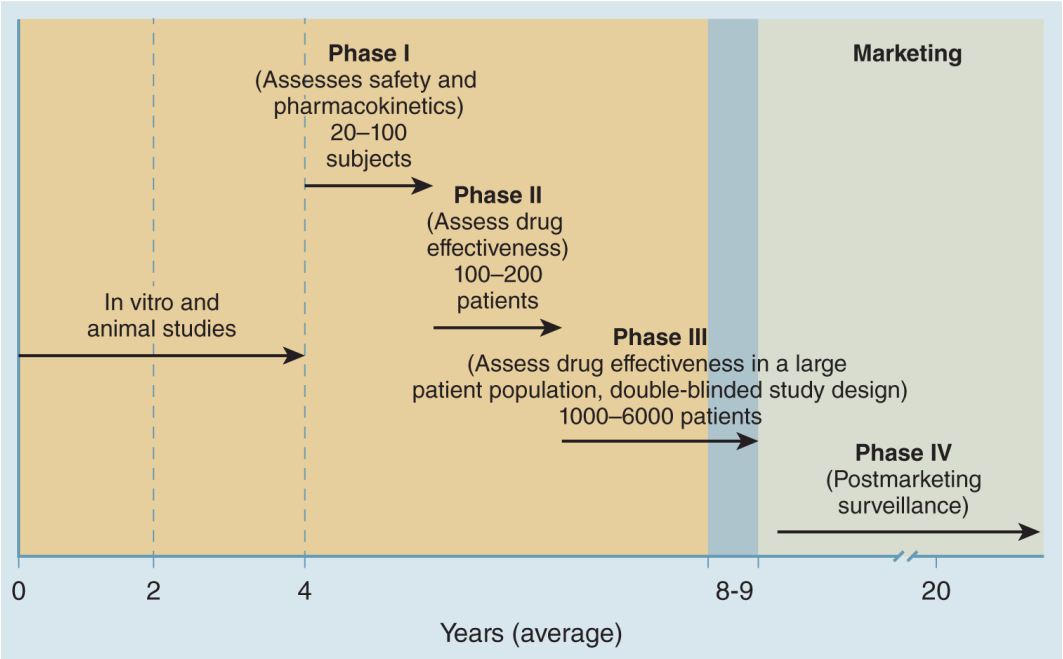


FIGURE 1-1 Phases of drug development in the United States.

Description

In Vitro and Animal Studies

Researchers first identify a molecule and develop multiple compounds that may find a way to reverse or stop the effects of a disease. After the molecules or compounds are identified as potential candidates for treatment in a laboratory, they will be further studied to determine the

mechanism in a specific disease state. The compound will then be tested in animals to determine if it is effective; information on safety relative to different doses is gathered; and how the compound is absorbed, broken down, and eliminated by the body of animals is determined. Once the FDA determines that the compound is effective and is relatively safe, it is then tested in humans.

Phase I

Phase I studies are conducted in a small population of human subjects involving 20–100 healthy volunteers. The purpose of phase I studies is to determine safety and tolerability in humans. This phase of research also studies how the drug works and how the body responds to the drug with respect to absorption, distribution, metabolism, and excretion.

Phase II

Phase II studies are conducted in several hundred people with the disease or condition that the drug is being studied to treat.[5,6] The purpose of phase II studies is to test the drug and assess whether it is effective in the treatment of the disease at varying doses. Safety and toxicity are also assessed during this phase. The majority of drugs will fail testing in this phase as a result of either significant toxicity or lack of efficacy.

Phase III

Phase III studies are conducted in a large number of humans (300–3000) who have the disease. This phase will confirm effectiveness and safety in a broad population of patients with the condition being treated and will be tested against placebo or the standard treatment for the disease. Phase III studies can take many years to enroll and test the drug in thousands of patients. If the drug is found to be

effective and safe, it will be presented to the FDA for review and approval for marketing.

Phase IV

Once the FDA approves a new drug, it can be marketed to the general public and prescribed in clinics and hospitals. Postmarketing surveillance or a phase IV study will determine if a drug continues to be safe and effective over time. Drug manufacturers do this surveillance to detect rare or long-term adverse reactions of a medication. The manufacturers will also determine if the drug can be used to treat any other conditions. If a drug or device is determined to be unsafe in postmarketing observation, the FDA may remove it from the market or change the drug labeling to include an additional safety warning.

Abuse of Prescription Drugs

Many drugs are abused today in our society, and those that are most often abused are those controlled by prescription. For the FDA to maintain control over the dispensing of drugs with significant abuse potential, the Comprehensive Drug Abuse Prevention and Control Act was passed in 1970. This Act is summarized in **Table 1-1**.

TABLE 1-1
Drug Schedules Defined in the Federal Comprehensive Drug Abuse Prevention and Control Act of 1970

Schedule	Examples of Controlled Drugs
Schedule I: drugs with high abuse potential and no accepted medical use	Heroin, lysergic acid diethylamide (LSD); these drugs are not to be prescribed
Schedule II: drugs with high potential for abuse and accepted medical use with severe restrictions	Narcotics (morphine), cocaine, amphetamines, pentobarbital; no refills without a new written or electronic prescription from the physician, dentist, etc.
Schedule III: drugs with less potential for abuse than schedule I and II drugs and accepted medical use	Anabolic steroids and accepted medical use barbiturates, preparations containing codeine plus aspirin or acetaminophen; may be refilled five times in 6 months when authorized by the physician
Schedule IV: drugs with low potential for abuse and accepted medical use	Antianxiety drugs (alprazolam and diazepam), zolpidem for sleep; prescription required, may be refilled five times in 6 months when authorized by the physician
Schedule V: drugs with low potential for abuse and accepted medical use	Cough medicine with codeine in low dosages

Only a practitioner registered with the Drug Enforcement Administration may write prescriptions for controlled substances. Which schedule a drug or substance should be placed in is dependent on the drug's abuse potential, pattern of abuse, risk to public health, psychological or physiologic dependence potential, or whether a drug is a precursor of a substance that is already controlled.

Sources of Drug Information

It is impossible to list all the comprehensive drug information resources available. Although printed drug resources may quickly go out of date, electronic references will have more reliable up-to-date drug information. Some of the main sources other than textbooks are as follows:

- *AHFS Drug Information*: This source is published every year as a collection of monographs that contain evidence-based drug information on FDA-approved uses and non–FDA-approved uses (**off-label**) of a medication. This resource is available in a print version, in an abbreviated print version, and also on mobile devices.
- *Facts and Comparisons*: This resource contains information about prescription and nonprescription medications. It is organized by drug class and provides comparisons of different drugs in the same class or category. It is available in print, online, and on mobile devices.
- *United States Pharmacopeia (USP)*: Published every 5 years, it includes single-entity drugs of established manufacturers and sets official, chemical, and physical standards that relate to purity and strength. It is available online and in print.
- *National Formulary*: Published every 5 years, it establishes formulations that are not in the *USP.*
- *Physicians' Desk Reference (PDR)*: This source is published every year; it provides a brief description of prescription drugs, including indications, dosage, side effects, and other information found in official prescribing information. It is indexed by manufacturer, product name, generic name, product category, and product information. It also contains prescription package inserts and is available online and on mobile devices. There are also other editions of the *PDR* that are specific for nonprescription drugs and herbal agents.

- *Micromedex*: This source provides easy online access to drug information, including clinical trials, latest news regarding drug developments and changes, drug interactions, and a color reference to various pills for identification. *Micromedex* is also available as an Android/iPhone application.
- *Drug Information Handbook*: This source is published every year. It is organized alphabetically by drug name and includes approved and off-label uses, dosing, safety, and monitoring of each drug. It is available in a print handbook as well as online and on a mobile device. The online and mobile device formats are in a product line called Lexicomp®. The online resource includes pill identification and pricing information.

Review Questions

1. Spiriva Handihaler® (tiotropium) is approved for use in the treatment of patients with chronic obstructive pulmonary disease. Tiotropium works by blocking acetylcholine at muscarinic receptors, thereby blocking the direct constrictor effects of acetylcholine on bronchial smooth muscle and causing bronchodilation. One capsule of 18 µg should be inhaled once daily. The most common effects that occur with use of this drug include dry mouth, cough, and upper respiratory tract infections. List the trade and generic names, therapeutic effect, dose, and adverse reactions of tiotropium.
2. Explain the difference between a teratogen and a carcinogen.
3. Compare and contrast drug tolerance and the development of tachyphylaxis to a drug.
4. Describe the types of patients, number of subjects studied, and the main purpose of phases I–IV of drug development.
5. Compare the difference in restrictions and abuse potential between schedule I and II and schedule III–V controlled substances.
6. List six drug information references that contain trade name, generic name, uses of drugs, dosing, and safety information.

Posttest

For each of the following questions, try to select the one best answer from the choices given.

1. An unexplained drug effect is called:
   a. potency.
   b. allergic reaction.
   c. hypersensitivity.
   d. idiosyncratic reaction.
2. Which of the following is another name for a side effect of a medication?
   a. Adverse drug reaction
   b. Tolerance
   c. Therapeutic effect
   d. Placebo effect
3. Warfarin, an anticoagulant or blood thinner, when used in pregnancy can lead to mental retardation and blindness and interferes with bone and cartilage formation in newborn babies. Warfarin is considered a teratogen. True or False?
4. What is another name for a drug or substance, such as alcohol, that is known to cause liver cancer or other types of cancer?
5. Which of the following phases of drug development studies the effectiveness and safety in the largest population of patients against placebo or the current standard of treatment?
   a. In vitro
   b. Phase I
   c. Phase II
   d. Phase III
6. Which of the following phases of drug development is required after marketing of a drug to monitor for safety issues that may result from long-term use?
   a. Phase I
   b. Phase II
   c. Phase III

d. Phase IV

7. Which of the following drug information references would be a good resource to use to determine the appropriate dose of inhaled epinephrine for stridor?
   a. AHFS Drug Information
   b. Drug Information Handbook
   c. Micromedex
   d. All of these are correct.

References/Recommended Readings

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

American Society of Hospital Pharmacy. ASHP guidelines on adverse drug reaction monitoring and reporting. *Am J Health Syst Pharm*. 1995;52:417-419.

Avorn J. The $2.6 billion pill—methodologic and policy considerations. *N Engl J Med*. 2015;372:1877-1879.

DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ*. 2003;22:151.

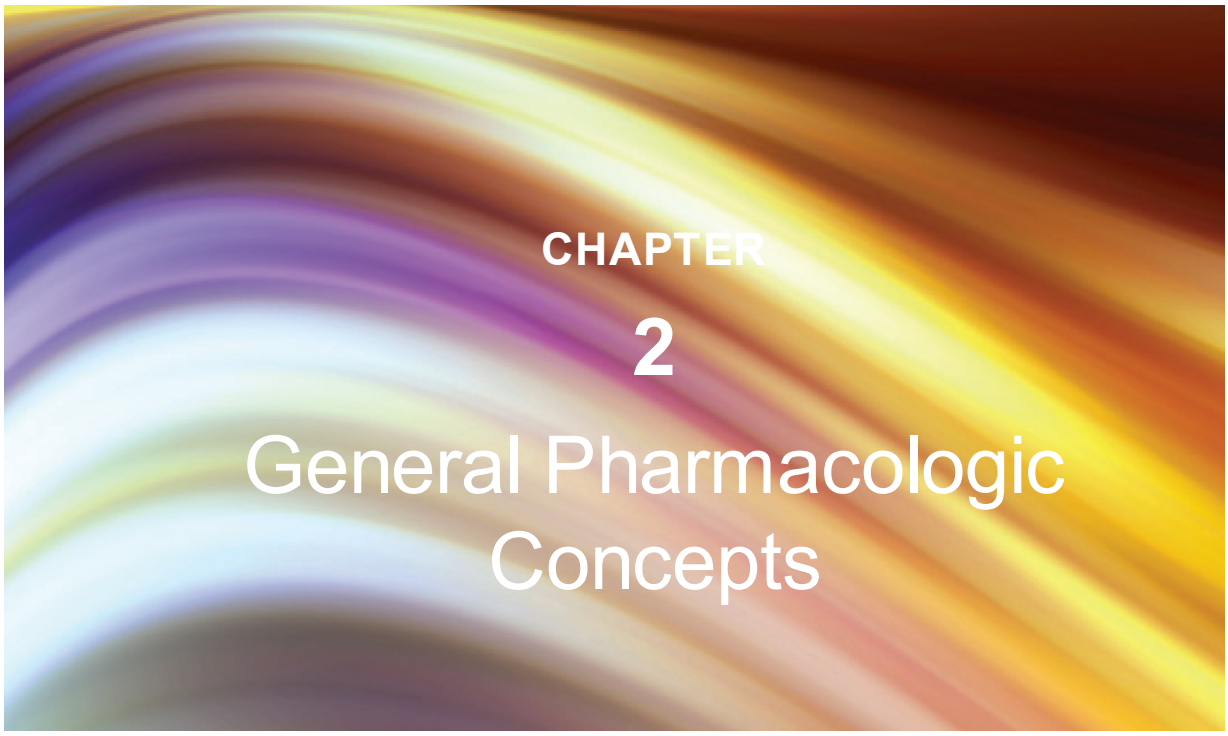
U.S. Food & Drug Administration. The drug development process. Step 3: clinical research. https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm. Accessed November 1, 2017.

Katzung BG. Introduction: the nature of drugs, drug development and regulation. In: Katzung BG, Trevor AJ, eds. *Basic & Clinical Pharmacology*. 13th ed. New York, NY: McGraw Hill Education; 2015:chap 1.

U.S. Drug Enforcement Administration. *Drugs of Abuse: A DEA Resource Guide*. Washington, DC: U.S. Department of Justice, Drug Enforcement Administration; 2017.

U.S. Department of Justice, Drug Enforcement Administration. Pharmacist's manual—section IX-XIV. https://www.deadiversion.usdoj.gov/pubs/manuals/pharm2/pharm_content.htm. Accessed February 14, 2019.

Malone PM, Kier KL, Stanovich JE, Malone MJ. *Drug Information: A Guide for Pharmacists*. 5th ed. New York, NY: McGraw-Hill Education; 2014.



© Anna RubaK/ShutterStock, Inc.

OUTLINE

Introduction
Pharmacology
Essential General Principles of Pharmacology
- Routes of Administration
- Drug Doses
- Drug Absorption
- Drug Mechanisms
- Drug Distribution
- Drug Metabolism
- Drug Excretion

Factors That Alter Drug Effects
- Patient Adherence
- Placebo Effect
- Pathologic State
- Administration with Meals
- Gender
- Age
- Genetic Variations
- Drug Interaction

OBJECTIVES

After completion of this chapter and its learning activities, you will be able to:

1. Define pharmacology and describe several disciplines within the area of pharmacologic study.
2. Compare and contrast the different routes of medication administration.
3. Determine the safety of a drug by calculating the therapeutic index.
4. Predict the action or effect of a receptor agonist and antagonist.
5. Explain how lipid solubility and ionization affect absorption of medications.
6. Identify the patient factors that may alter drug effects.
7. Describe the process of drug metabolism and excretion and list the most common organs responsible for each.

KEY TERMS

Absorption
Agonists
Antagonists
Biotransformation
Excretion
Intravenous
Metabolism
Parenteral
Pharmacodynamics
Pharmacokinetics
Pharmacology
Pharmacotherapy
Pharmacy
Receptor
Subcutaneous
Sublingual
Toxicology

Introduction

As one looks at the broad subject areas covered by pharmacology, one might ask why a respiratory care practitioner needs to be informed about drugs other than those that are used specifically in respiratory care. By studying the principles that govern all drugs and having specific drug knowledge, it is possible to make assessments and predict drug effects, incompatibilities, and interactions that might be encountered in patients who are being treated for various respiratory diseases.

This chapter discusses the purpose and value of studying pharmacology. Terminology that is essential to the study of pharmacology is defined, what happens to a drug when it is introduced into the body is clarified, and biologic factors that affect the action of drugs are explained.

Pharmacology

Pharmacology is the study of drugs—their origin, properties, how they work and affect living organisms. As a discipline, it is one of the important basic sciences of medicine and other health professions. In the health care pharmacology is the study of substances that are used to prevent, diagnose, and treat diseases.

There are multiple factors that determine a drug's effects. Pharmacology as a science can be subdivided into several divisions/categories. **Table 2-1** lists some of these areas and gives a brief definition of each.

TABLE 2-1
Areas of Pharmacology

Area of Pharmacology	Definition
Pharmacotherapy	A therapy that uses a specific medicine or drug to treat a specific disease
Pharmacodynamics	Study of the actions of drugs on living organisms; what the drug does to the body
Pharmacokinetics	Study of what the body does to the drug related to absorption, duration of action, distribution in the body, metabolism, and method of excretion
Pharmacy	The practice of compounding, preparing, and dispensing drugs and assuring rational medication use
Toxicology	Study of harmful effects of drugs on living organisms, tissues, and the human body

Essential General Principles of Pharmacology

This section discusses routes of administration, **absorption**, distribution, **metabolism** (biotransformation), and **excretion** of a drug. Absorption, distribution, metabolism, and excretion are collectively known as the **pharmacokinetics** of a drug.

Routes of Administration

For a drug to exert therapeutic action on the body, it must first enter by one of the routes indicated in **Table 2-2**. The most common and usually safest route is the oral route or per os, which means by mouth. This route is the most convenient and is acceptable to most patients. It is also the safest because, in case of overdose or any toxic reaction, the drug can be partially removed by inducing vomiting or by gastric lavage (stomach pumping). The disadvantage of the oral route is that the onset of action is usually 30–60 minutes and the absorption also can be altered by multiple factors, for example, the presence of food. In some cases, the drug may be irritating to the stomach lining and may cause nausea, vomiting, or heartburn.

TABLE 2-2
Common Routes of Administration

Route	Route Meaning	Time of Onset	When Appropriate	Example
Oral	By mouth	30–60 min	Outpatient and for convenience	Most drugs and particularly over-the-counter drugs
Rectal	In rectum	30 min	When patient is unable to take by mouth	Antinausea medications
Sublingual	Under the tongue	1–3 min	When rapid absorption is needed, bypasses the gastrointestinal tract	Nitroglycerin tablets
Transdermal	Applied to skin in a patch form	several hours to days (varies)	Continuous low dosage, usually outpatient	Nitroglycerin patches
Inhalation	Into the lungs	Within 1 min	Local, effects on respiratory tract	Albuterol and other bronchodilators
Intramuscular (IM)	Into the muscle	15–30 min	Drugs that have poor oral absorption or poor solubility in water	Benzodiazepines (sedatives), vaccines, hormonal therapies
Intravenous	Into a vein	Within 1 min	Emergency situations and infusions	General anesthetics, nutrient solutions, antibiotics, vasoactive drugs
Subcutaneous	Into the fatty tissue beneath the dermis or skin	Up to 24 h	Drugs that have poor oral absorption and when higher levels are needed rapidly, but slower than IM	Insulin
Intra-arterial	Into an artery	<1 min	Deliver drug to a specific organ (e.g., liver)	Anticancer drugs delivered to the affected organ but not routinely used for other medications

The **parenteral** route refers to administration of a drug by a needle. There are four types of parenteral routes: intradermal, subcutaneous, intramuscular (IM), and **intravenous** (IV). Intradermal medication is administered under the epidermis of the skin. This route is used for allergy testing, tuberculin testing, and some vaccinations. **Subcutaneous** injection is administered into the fatty layer of tissue beneath the dermis of the skin. IM injection is administered deep into the muscle, usually the buttocks, thighs, or deltoid muscles, and has a rapid onset of action (15–30 minutes). The primary reason for the use of the IM route is for medications that are poorly soluble in water or medications that are required to be absorbed slowly over a prolonged amount of time. Some drugs that are highly soluble in water may be given via the IM route and are absorbed quickly. The parenteral route that has the fastest onset of action is IV, which usually is restricted to use in the hospital setting. Drugs given via a parenteral route incur some degree of risk because once the drug is administered, it cannot

be withdrawn. Miscalculating dosage can have serious, even fatal, results.

Drug Doses

Dose–Response Curve

Whenever a drug is tested for a particular response, a dose–response curve is obtained. This curve is a graphic representation of the relationship between dose in milligrams and the response to or effect of the drug. **Figure 2-1** illustrates the appearance of a typical response.

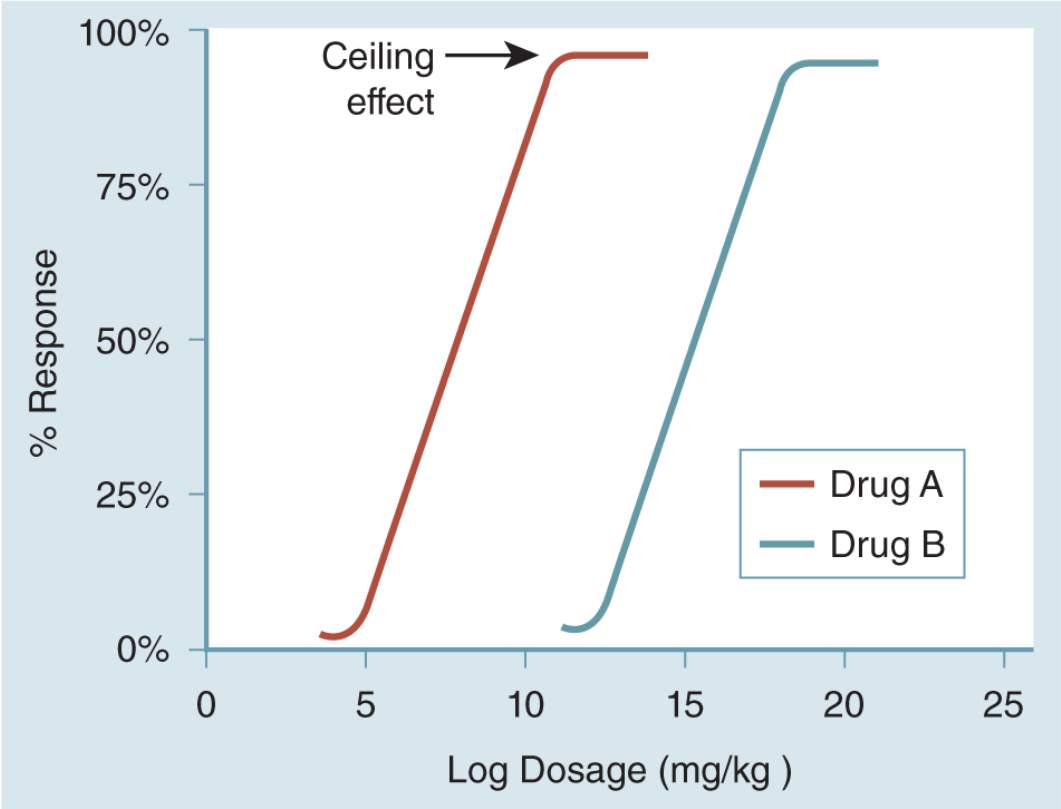


FIGURE 2-1 Dose–response curve.

Description

As the figure indicates, the dose and response increase in a corresponding fashion. The response increases until additional dosage causes no increase in the effect. This point is called the

ceiling effect. It should be noted that when the ceiling effect is reached, increasing the dose has no additional therapeutic advantage and may cause toxic effects. The dose–response curve can also be used to evaluate and compare similar drugs. Regarding potency, as seen in Figure 2-1, drug A and drug B are both effective, but drug A is more potent than drug B because only a smaller dose of drug A is needed to produce the same effect.

Potency

When comparing one drug with another, the drug that reaches an effective level with a smaller dose is the more potent of the two drugs. It should also be remembered that a more potent drug can reach toxic levels at smaller dosage.

Therapeutic Dose

Therapeutic dose is the recommended amount of a drug that should be used to obtain the desired clinical effect.

Median Lethal Dose

To determine the safety of a drug, the Food and Drug Administration requires extensive testing on animals before the drug is allowed for human testing. One of the first tests that are conducted, using several different species of animals, is the median lethal dose (LD_{50}). This is the dose at which 50% of the test animals die.

Median Effective Dose

The median effective dose (ED_{50}) is the dose at which 50% of the test animals show the desired effect.

Therapeutic Index

The therapeutic index (TI) is the ratio of LD_{50} to ED_{50} and gives a relative indication of the safety of a drug. The formula for calculation

of the TI is:

$$TI = \frac{LD_{50}}{ED_{50}}$$

If a particular drug has an LD_{50} of 1000 mg and an ED_{50} of 100 mg, the TI would be 10.

$$TI = \frac{1000}{100} = 10$$

The higher the TI, or the higher the difference between the LD_{50} and the ED_{50} values, the greater the safety of the drug. Drugs that have low TIs must be carefully monitored during clinical use to avoid toxic and perhaps lethal results. Another way of expressing this concept is that the closer the TI is to 0, the more toxic is the drug.

Drug Absorption

Absorption means to “pass through” or “soak in.” With the exception of IV or intra-arterial routes, drug absorption includes passing through a barrier or membrane. In the case of the oral route, a drug must pass through the membrane of the gastrointestinal (GI) tract, and transdermal medications must be absorbed through the skin to gain access to the bloodstream and eventually to the cells at the desired site of action.

For a drug to be absorbed through the complex structure of cell and tissue membranes, there are several factors to be considered, such as transport mechanisms, lipid solubility, and drug ionization or electrostatic charge of a drug molecule.

Transport Mechanisms of Drugs Across Membranes

There are several different mechanisms whereby drugs and other substances pass through membranes (**Figure 2-2**). These include passive diffusion, filtration, and active transport. The most common is passive diffusion, which is governed by concentration gradient. For example, when a drug enters the GI tract, it has a high concentration relative to the surrounding blood supply. By moving from high to low concentration, the drug passes from the GI tract into the bloodstream. Active transport is a process that requires energy, another substance or transporter to carry a drug or molecule across a membrane.

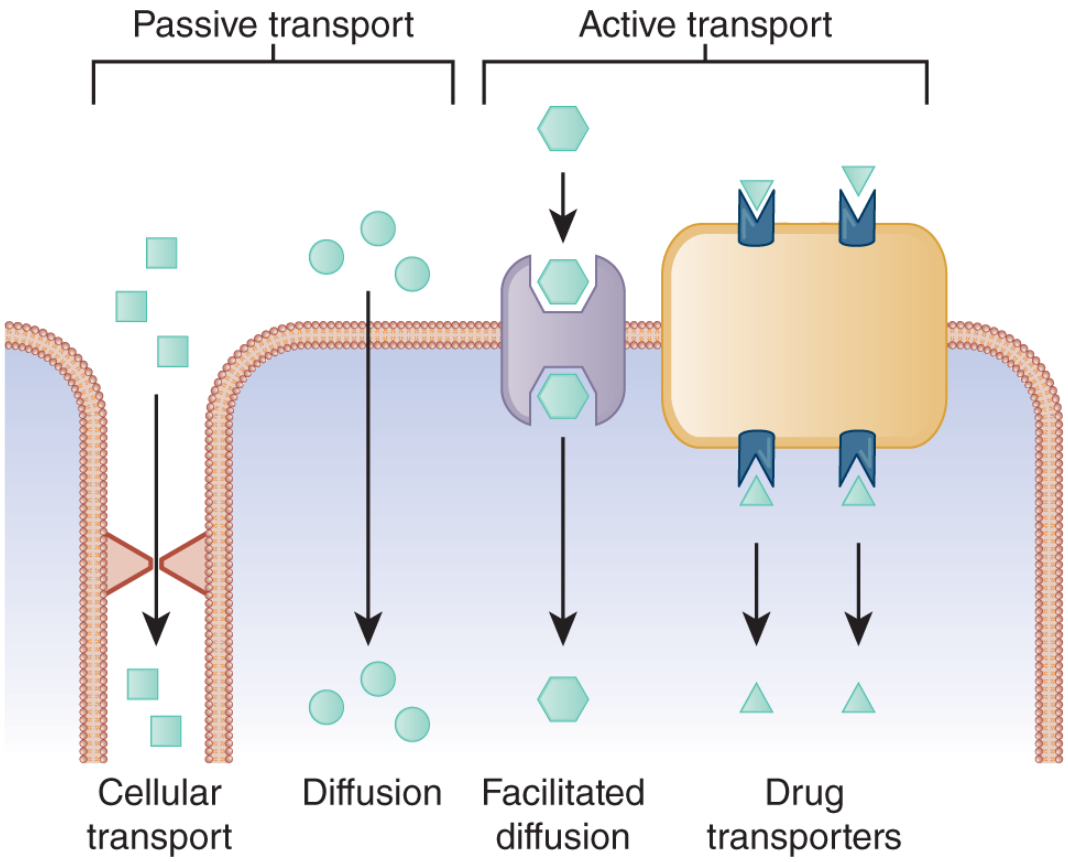


FIGURE 2-2 Mechanisms of drugs passing through membranes.

Description

The body is well protected from the outside world by skin and mucous membranes. For a drug to interact with the basic structure and functional entity of an organism (the cell), it must pass through

some type of membrane, whether the multiple cell membranes of the gut and capillaries or the plasma membrane of the cell.

The currently accepted molecular structure of the plasma cell membrane is often referred to as a fluid mosaic model. The principal structure of the cell membrane comprises two layers of lipid material (lipid bilayer), and situated within the lipid bilayer are the integral proteins. Because integral proteins constantly change their location, a "mosaic-like" distribution is created (i.e., the cell membrane is not a static entity). In addition to this pattern of proteins in a lipid bilayer background, there are also some openings or "channels" that allow water and very small water-soluble molecules to pass through (see **Figure 2-3**).

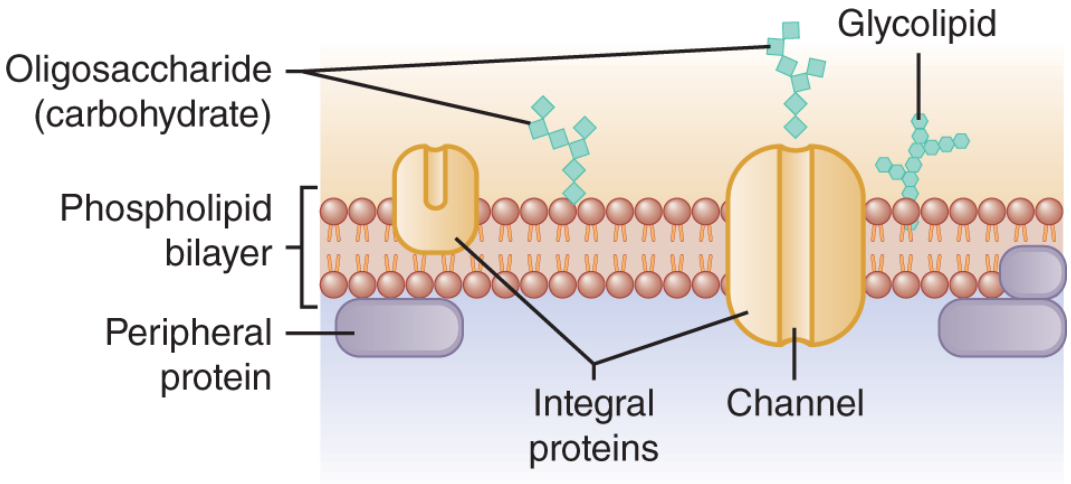


FIGURE 2-3 Fluid mosaic model.

Description

Capillary endothelia are cells that line all vessels in the vascular system. Membranes in the capillary endothelium have intercellular channels that allow the movement of water and water-soluble materials. These channels are much larger than those present in the plasma membrane. Because of their larger size, the channels in the capillary endothelium will allow small- and medium-sized molecules not only to pass into the bloodstream but also to pass through the cells lining the intestines. The major process by which substances pass through this type of channel by means of either osmosis or

hydrostatic pressure is termed filtration. It should be noted that capillary membranes in the central nervous system (CNS) have very small, intercellular channels between cells (tight junctions) that allow only lipid-soluble and very small substances to pass through. This specialized structural phenomenon is probably responsible for the so-called blood–brain barrier.

Lipid Solubility

Because the cell membrane comprises significant amounts of lipid (fat) material, drugs that are lipid-soluble will pass through the cellular membrane rapidly. There are a number of drugs that are very lipid-soluble, such as general anesthetics. Because of their lipid solubility, general anesthetics are readily absorbed into the lipid-rich CNS, where they alter neurologic activity.

Drug Ionization

If a drug is primarily water-soluble and only partially lipid-soluble, it must be either a weak acid or a weak base for it to be absorbed rapidly. Weak acids and weak bases, when in solution, are mostly in the unionized form and thus have fewer electrical charges that interfere with absorption. Drugs in an unionized form are most rapidly absorbed. If drugs are in an ionized state, absorption of the charged or ionized form of the drug is very difficult because of two factors: (1) the ionized molecules are poorly soluble in the lipid material of the cellular membrane and (2) the small, ionized molecules are highly charged and have difficulty moving through the channels in the membrane because of repulsion by fixed charges in both the channels and the membrane surface.

Because of the aforementioned phenomenon, the pH of tissue fluids into which a drug is administered is very important to absorption rate. The more neutral (unionized) the drug is (weak acid or weak base), the better it will be absorbed. The pH of the tissue fluids in which the drug is present will determine the ratio of unionized and ionized forms of the drug. The chemical and mathematical description

of this relationship can be explained by the Henderson–Hasselbalch equation:

$$\mathrm{pH} = \mathrm{p}K_{\mathrm{a}} + \log \frac{\text{ionized drug}}{\text{unionized drug}}$$

We will not actually use this equation in this text but, in general, the relationship between the pK_a of a drug and the pH of tissue fluids will determine whether a drug will be readily absorbed. (The pK_a is the pH at which 50% of the drug is ionized and 50% is unionized.) This equation generally means that weak acids are more readily absorbed in fluids with an acidic pH, whereas weak bases are more readily absorbed in fluids with an alkaline pH. For example, when an acid drug, such as aspirin, is in an acid environment, as in the stomach, it is mostly in the unionized state, favoring absorption.

Drug Mechanisms

Mechanism of Action

The mechanism of action explains how a drug produces its effect. There are several drugs for which the specific mechanism of action is known. For example, it has been shown that the mechanism of the anticoagulant effect of aspirin is the prevention of the aggregation of platelets, thus interfering with the clotting mechanism of the blood. Obviously, knowledge of the specific mechanism of action for a particular drug is extremely helpful for identifying the proper clinical application of the drug.

Site of Action

Once a drug passes through a biologic membrane, it must be carried to a location in the body where it can exert its therapeutic effect. The specific site of action is not completely identified or understood for all drugs, but there are many drugs for which the general site has been

determined. For example, the hypothalamus controls body temperature, and it has been shown that aspirin alters the activity of the hypothalamus so that the temperature of the body is decreased whenever a fever is present.

Receptor Site

Most drugs exhibit their effects by specific interaction with a protein on cellular membrane surfaces called **receptors**. A receptor can be defined as a part of a cell or organism that will respond in a specific way when combined with a hormone, neurotransmitter, or drug. When the receptor and a drug combine, a series of events occur in the cell that leads to the drug's effect. Receptors have been shown to consist mainly of large molecules (macromolecules) or groups of molecules that are protein in structure. Receptors are usually located on cell membranes but also can be located in the cellular cytoplasm or the cell nucleus. Various tissues may contain more than one receptor type, and identical receptors may be located in more than one tissue. Generally, a specific drug will combine with a specific receptor. Some authors compare the binding to a key-and-lock arrangement. Such a receptor–drug relationship is illustrated in **Figure 2-4**.

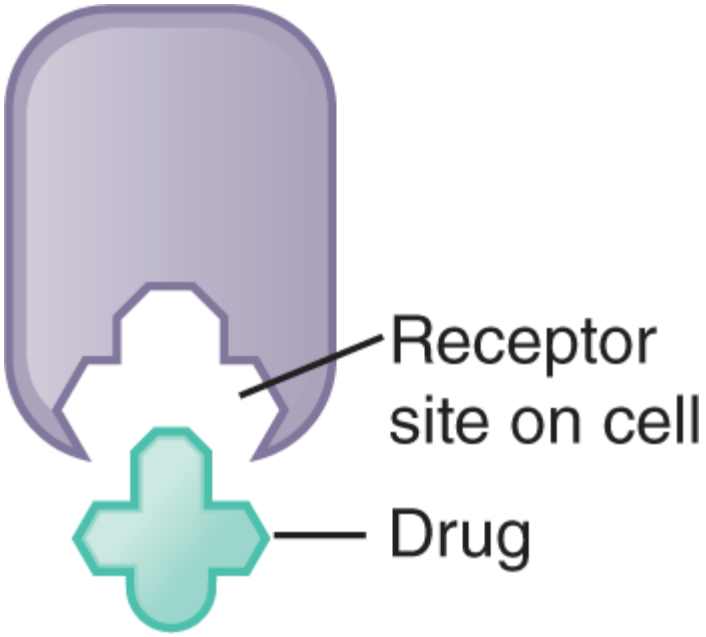


FIGURE 2-4 Drug–receptor relationship.

Drugs that combine with specific receptors to cause a drug action are called **agonists**, and drugs that combine with receptors and cause no action or block an effect are called **antagonists** (**Figure 2-5**). Another term for an antagonist is "blocking agent." An example of a blocking agent is the drug naloxone, which blocks the effects of narcotics. Because of its narcotic antagonist properties, naloxone is given to reverse the effects of narcotic overdose. Antagonists and agonists often compete for the same receptor site; an example of this type of competitive antagonism is found in a group of drugs called antihistamines. The antihistamine competes with histamine for the same receptor site and reduces the binding of histamine to that site, therefore reducing the effects of histamine.

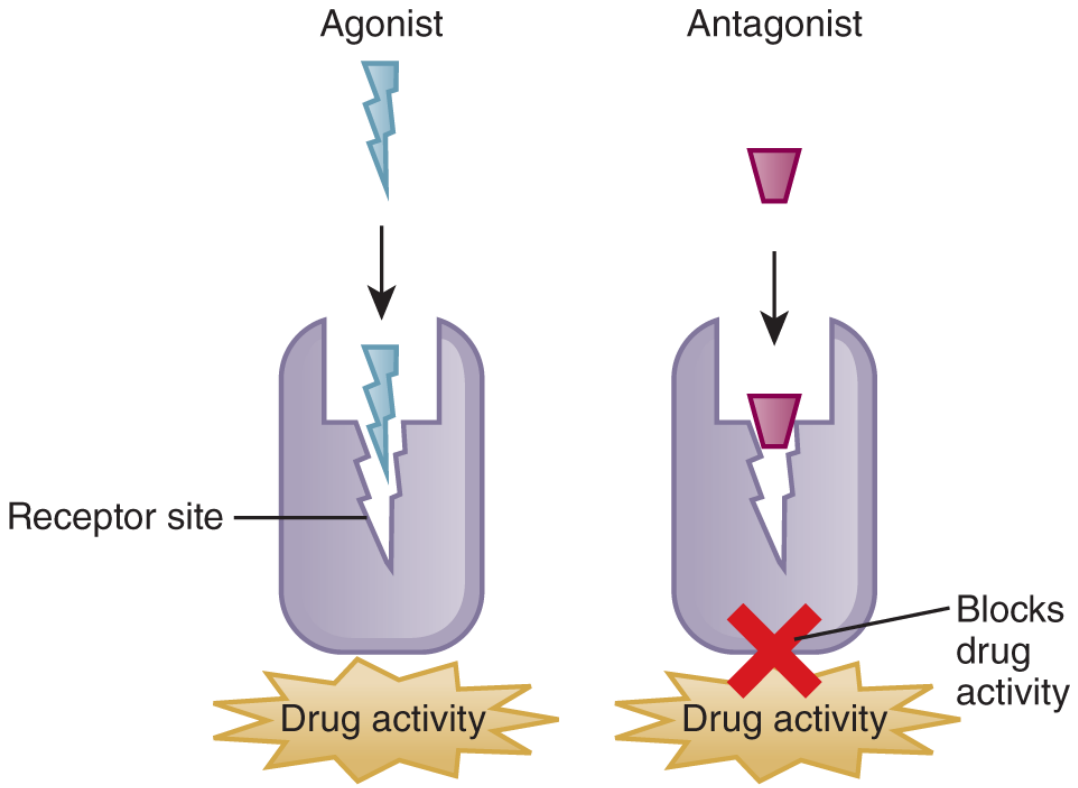


FIGURE 2-5 Agonist and antagonist receptor relationship.

Description

Drug Distribution

Once a drug has gained access to the blood plasma, it is carried by the blood to various tissues and compartments throughout the body, where it can combine with receptor sites. There are several factors that determine how much drug actually reaches the receptor site, such as plasma protein binding, tissue affinity, and blood flow.

Plasma Protein Binding

In the plasma, there are hundreds of circulating proteins (e.g., albumin, globulins). These molecules, because of their large size, do not pass through membranes readily. However, these plasma proteins chemically attract certain drugs, and because of this attraction, many drugs become bound and are not available for pharmacologic action. Only the free drug or drug not bound to protein is available for drug action. For those drugs that do have an affinity for plasma proteins, an equilibrium is established between the free drug and bound drug, and changes in the fraction of the bound drug can alter the degree of drug effect. For example, there are many drugs that compete for the same plasma-binding site, and this can result in a sudden release of drugs that are normally bound. This could cause exaggerated drug effects or, in some cases, toxic drug reactions.

Tissue Affinity

Some drugs have a strong affinity for certain tissues or organs of the body, and this tends to create a potential reserve of drugs that may later be released into the bloodstream. One example of this phenomenon is the barbiturates, which are bound in fatty tissues of the body and are slowly released into the plasma over a long period. This partially explains the long duration of action of phenobarbital or the “hangover” feeling that patients sometimes experience when taking this drug.

Blood Flow

Obviously, different tissues and organs receive varying amounts of blood. Organs such as the liver, kidneys, and brain receive the largest amount of blood and are therefore ultimately exposed to the largest amount of drug.

Drug Metabolism

Drug metabolism is the process by which drugs and other foreign chemicals that enter the body are altered, changed, inactivated, and prepared for elimination. This process is also referred to as **biotransformation**. The substance or molecule that results from a drug being broken down or transformed during metabolism or biotransformation is called a metabolite. Metabolites may be able to exert some activity or may be inactive and excreted from the body. Some drugs that enter the body are not metabolized but are excreted unchanged; however, most drugs are altered by biotransformation. Metabolism primarily occurs in the liver, but they can take place in other organs as well. Located within the parenchymal (functional) cells of the liver are a group of enzymes that specifically alter the structure and assist in metabolism of drugs. This enzyme system is called the microsomal enzyme system.

An important phenomenon that occurs in the liver is that some drugs have the ability to stimulate the rate of action of this enzyme system and thus increase the metabolic rate of other drugs. This phenomenon is called enzyme induction, meaning that more enzymes are activated, in turn increasing the rate of metabolism. Drugs that are affected by enzyme induction are metabolized quickly and eliminated, which will decrease the activity of these drugs. Rifampin, an anti-infective agent used for tuberculosis, is an enzyme inducer. When administered with apixaban, an anticoagulant or blood thinner, rifampin will increase the metabolism of apixaban, and the anticoagulant effects of the drug will be decreased because apixaban will be cleared from the body quicker than usual. Enzyme inhibition is due to a drug that slows or decreases metabolism by enzymes. This

may lead to an increased/enhanced activity or toxicity of a drug that is affected by enzyme inhibition. Cimetidine is an agent used to decrease gastric acid. It will inhibit the metabolism of theophylline, an orally administered bronchodilator used for asthma or chronic obstructive pulmonary disease, and potentially lead to increased theophylline in the body, producing toxic effects such as arrhythmias and seizures.

First-Pass Effect

When a drug is taken orally, it is absorbed from the stomach or the intestine and then passes into the bloodstream. When this blood reaches the liver through the portal veins, some of this drug is metabolized and cleared from the body before it reaches its intended site of action. The loss of drug from metabolism before it reaches its intended site of action is called first-pass effect. Certain drugs, for example, nitroglycerin, propranolol, and fluticasone, have a high first-pass effect when taken orally. This means that very little of the drug will leave the liver to reach its site of action; thus, increased oral dosages may be required to achieve a therapeutic effect. Administering these drugs by aerosol, **sublingual** (under the tongue), or parenteral routes will circumvent the first-pass effect because the drugs will be administered directly to the site of action (inhaled) or bypass the GI tract (sublingual or parenteral).

Drug Excretion

There are several different sites where drugs are excreted from the body; these include the kidneys, respiratory system, and GI tract. The majority of drugs are excreted by the kidneys. Most substances in the blood are filtered in the glomerulus of the nephron, followed by reabsorption of essential substances and electrolytes back into the blood by the renal tubule. The substances that are not reabsorbed are urinary waste products; this includes drugs that are metabolized in a water-soluble form. In other words, many metabolized drugs are

converted to an ionized form so that they will not be readily reabsorbed into the bloodstream and can be eliminated from the body via urination. It is possible, and sometimes desirable, to alter the pH of the urine to enhance excretion of some drugs or to increase their absorption. The relationships among absorption, distribution, metabolism, and excretion are presented in **Figure 2-6**.

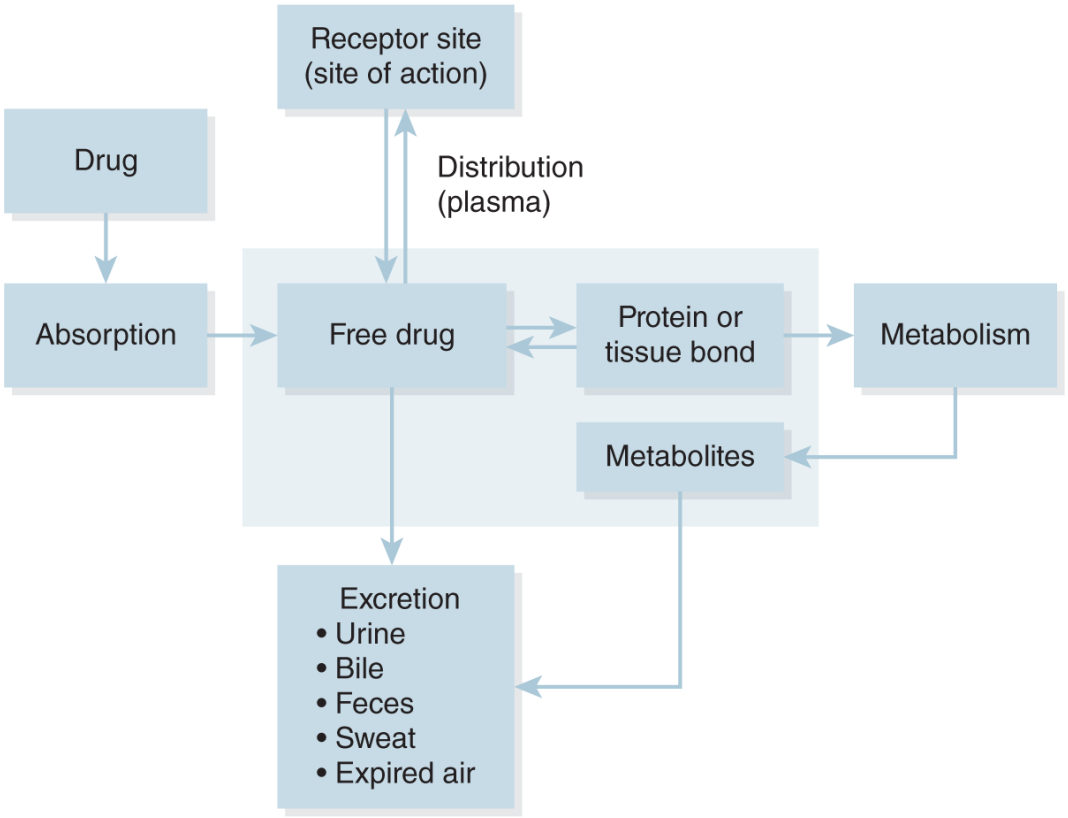


FIGURE 2-6 Relationship among absorption, distribution, metabolism, and excretion.

Description

Factors That Alter Drug Effects

In addition to physical–chemical and physiologic factors that alter drug effects, there are several other factors that can have a profound modifying effect on a drug.

Patient Adherence

For a drug to be maximally effective, it must be used according to specific directions given by the prescribing practitioner. This is particularly true when patients are taking medication on an outpatient basis, such as for the management of hypertension and asthma. A medication will not exert its intended effect if a patient does not take it or does not take it appropriately. The role of patient education with respect to the use of these medications will be reinforced in later chapters.

Placebo Effect

As mentioned in Chapter 1, placebo can have a positive as well as a negative effect, and the magnitude of the effect depends on the patient's own perception of what a drug should or should not do. In addition, the power of suggestion by the health practitioner can have profound results.

Pathologic State

Patients in various disease states will respond very differently to a given drug. Liver or kidney diseases are the most common condition that can alter drug effects. Impaired metabolism or elimination in a patient who has chronic liver or kidney disease could cause toxicity with a normal or regular dose of a drug. Uncontrolled hyperthyroidism

can cause increased metabolism of a drug, leading to a diminished effect.

Administration with Meals

The time of day (morning, noon, nighttime, mealtime, etc.) that a drug is administered can have dramatic effects. Some drugs are less toxic and have fewer side effects when taken with meals, whereas other drugs are not absorbed well at mealtimes and have to be taken on an empty stomach. Ciprofloxacin, a fluoroquinolone antibiotic, will have decreased absorption if taken with milk products, and this may lead to decreased clearance of an infection.

Gender

It is a common misconception that females are “more sensitive” to medication than males. There is very little scientific information to substantiate this concept on the basis of sex. There are, however, important differences in sensitivity based on total body weight, physical size, muscle mass, and metabolic rate.

Age

Generally, both the very young and the elderly are most sensitive to drug effects. This is partially a result of total body weight and size but is also a result of immature liver and kidney function in the young and decreased liver and kidney function in the elderly.

Genetic Variations

There are many differences in a patient’s response to drug therapy, and some of these differences are due to genetic variation. In most individuals, this probably occurs at the level of the liver microsomal enzyme system. That is, some individuals have different genetically

determined enzymes that are capable of metabolizing different drugs at different rates, resulting in differences in drug inactivation and/or elimination.

Drug Interaction

Individuals often take several different drugs simultaneously, as either inpatients or outpatients. There are many different mechanisms by which drugs affect each other. One of the most common mechanisms is the stimulation of the liver microsomal enzyme system by one group of drugs, which in turn speeds up the metabolism (enzyme induction) or decreases the metabolism of other drugs (enzyme inhibition) that are also metabolized by the same system. Such an interaction would reduce or increase drug effects.

Review Questions

1. Why should a respiratory therapist have a general knowledge of all types of drugs and not just respiratory therapy drugs?
2. Define pharmacology.
3. Explain the differences between pharmacotherapy, pharmacodynamics, pharmacokinetics, pharmacy, and toxicology.
4. Explain the differences in how drugs are given through the oral, sublingual, and parenteral routes in terms of site of administration. List one pro and one con of each route of administration (e.g., oral, sublingual, and parenteral).
5. How can you determine the safety of a drug using LD_{50} and ED_{50}?
6. Would a lipid-soluble drug increase or decrease absorption? Explain your answer as it relates to the structure of the cell membrane.
7. How does ionization of a drug affect its absorption?
8. Describe the difference between mechanism of action and site of action.
   Mechanism of action:
   Site of action:
9. When a β_1-receptor is activated, increased heart rate or tachycardia results. Describe how epinephrine, which is a β_1-receptor agonist, will affect heart rate and how metoprolol, a β_1-receptor antagonist, will affect heart rate.
10. List the most common organs responsible for metabolism and elimination of drugs.
11. With respect to drug metabolism, explain what is meant by microsomal enzyme induction and inhibition.
12. Explain how patient compliance, pathologic state, and drug interaction might alter the effects of a drug.
    Patient compliance:

Pathologic state:
Drug interaction:

Posttest

For each of the following questions, try to select the one best answer from the choices given.

1. It is important for a respiratory therapist to have a general knowledge of drugs:
   a. to administer the proper dose.
   b. to treat a specific disease.
   c. to predict a drug effect.
   d. to prevent side effects.
2. Drugs administered by which of the following routes have the quickest onset of action?
   a. Oral
   b. Intravenous
   c. Rectal
   d. Subcutaneous
3. Which of the following is considered a parenteral route of administration?
   a. Intramuscular
   b. Transdermal
   c. Inhalation
   d. Sublingual
4. If the LD_{50} of a drug is 50 mg and the ED_{50} is 1 mg, which of the following is true?
   a. The TI is 0.02 and the drug is toxic.
   b. The TI is 50 and the drug is relatively nontoxic.
   c. The TI is 50 and the drug is relatively toxic.
   d. The TI is 0.02 and the drug is nontoxic.
5. The dose–response curve represents all of the following, except:
   a. the ceiling effect.
   b. the relationship between the drug effect and dose.
   c. the relative potency of one drug compared with another drug.
   d. therapeutic effect.

6. An agonist is a drug that combines with a receptor causing a drug action to occur. True or False?
7. A cell membrane can be termed a fluid mosaic because of:
   a. a lipid bilayer membrane.
   b. proteins that change position within the membrane.
   c. pores.
   d. lipid solubility.
8. A drug interacts with its receptor site and causes a similar action as activation of the receptor. This drug is a/an:
   a. agonist.
   b. antagonist.
   c. placebo.
   d. phospholipid.
9. Drugs in which of the following forms are least readily absorbed?
   a. Lipid-soluble
   b. Ionized
   c. Unionized
   d. Small molecules
10. Which of the following factors are important in distribution of a drug?
    a. Plasma protein binding
    b. Metabolism
    c. Excretion
    d. Potency
11. Which of the following organs are most commonly involved in the process of metabolism or biotransformation of a drug?
    a. Brain
    b. Heart
    c. Liver
    d. Skin
12. Which of the following organ system are responsible for excretion of drugs from the body? (Select all that apply.)
    a. Respiratory tract
    b. GI tract
    c. Kidney
    d. Liver

References/Recommended Readings

Bauer LA. Clinical pharmacokinetic and pharmacodynamic concepts. In: *Applied Clinical Pharmacokinetics*. 3rd ed. New York, NY: McGraw-Hill; 2014:chap 1.

Broyles BE, Reiss BS, *Pharmacological Aspects of Nursing Care*. Clifton Park, NY: Delmar Cengage Learning; 2013.

Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*. 12th ed. New York, NY: McGraw-Hill Medical Publishing; 2011.

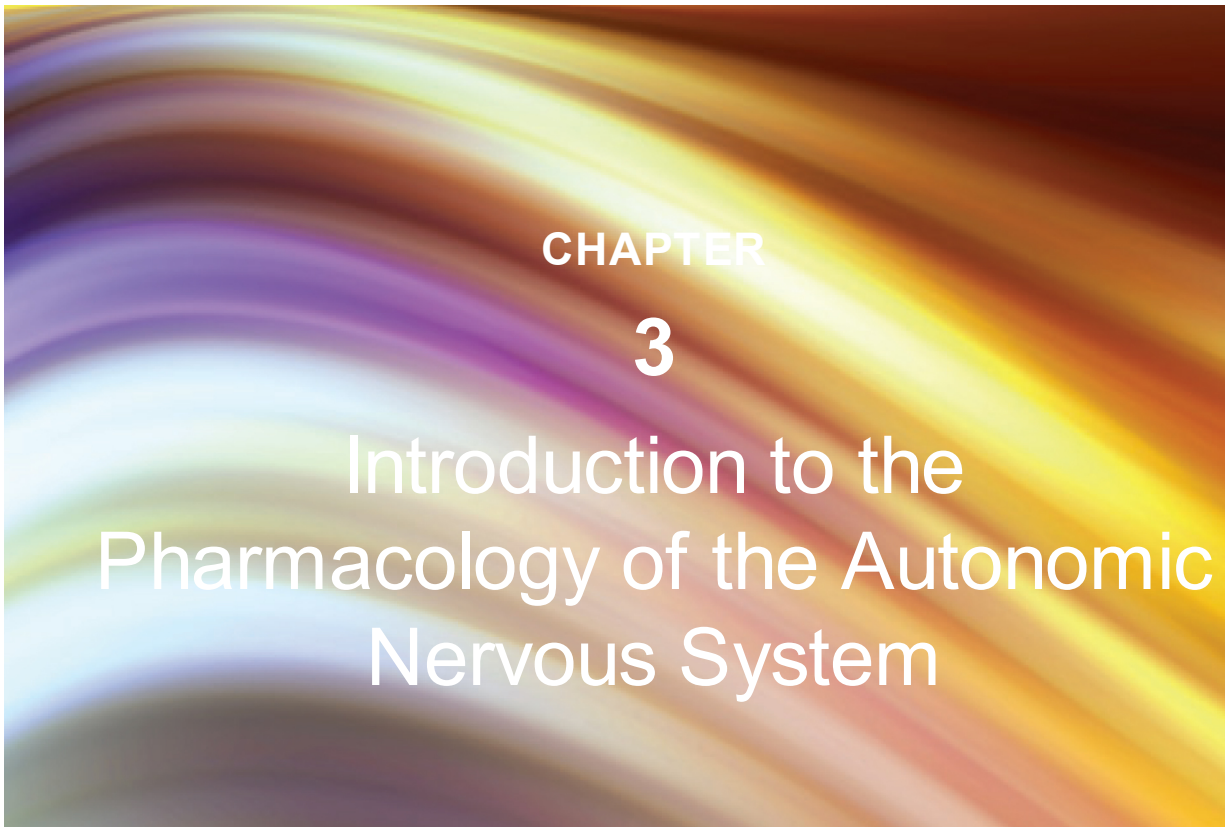
Buxton IO. Pharmacokinetics: the dynamics of drug absorption, distribution, metabolism, and elimination. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. 13th ed. New York, NY: McGraw-Hill. http://accesspharmacy.mhmedical.com.libproxy.temple.edu/content.aspx?bookid=2189&sectionid=166182905. Accessed January 28, 2019.

Hitner H, Nagle BT. *Pharmacology: An Introduction*. 6th ed. San Jose, CA: Glencoe Publishing Co; 2011.

Rizzo DC. *Fundamentals of Anatomy and Physiology*. Clifton Park, NY: Delmar Cengage Learning; 2010.

Smith BT. *Pharmacology for Nurses*. 1st ed. Burlington, MA: Jones & Bartlett Learning; 2016.

Tozer T, Rowland M. *Introduction to Pharmacokinetics and Pharmacodynamics: The Quantitative Basis of Drug Therapy*. 4th ed. Baltimore, MD: Lippincott Williams and Wilkins; 2011.



© Winui/Shutterstock.

OUTLINE

Introduction
Nervous System
Function and Anatomy of the ANS
Neurotransmitters
  General Physiologic Functions Controlled by the ANS
The Sympathetic Nervous System
  The Sympathetic Nerve Ending
  Sites of Action of Adrenergic Drugs
  α-Adrenergic Drugs
  α-Blocking Drugs
  β-Adrenergic Drugs
  β-Blocking Drugs
  Adrenergic Neuronal Activators and Blockers
Overall Effects of the Parasympathetic Division
  The Parasympathetic Nerve Ending
  Mechanism of Action of Cholinergic Drugs
  Definitions of Cholinergic Drugs

Anticholinesterase Drugs/Cholinesterase Inhibitors
Anticholinergic Drugs

OBJECTIVES

After completion of this chapter and its learning activities, you will be able to:

1. Describe the overall function and differences among the somatic nervous system, the sympathetic division, and the parasympathetic division of the autonomic nervous system.
2. Explain the function of neurotransmitters.
3. Compare and contrast the sites of action, neurotransmitters at the ganglion site, and neuroeffector sites of the somatic, the sympathetic, and the parasympathetic nervous systems.
4. List the characteristic physiologic functions that are controlled by the sympathetic and parasympathetic divisions.
5. If given an adrenergic agonist drug and the receptors it acts on, be able to predict its effects on the blood vessels, heart, and lungs.
6. Determine the effects each α-adrenergic drug will have on the patient's vital signs and list the possible side effects, when given a patient case with low blood pressure.
7. Summarize the mechanism of action, clinical effects, and adverse reactions expected to be seen with α-blocking and β-blocking drugs.
8. List the names of the parasympathetic receptors and the organ function affected by each.
9. Describe the mechanism by which the choline esters and anticholinesterase drugs work and the clinical effects one would expect to see with their use.
10. Explain in which clinical situations you would use an anticholinergic agent and what clinical and toxic effects you would expect to see.

KEY TERMS

Acetylcholine (ACh)
Adrenergic
Antiadrenergic
Anticholinergic
Antimuscarinic
Cholinergic
Ganglion cells
Neuroeffector
Neurotransmitters
Norepinephrine (NE)
Parasympathetic
Parasympatholytic
Postganglionic
Preganglionic
Sympathetic
Sympathomimetic

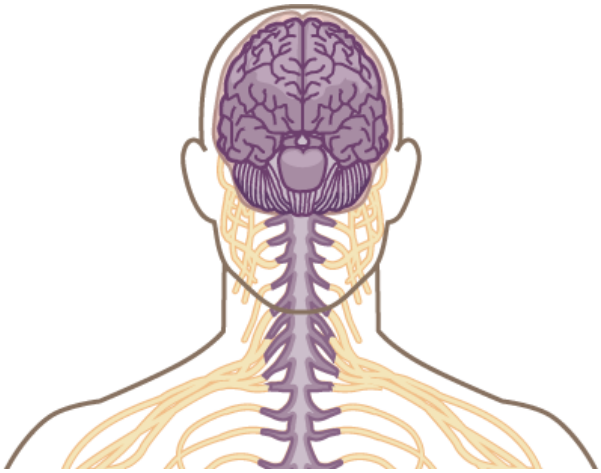
Synapse
Synaptic cleft

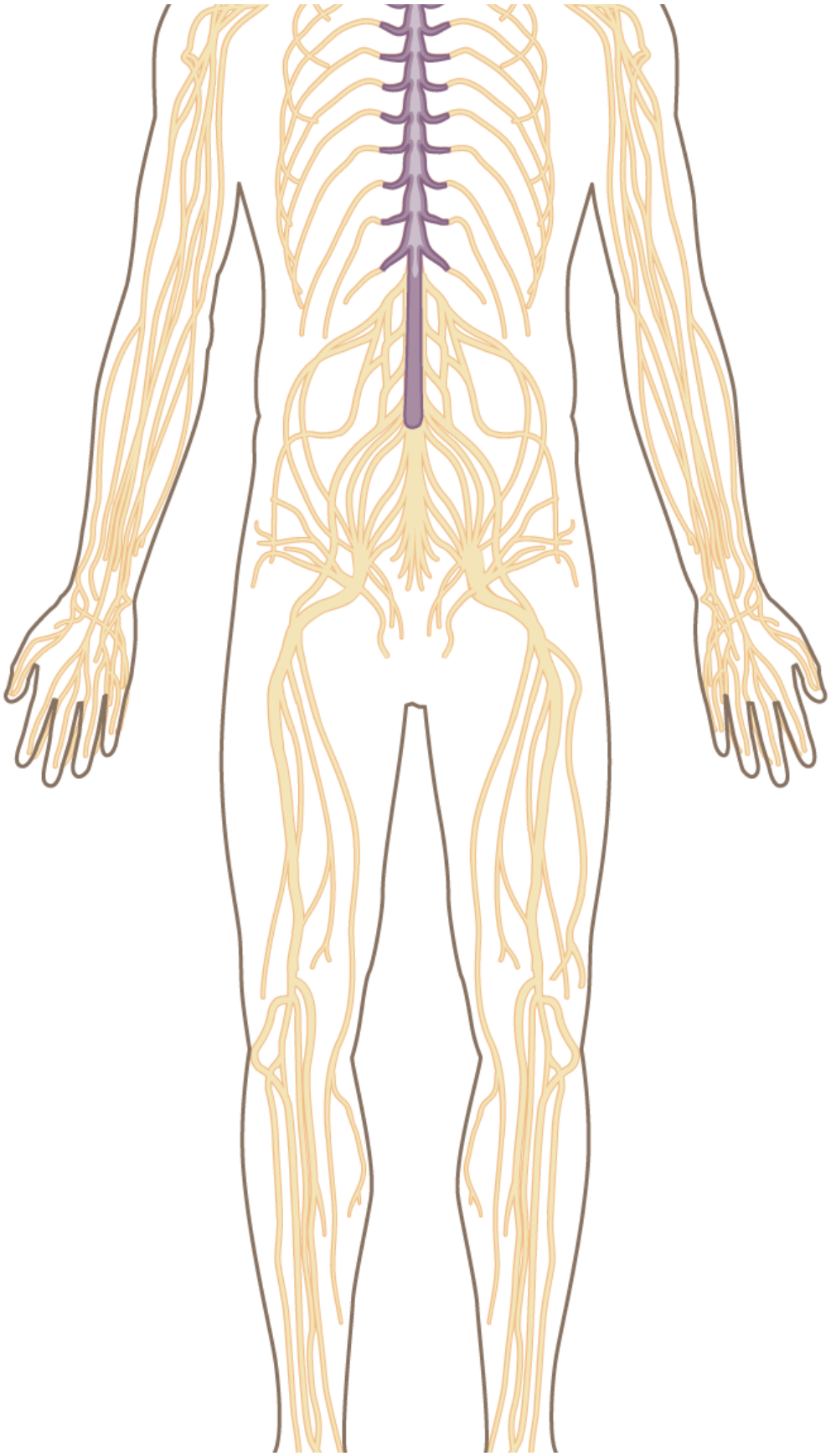
Introduction

The pharmacology of the autonomic nervous system (ANS) is a useful model for understanding how a drug interacts with its receptor site. This system controls many organ systems of the body, including ones under involuntary control (heart, blood flow, gastrointestinal [GI] function). To understand the many drugs that are affected by modifications in the ANS, it is important to understand the physiology of this system.

Much of the early theory of the mechanism of action, identification of neurotransmitters, and location of receptor sites was established on the basis of research on the ANS. There is considerable detail in this section so that the student will not only understand the pharmacologic principles in other drug groups, but also better understand some of the commonly used respiratory care drugs.

The nervous system is divided into the central nervous system (CNS) (brain and spinal cord) and the peripheral nervous system (nerve tissue outside the brain/spinal cord) (**Figure 3-1**). The motor (efferent) section of the nervous system can be divided into the autonomic and somatic systems. The somatic system is responsible for the conscious control of the body systems, such as respiratory function and conscious movement. The ANS controls activities that are involuntary, such as blood flow, heart function, and GI function, which will be described in more detail in this chapter.





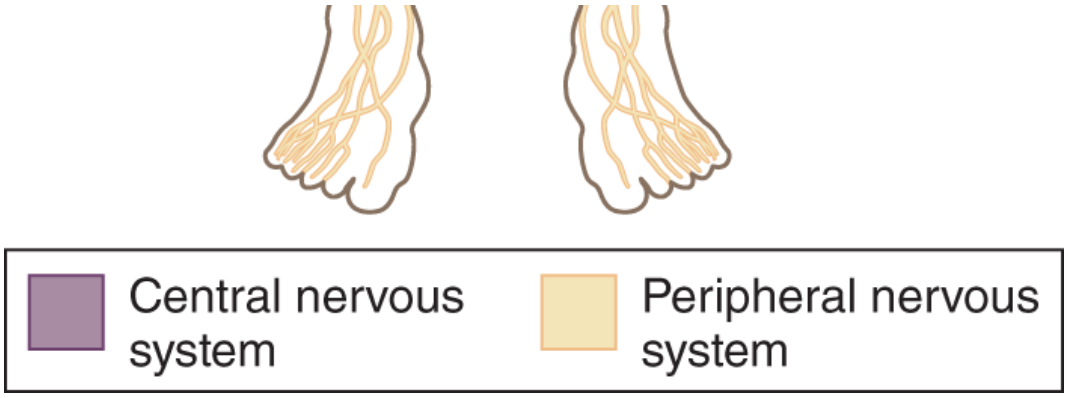


FIGURE 3-1 Components of the nervous system.

Nervous System

The nervous system sends signals to organs and muscles of the body through neurons (nerve cells) or **ganglion cells**, which are a group of neurons (**Figure 3-2**). In the nervous system, when nerves communicate with other nerves or neuroeffector sites, there is a gap between the nerves or between the nerve and the organ that is innervated. This gap is called a **synapse**, **synaptic cleft**, or **neuroeffector** junction. Nerves transmit electrical signals to other nerves across these gaps by means of **neurotransmitters**. Neurotransmitters are chemical substances that “transmit messages” across synaptic clefts and neuroeffector junctions. In the somatic nervous system, the nerve cell body originates in the CNS; an axon then travels to the site of innervation at the skeletal muscle without any interruption or synapses. In the ANS, there is an interruption between the CNS and the site of innervation. There are **preganglionic** neurons and **postganglionic** neurons. A preganglionic neuron leads from the vertebrae to a synapse outside the spinal cord and the postganglionic neuron leads from the synapse to the organ or gland being affected. It should be noted that multiple synapses occur in the ganglia, and because neurotransmitters are released at the ganglion site, drugs also can have an effect here.

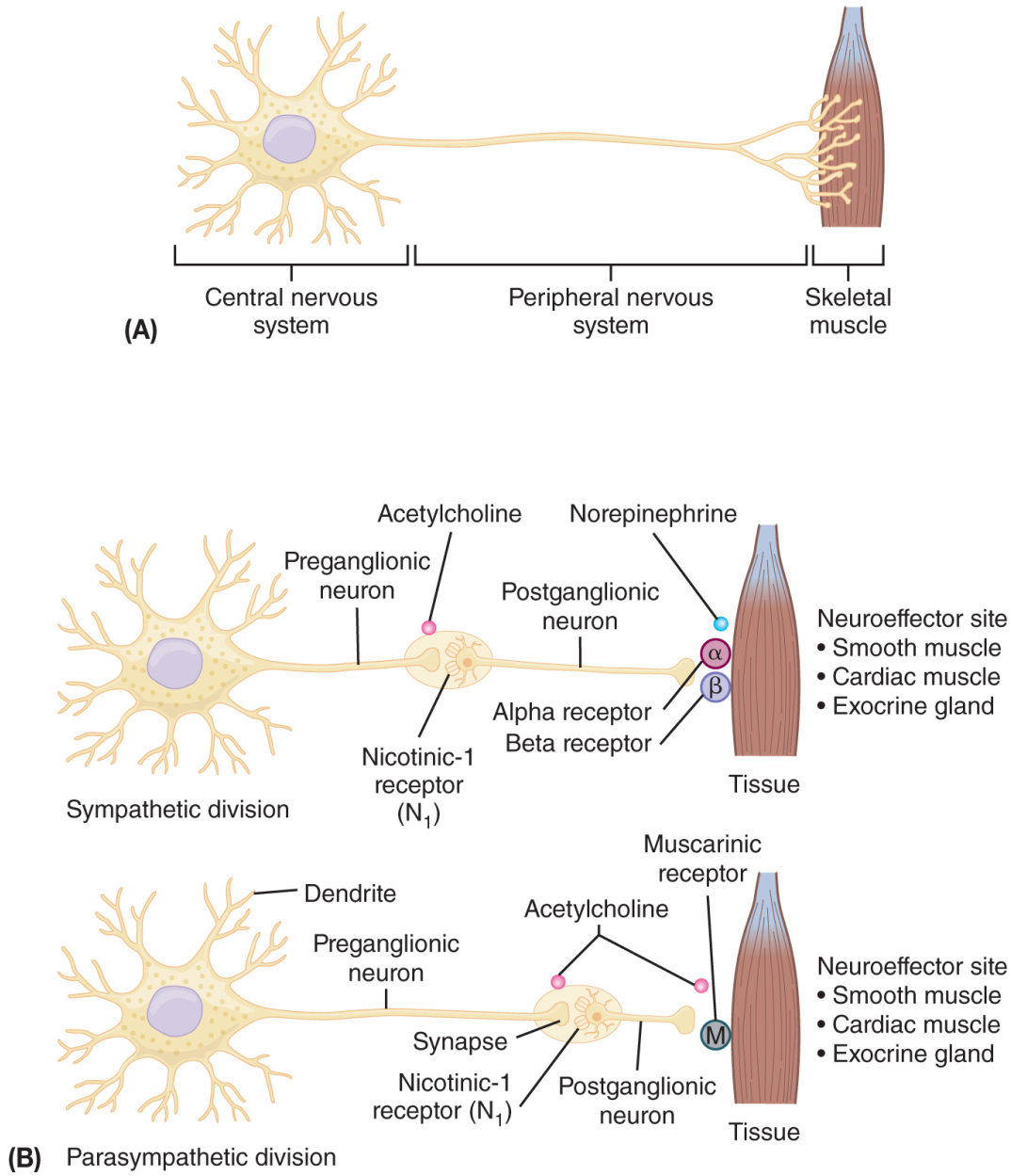


FIGURE 3-2 **(A)** Nerve of the somatic nervous system. **(B)** Synapses and ganglia of the autonomic nervous system.

Description

Function and Anatomy of the ANS

The ANS is the division of the body's nervous system controlling physiologic functions that are generally involuntary. These involuntary functions, such as control of heart rate, blood pressure, glandular secretions, and digestion, also are sometimes called automatic or vegetative. The two main divisions of the ANS are the **parasympathetic** and the **sympathetic** systems.

In both the parasympathetic and the sympathetic divisions, the interruptions (synapses) between the CNS and the receptor sites occur in autonomic ganglia. In the sympathetic division, most of these ganglia are located close to the spinal cord; in the parasympathetic division, most are located close to the effector site. With few exceptions, this is the typical anatomical arrangement of the autonomic ganglia. Because of the existence of these ganglia, there must be a preganglionic neuron and a postganglionic neuron. In the sympathetic division, the preganglionic neurons are short and the postganglionic neurons are longer, whereas in the parasympathetic division, the preganglionic neurons are very long and the postganglionic neurons are short (**Figure 3-3**). Another important anatomical feature is that the parasympathetic division branches off the CNS through the cranial and sacral segments of the spinal cord and the sympathetic division branches off the CNS through the thoracic and lumbar segments of the spinal cord.

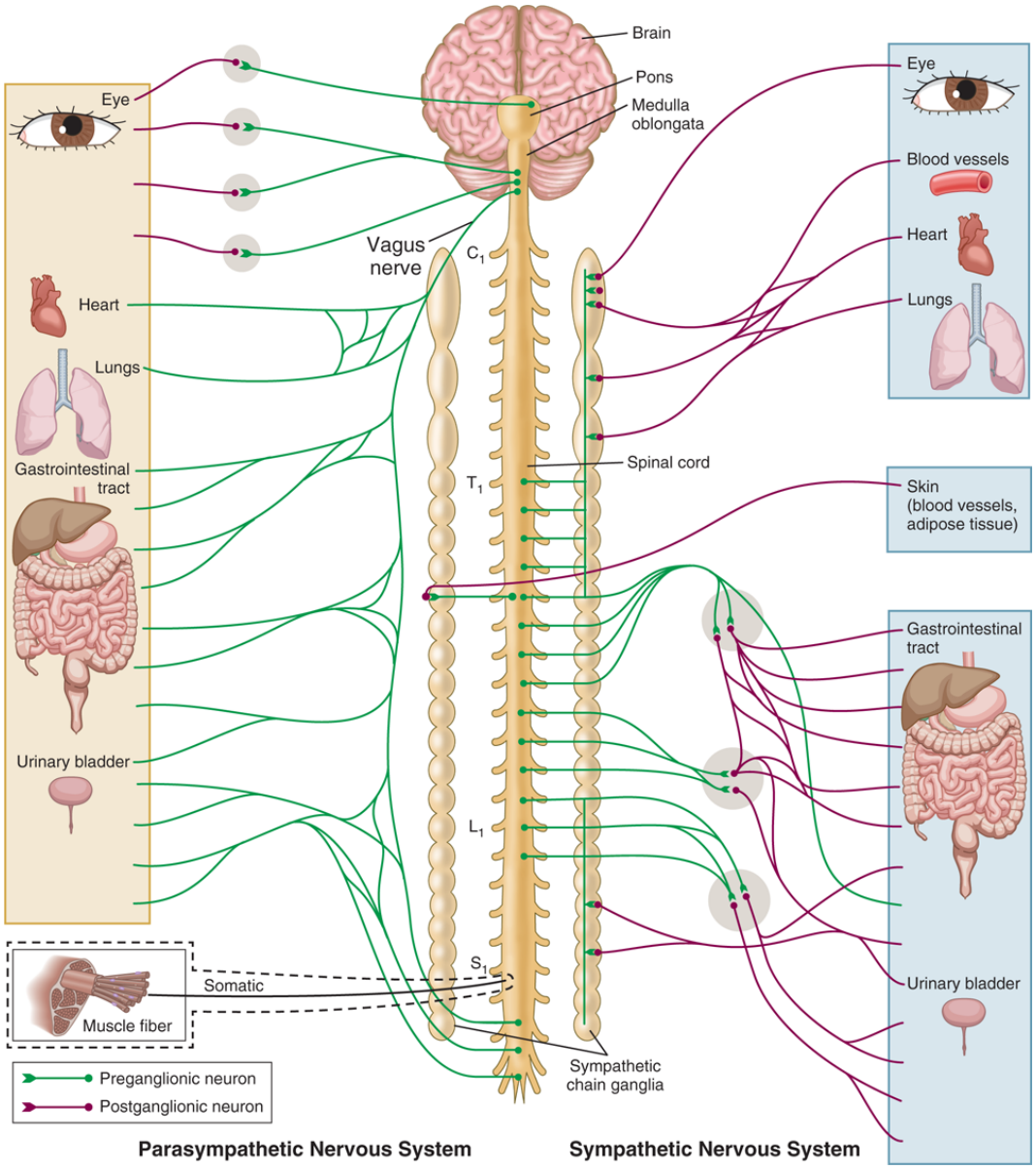


FIGURE 3-3 Origin and distribution of the autonomic nervous system.

Description

Neurotransmitters

An important concept in the function of the ANS is that of the neurotransmitter. The end of a nerve fiber is called the nerve terminal and contains neurotransmitters that are stored in small membrane-bound vesicles. When an impulse is transmitted along the axon to the nerve terminal, these vesicles fuse with the nerve terminal membrane and the contents are released into the synaptic cleft or the neuroeffector junction. The neurotransmitter then diffuses across the cleft to the postsynaptic or postjunctional site, where it interacts with receptors. The interaction between neurotransmitter and receptor initiates a chain of events leading to the production of electrical signals in the postsynaptic neuron or causes physiologic changes in the neuroeffector organ (**Figure 3-4**). The two main neurotransmitters of the ANS are **acetylcholine (ACh)** and **norepinephrine (NE)**. ACh affects the motor neurons of the peripheral nervous system at the skeletal muscle. ACh is also the neurotransmitter at both the ganglionic synapse and the neuroeffector site in the parasympathetic system. In the sympathetic system, ACh is the neurotransmitter at the ganglionic synapse and NE is the neurotransmitter at the neuroeffector site. Each organ system or gland, controlled by either the somatic nervous system or the ANS, has specific receptors that neurotransmitters act on specific sites. When these receptors are activated or blocked, a specific action of the organ system will occur. The neurotransmitters that act on each specific receptor are summarized in **Table 3-1**.

TABLE 3-1
Sites of Action, NTs, and Receptors of Somatic Nervous System and Autonomic Nervous System

Nervous System	Neuroeffector Site	NT at Ganglion Site	NT at Neuroeffector Site	Receptor
Somatic	Skeletal muscle	None	ACh	Nicotinic-2
Autonomic:				
Sympathetic	Smooth muscle	ACh	NE	α, β_2
	Cardiac muscle	ACh	NE	β_1
	Glands	ACh	ACh (sweat glands)	β_2
Parasympathetic	Smooth muscle	ACh	ACh	Muscarinic
	Cardiac muscle	ACh	ACh	Muscarinic
	Glands	ACh	ACh	Muscarinic

ACh, acetylcholine; NE, norepinephrine; NT, neurotransmitter.

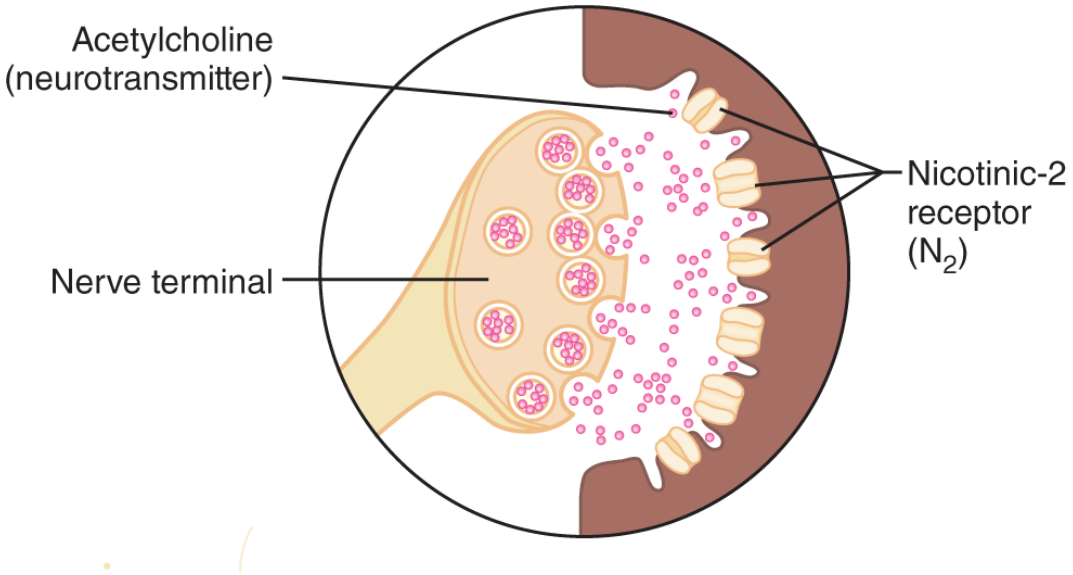


FIGURE 3-4 Neurotransmitter action at the synapse.

Most drugs that affect the ANS do so by affecting the synapses or receptors on neuroeffector sites in a manner similar to that of neurotransmitters. Drugs that affect a ganglion, parasympathetic neuroeffector site, or muscular junction by stimulating the release of ACh are referred to as **cholinergic** agents. **Anticholinergic** agents block a receptor for ACh or prevent the release of ACh. **Adrenergic** agents stimulate a receptor to release NE or epinephrine. Another term for epinephrine is adrenaline. The term adrenergic is derived from adrenaline. **Antiadrenergic** or adrenergic blockers refer to agents that block a receptor from NE or epinephrine having an effect.

General Physiologic Functions Controlled by the ANS

In general, both parasympathetic and sympathetic divisions innervate most organs of the body, and usually the two systems have opposite effects. In other words, one system will enhance a certain function and the other will decrease that same function; for example, the sympathetic innervation to the heart causes an increase in heart rate, whereas the parasympathetic innervation causes a decrease in heart rate. The innervation by both systems to a particular organ is known as dual innervation. **Table 3-2** illustrates the dual innervation and opposite effects in selected areas of the body.

TABLE 3-2
Effects of Parasympathetic and Sympathetic Divisions

Neuroeffector Site	Sympathetic Effect (Norepinephrine)	Parasympathetic Effect (Acetylcholine)
Arteries	Vasoconstriction (*exception*: coronary and skeletal arteries are dilated)	Most are not affected
Heart	Increased rate and force of contraction	Decreased rate and force of contraction
Intestines and gastrointestinal activity	Decreased	Increased
Pupil of eye	Dilation (mydriasis)	Constriction (miosis)
Respiratory tract	Bronchodilation	Bronchoconstriction
Urinary bladder	Relaxation	Contraction
Urinary sphincter	Constriction	Relaxation

The Sympathetic Nervous System

Generally, the sympathetic division is the dominant system when the body is under stress or in a state of increased activity. Sympathetic activity is also prominent when the body is in a dangerous or life-threatening situation. This condition is called the fight or flight response, and if the homeostatic balance is kept in this state for a prolonged period, complete exhaustion can occur and may lead to death.

The term adrenergic is often used to describe drugs that mimic the action of the sympathetic nervous system and, as already discussed, stimulate release of NE or epinephrine. Another term that is often used and has the same meaning is **sympathomimetic** ("sympathetic-like").

The Sympathetic Nerve Ending

The basic anatomy of the sympathetic nerve ending at the neuroeffector site is presented in **Figure 3-5**. The neurotransmitter at the neuroeffector site is NE, which is synthesized in the nerve ending and packaged in vesicles. When an impulse reaches the nerve ending, NE is released into the synaptic cleft and combines with the type of receptor present. The adrenergic receptors have been classified according to the response of various organs when their receptors interact with adrenergic drugs or NE, and are identified as α_1-, α_2-, β_1-, and β_2-receptors. (*Note:* There are a number of α_2-receptors that have been identified, but they do not play a major role in the autonomic drugs. Therefore, in this text, we consider all α-receptors to be the same.) **Table 3-3** indicates the general locations and actions of α-, β_1-, and β_2-receptors; the general responses of these receptors to NE and epinephrine are also listed.

TABLE 3-3
Location and Action of Adrenergic Receptors

Receptor	Organ	Spectrum of Action
α	Most arteries and veins	Vasoconstriction
β_1	Heart	Increase in rate, force of contraction
β_2	Lungs, bronchial smooth muscle	Bronchodilation
	Uterus	Relaxation
	Skeletal muscles (blood vessels)	Vasodilation

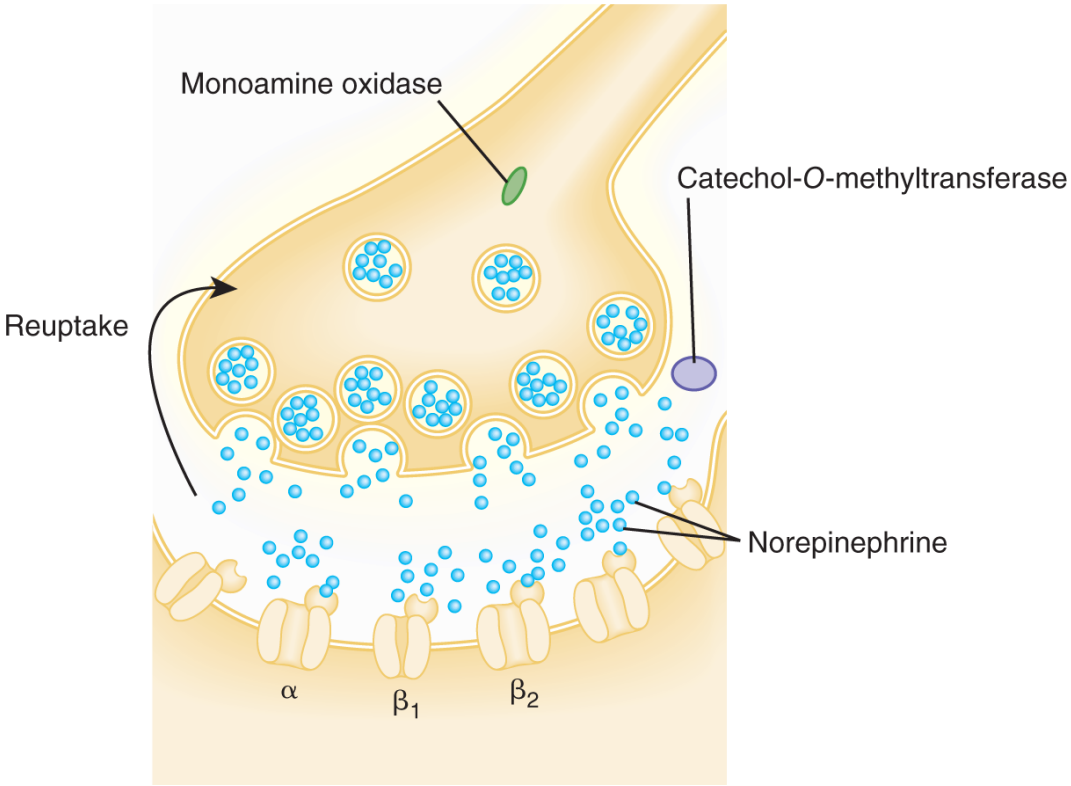


FIGURE 3-5 Sympathetic nerve ending.

The physiologic effects of NE are terminated by two means: (1) NE is actively transported back into the nerve terminal and

repackaged into the vesicles (reuptake) or (2) NE diffuses away from the site where enzymes—monoamine oxidase and catechol-*O*-methyl-transferase—ultimately metabolize NE. Although these enzymes do metabolize NE, they usually do not interfere with the neurotransmitters' synaptic action.

Sites of Action of Adrenergic Drugs

Referring back to Figure 3-5 it can be seen that there are many possibilities for drug–receptor interactions at the various sites with which NE combines. First, there are several drugs that affect the adrenergic transmission presynaptically in the nerve ending. Some of the mechanisms by which these drugs work include altering NE transmission by creating false transmitters, blocking the reuptake of NE, depleting NE from storage vesicles, increasing release of NE from nerve endings, and blocking release of NE from nerve terminals. The various drugs that work by these mechanisms are collectively called "neuronal activators" or "neuronal blockers."

Second, at the postjunctional site where the receptors are located, there are also many possibilities for drug–receptor interaction. Some drugs stimulate α-receptors, β-receptors, or both, and some drugs block α-receptors or β-receptors. (*Note:* It has recently been shown that long-term medications can alter the number of receptors and thus increase or decrease tolerance to drugs; that is, the number of receptors can vary according to pharmacologic, physiologic, and pathologic factors. It is not within the scope of this text to discuss these phenomena.)

The following list defines the mechanisms of action of the adrenergic drugs:

- *α-adrenergic*: drugs that stimulate the α-receptor sites
- *β-adrenergic*: drugs that stimulate the β-receptor sites
- *α-blockers*: drugs that block the α-receptors
- *β-blockers*: drugs that block the β-receptors

- *neuronal activators* or *blockers*: drugs that either increase or inhibit the levels of NE in the nerve ending

α-Adrenergic Drugs

The α-adrenergic drugs stimulate the α-receptor sites; a few stimulate both α- and β-receptors but have a stronger affinity for the α-receptor sites. The most commonly used agents are NE, epinephrine, and phenylephrine. The most dominant clinical effect of these agents is vasoconstriction due to the activity on the α-receptors. They are most frequently administered intravenously for the treatment of hypotension and shock and are commonly referred to as vasopressors or "pressors." Ephedrine's use is limited to the operating room for anesthesia-induced hypotension. It has been used orally for the treatment of wheezing resulting from asthma but is not recommended due to the use of safer inhaled agents. NE is the most commonly used vasopressor agent for the treatment of all types of hypotension or shock. Epinephrine is an endogenous substance that is released by the adrenal gland. It has a profound effect on both α- and β-receptors, with a stronger affinity for the β_1- and β_2-receptors. When administered intravenously, it causes vasoconstriction and can increase the rate and force of contraction of the heart. Phenylephrine is primarily an α-agonist, and its overall effect is vasoconstriction. It is used to increase blood pressure, but when used topically in the nose or on hemorrhoids, it causes vasoconstriction of the vessels and decreases nasal congestion and shrinks the blood vessels that cause hemorrhoids. The major adverse effects of each agent can be found in **Table 3-4**.

TABLE 3-4
***α*-Adrenergic Drugs**

Drug	Mechanism of Action			Clinical Uses	Adverse Reactions
	α	β_1	β_2		
Norepinephrine (Levophed®)	+	+		Hypotension/shock	Agitation, headache, tremor, peripheral ischemia, low potassium, hyperglycemia
Epinephrine	+	+	+	Hypotension/shock, anaphylaxis, cardiac arrest, inhaled for bronchodilation or stridor	Agitation, tremor, headache, tachyarrhythmias, hyperglycemia, decreased gastrointestinal circulation, low potassium
Ephedrine	+	+	+	Anesthesia-induced hypotension	Same as epinephrine
Phenylephrine	+			Hypotension/shock, intranasal as a nasal decongestant or in eye to dilate pupils, topically for hemorrhoids	Bradycardia, decreased gastrointestinal circulation, rebound congestion when overused as a nasal decongestant

α-Blocking Drugs

This group of drugs blocks the α-receptor sites and has an overall effect on vasodilation. Because they produce a competitive blockade of the α-receptor sites, NE cannot cause vasoconstriction. These drugs create such a generalized, nonselective vasodilation that they have only limited clinical use and are considered as second-line antihypertensives. There are also α-receptor sites located in the bladder and prostate gland. Certain α-blocking drugs work specifically at those sites and cause vasodilation to improve the flow of urine and alleviate symptoms of benign prostatic hypertrophy (BPH). The activity of each agent on α-receptors and location of activity determine the use and adverse effects of these agents as seen in **Table 3-5**. Phenoxybenzamine causes a profound blockade of α-receptors that lasts 3–4 days. It also enters the CNS, resulting in fatigue, sedation, and nausea. This drug is used rarely but can be seen in the treatment of a rare kind of adrenal gland tumor (pheochromocytoma) that causes a massive release of epinephrine and NE in the body. Phentolamine produces moderately effective blockade of the α-receptors and has a short duration of action. It also enhances release of NE leading to cardiac stimulation. Phentolamine is also used to treat extravasation and tissue injury caused by inadvertent administration of intravenous α_1-agonists (e.g., NE, epinephrine, phenylephrine, and dopamine) into soft tissue. It may

reverse the tissue damage caused by severe vasoconstriction effects of these agents. It may also be used to treat pheochromocytoma.

TABLE 3-5
***α*-Blockers**

Drug	Clinical Use	Adverse Effects
Phenoxybenzamine	Pheochromocytoma	Orthostatic hypotension, reflex tachycardia, miosis, sedation, fatigue, nausea
Phentolamine	Acute treatment of hypertension associated with pheochromocytoma, extravasation of vasopressors	Tachycardia, hypotension, arrhythmias
Doxazosin, prazosin, and terazosin	Hypertension and benign prostatic hypertrophy	Dizziness, orthostatic hypotension, sedation, edema
Alfuzosin, silodosin, and tamsulosin	Benign prostatic hypertrophy	Orthostatic hypotension, dizziness, floppy iris syndrome, dry ejaculation or loss of libido

Doxazosin, prazosin, and terazosin selectively block the α-receptors in the vasculature causing vasodilation in the blood vessels, bladder, and prostate without causing tachycardia as seen with phentolamine. Alfuzosin, silodosin, and tamsulosin block α-receptors selectively in the prostate and bladder without affecting the vasculature. These agents are used for BPH and have minimal influence on blood pressure.

β-Adrenergic Drugs

These drugs stimulate mainly the β_1- and β_2-receptors, but some also stimulate α-receptors. Drugs that affect β_1-receptors, epinephrine, ephedrine, dopamine, and isoproterenol are used to increase heart rate, to treat bradycardia, or to stimulate the force of cardiac contraction in cases of heart failure. A brief discussion of some of the more common β-adrenergic drugs follows, along with some clinical uses and pertinent adverse effects (**Table 3-6**). Epinephrine has prominent effects at α-, β_1-, and β_2-receptors. Because of the widespread effect at all sympathetic receptors, it has a number of clinical uses: (1) to increase blood pressure in shock states; (2) because of vasoconstriction properties, it can be used to reduce bleeding during surgical procedures when injected into bleeding vessels; (3) as a heart stimulant to increase heart rate and strength of contraction; and (4) as a bronchodilator, particularly in emergency treatment of bronchospasm and constriction during anaphylactic shock. Epinephrine is a primary drug in advanced cardiovascular life support and will be discussed further in a later chapter. Dopamine (Intropin®) is an α- and β_1-stimulator and a precursor to NE, but its effects are dose-dependent. At low-to-moderate doses, it affects the β_1-receptors, and at higher doses, it affects the α-receptors. Dopamine also affects dopamine receptors, which promotes vasodilation of renal, splanchnic, coronary, and cerebral vessels. Isoproterenol (Isuprel®) is closely related to NE and epinephrine in chemical structure but has pure β-receptor effects. It is one of the original bronchodilator drugs, but because it has strong β_1-effects causing undesirable cardiac stimulation, it is no longer used as a bronchodilator.

TABLE 3-6
β-Adrenergic Drugs

Drug	Mechanism of Action			Clinical Use	Adverse Effects
	α	β_1	β_2		
Epinephrine	+	+	+	Hypotension/shock, anaphylaxis, cardiac arrest, inhaled for bronchodilation or stridor	Agitation, tremor, headache, tachyarrhythmias, hyperglycemia, decreased gastrointestinal circulation, low potassium
Ephedrine	+	+	+	Anesthesia-induced hypotension	Same as epinephrine
Dopamine (Intropin®)	+	+		Hypotension/shock, bradycardia, heart failure	Nausea, headache, tachyarrhythmias, peripheral vasoconstriction
Dobutamine (Dobutrex®)	+/–	+		Heart failure	Tachyarrhythmias, myocardial ischemia, hypotension (rarely), headache, tremor, hypokalemia
Isoproterenol (Isuprel®)		+	+	Bradycardia	Tachycardia

Medications that are used clinically for bronchodilation have effects on β_2-receptors only. This limits the adverse reactions that can be seen with drugs that affect β_1 and β_2 receptors. Albuterol (Proventil®, Ventolin®) and levalbuterol (Xopenex®) are inhaled short-acting bronchodilators used for the treatment of acute bronchospasms. Arformoterol (Brovana®), formoterol (Foradil®), indacaterol (Arcapta Neohaler), olodaterol (Striverdi Respimat), salmeterol (Serevent®), and vilanterol are inhaled long-acting β_2-agonists used in the chronic management of obstructive lung diseases. Terbutaline (Brethine®) and metaproterenol (Alupent®) are systemically (injection or oral) available β_2-agonists that have limited use due to higher adverse effects compared with the inhaled agents. The common uses and side effects are summarized in **Table 3-7**. These agents will be discussed in detail in Chapter 6.

TABLE 3-7
Bronchodilator β_2-Agonist Drugs

Drug	Clinical Uses	Adverse Effects
Albuterol and levalbuterol	Short-acting bronchodilators for treatment of acute bronchospasms	Chest pain, nervousness, tachycardia, tremors, insomnia, cough,

Arformoterol, formoterol, indacaterol, olodaterol, salmeterol, and vilanterol	Long-acting bronchodilators for chronic treatment of asthma and chronic obstructive lung disease	headache, decreased potassium
Metaproterenol and terbutaline	Bronchospasm, but use is limited due to side effects	

β-Blocking Drugs

These drugs include a group of agents that are extremely useful and commonly used in clinical practice. There are many different β-blockers available, with some affecting both β_1- and β_2-receptors and some that are relatively selective for β_1-receptors (**Table 3-8**). These drugs block the effects of NE and epinephrine on β-receptors, causing a decrease in heart rate and the force of heart contractions. Propranolol was one of the earliest β-blockers used. This is the prototype drug of the β-blockers. Propranolol, nadolol, and timolol are nonselective drugs that block both β_1- and β_2-receptors, which are most commonly used for indications other than for the treatment of hypertension. Timolol and other β-blockers used for the treatment of glaucoma cause a decrease in intraocular pressure by decreasing the production of aqueous humor in the eye. The use of these drugs is limited in patients with asthma. These agents cause blockade of β_2-receptors in bronchial smooth muscle and can cause bronchoconstriction and wheezing in this susceptible population. The β_1-selective blocking agents, atenolol, bisoprolol, esmolol, metoprolol, and nebivolol, are the most commonly used β-blockers. At low and moderate doses, these agents are safe to use in patients with asthma. At maximum doses, they lose their selectivity for β_1-receptors and can affect β_2-receptors as well. Carvedilol and labetalol are nonselective β-blockers that also block α-receptors and should also be used cautiously in patients with asthma. All β-blockers can cause hypotension, bradycardia, and fatigue. Sedation, vivid dreams, and depression may occur with β-blockers that penetrate

the CNS, such as propranolol, and to a lesser extent carvedilol, metoprolol, and timolol.

TABLE 3-8
β-Blockers

Drug	β_1	β_2	Clinical Use
Propranolol (Inderal®) and nadolol (Corgard®)	+	+	Hypertension, angina, cardiac arrhythmia, migraine headache
Timolol (Blocadren®)	+	+	Same as propranolol, but also used in treating open-angle glaucoma (very potent)
Atenolol (Tenormin®), bisoprolol, esmolol (Brevibloc), metoprolol (Lopressor®), and nebivolol (Bystolic)	+		Hypertension, angina, heart failure, acute myocardial infarction
Carvedilol (Coreg) and labetalol	α-, β_1-, β_2-blockers		Hypertension, heart failure (carvedilol)

Therapeutic uses: to treat hypertension, angina, cardiac arrhythmias, myocardial infarction, open-angle glaucoma, and tremor.

Also used prophylactically in the prevention of migraine headaches. *Adverse effects*: weakness, fatigue, depression, bradycardia, hypotension, and agents that block β_2 should not be used or used cautiously in asthmatics. Inhaled β-agonists will not be effective for these patients if they are taking a β-blocker.

Adrenergic Neuronal Activators and Blockers

In general, these agents decrease adrenergic nerve function by affecting the release of NE from the presynaptic nerve terminal. In addition, these drugs affect all sites where NE is released and thus tend to influence both α- and β-receptors. (In addition, some of these drugs activate the effects of NE.) The agents in this class are reserpine, the prototypical agent in this class, methyldopa, and clonidine. Reserpine is the prototype drug for this drug class. It depletes NE and dopamine from nerve terminals by preventing storage of NE in the vesicles and formation of dopamine. This results in less NE and dopamine being available for combination with receptors. This drug is no longer available and is clinically not useful due to its sedative effects, its potential to cause depression, Parkinson-like movement disorders, and also worsen peptic ulcers.

α-Methyldopa (Aldomet®) and Clonidine (Catapres)

Methyldopa works with either presynaptic or postsynaptic nerve endings and causes activation of the receptor site by a metabolite (α-methylnorepinephrine) and stimulates centrally acting α_2-receptors. α_2-Receptors are located on presynaptic and postsynaptic adrenergic neurons, which decrease the release of NE. Clonidine reduces sympathetic tone and acts directly on the cardiovascular center in the brain stem to decrease sympathetic outflow from the CNS and increases parasympathetic tone causing bradycardia. Methyldopa and clonidine are not considered as first-line antihypertensive agents. Methyldopa's use is limited to hypertension during pregnancy. Adverse effects include sedation, decreased concentration,

depression, dizziness, and lactation. Clonidine’s use is limited to patients with resistant hypertension due to side effects of dry mouth, sedation, and bradycardia. If clonidine is stopped abruptly, it can lead to life-threatening rebound hypertension due to a rapid increase in sympathetic activity.

Overall Effects of the Parasympathetic Division

Generally, the parasympathetic division is dominant when the body is at rest. When the body is in a quiet state, this division controls and stimulates digestion, waste elimination, and the genitourinary system. Also, the activity level of the cardiovascular system generally is decreased. The term cholinergic is often used to describe drugs that mimic the parasympathetic system and literally means “acetylcholine-like.” A similar term is parasympathomimetic, which means “parasympathetic-like.”

The Parasympathetic Nerve Ending

The basic anatomy of the parasympathetic nerve ending at the neuroeffector site is represented in **Figure 3-6**. As stated previously, the neurotransmitter at the neuroeffector site in the parasympathetic division is ACh. This substance is synthesized in the nerve ending and packaged in vesicles. When a nerve impulse reaches the nerve ending, ACh is released into the synaptic cleft and combines with the type of receptor present. In the sympathetic division, there is no enzyme available to metabolize excess NE; however, in the parasympathetic division, or wherever ACh is released, there is acetylcholinesterase (ACHE), which metabolizes any excess ACh that does not combine with the receptor. The significance of this fact is that the effect of ACh throughout the body is rather short-lived. Thus, the parasympathetic division is more discrete in its action, and, in contrast to the sympathetic division, does not have a generalized effect.

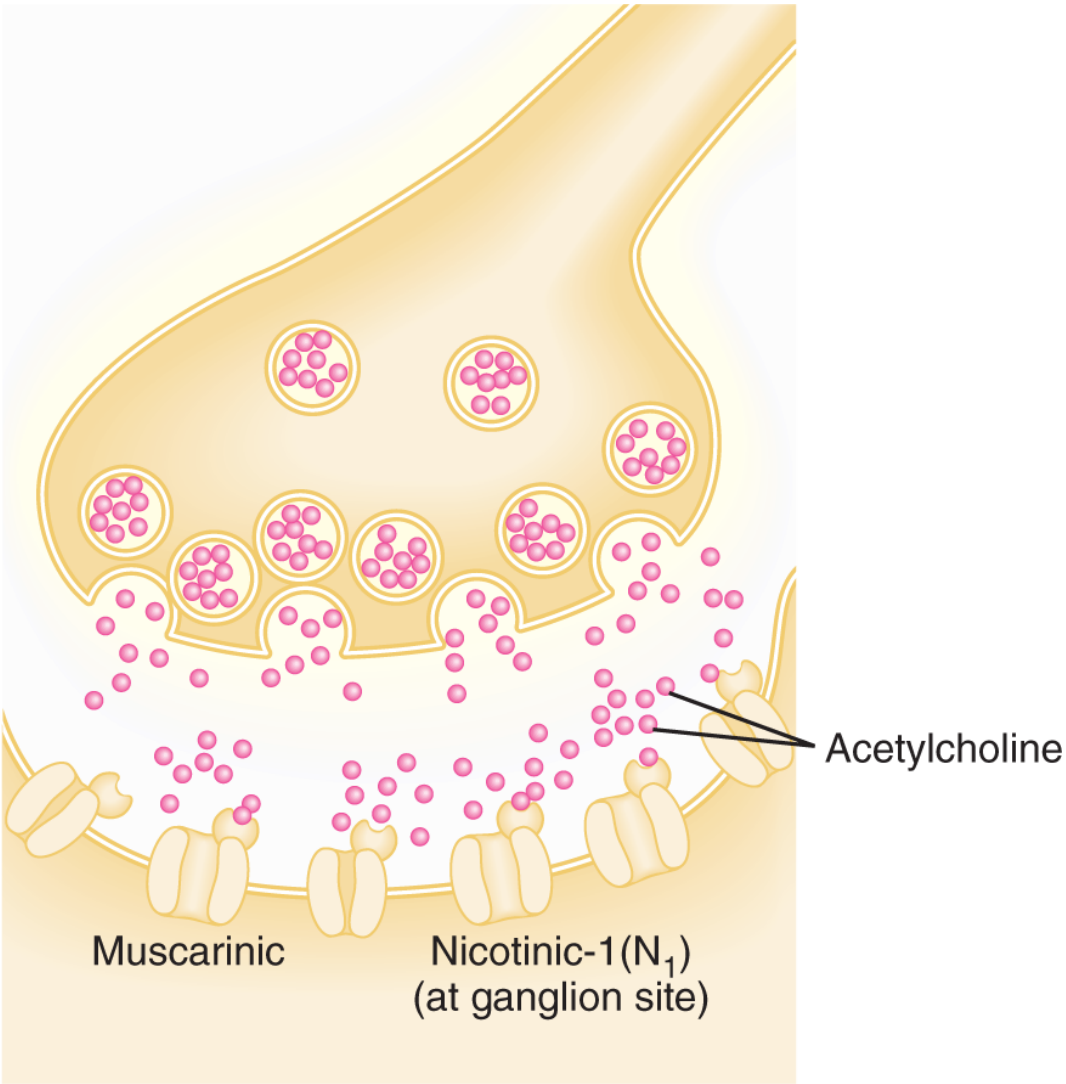


FIGURE 3-6 Parasympathetic nerve ending.

The cholinergic receptors have been classified and named on the basis of two experimental drugs muscarine and nicotine, which initially were used to identify the action of the receptor sites when these drugs were administered. The names of the receptors are muscarinic (M), nicotinic-1 (N_1), and nicotinic-2 (N_2). There are five muscarinic receptors, M_1–M_5, located at different locations in the body. The neuroeffector sites of the parasympathetic division contain M-receptors, the N_1-receptors that are located at all ganglion sites in the ANS, and the N_2-receptors that are located at the neuromuscular junctions in the somatic nervous system. With knowledge of the

responses when these receptors are stimulated and knowledge about their location, one can predict the action of various cholinergic drugs when they combine with their respective receptors. (*Note:* Although the neuromuscular junctions in the somatic nervous system have N_2-receptors, they are stimulated by ACh. The effects of drug action at this site will be discussed in Chapter 12.) **Table 3-9** indicates the general location of the cholinergic receptors and their response to ACh.

TABLE 3-9
Location and Action of Cholinergic Receptors

Receptor*	Organ	ACh
Muscarinic (M), M1–M5	Not located in most arteries and veins	None
	Pupil of eye (miosis)	Constricting
	Heart	Decrease in heart rate
	Bronchial smooth muscle	Bronchoconstriction
	Uterus	Contraction of smooth muscle
	Urinary bladder	Contraction of muscle
	Gastrointestinal tract	Increased mobility and peristalsis
Nicotinic-1 (N_1)	All autonomic ganglia	Stimulation of postganglionic neuron
Nicotinic-2 (N_2)	Neuromuscular junction of skeletal muscle	Contraction of skeletal muscle

*The muscarinic receptors recently have been subdivided into M_1, M_2, M_3, M_4, and M_5 types. However, there are few drugs that have yet been identified as specific for these types.

Mechanism of Action of Cholinergic Drugs

Referring back to Figure 3-3, one can observe that because of the many locations wherein ACh acts as a transmitter, there are more possibilities for drugs to interact with cholinergic receptors. Thus, cholinergic drugs produce a much broader spectrum of unwanted side effects because the parasympathetic system, unlike the sympathetic system, does not function as a unit. Therefore, most clinically useful cholinergic drugs are quite specific and affect the postsynaptic receptor site.

At the postsynaptic site, there are three possible drug–receptor interactions. First, drugs can stimulate the muscarinic receptor, producing a cholinergic effect (i.e., these drugs mimic the activity of the parasympathetic nerves). Second, there are drugs that block the cholinergic receptors and prevent ACh from interacting. Third, there are drugs that block ACHE. These drugs are called anticholinesterase drugs or cholinesterase inhibitors, which increase the accumulation of ACh and enhance the duration of parasympathetic impulses or cholinergic drugs.

Definitions of Cholinergic Drugs

There are various mechanisms by which cholinergic drugs can work. The definitions and categories of these drugs are as follows:

- *Choline esters*: stimulate the muscarinic receptors and in general mimic the effects of ACh.
- *Anticholinesterases*: block the enzyme ACHE.
- *Anticholinergics*: block the receptor sites where ACh interacts.
- **Antimuscarinic**: specifically block the muscarinic receptor sites.

Choline Esters

This group of drugs exerts their effects primarily by stimulation of the muscarinic receptors at the neuroeffector site junction. Some of the

commonly used drugs are discussed in **Table 3-10**, along with their therapeutic uses and adverse effects.

TABLE 3-10
Choline Esters

Drug	Clinical Use
Acetylcholine	Used topically as a miotic in ophthalmic surgery
Methacholine (Provocholine®)	Solution for inhalation used in bronchial provocation testing
Bethanechol (Urecholine®)	Orally for the treatment of urinary retention and neurogenic bladder
Pilocarpine (Salagen®)	Topically as a miotic and in the treatment of glaucoma, systemically for dry mouth

Acetylcholine

This substance is an endogenous neurotransmitter that has effects of muscarinic and nicotinic receptors. It has no clinical use, except being used topically in the eye to cause miosis, primarily because of its short duration of action brought about by its rapid destruction by ACHE. Also, because of ACh's wide distribution throughout the body at both ganglionic and neuroeffector sites, the clinical effects are too widespread when used systemically.

Methacholine (Provocholine®)

This is a synthetic choline ester with a longer duration of action because it is slowly metabolized by ACHE. It has no effect on nicotinic receptors. *Therapeutic uses*: used diagnostically to induce bronchospasm in a bronchial challenge test (this test is described in Chapter 11). *Adverse effects*: severe bronchoconstriction.

Bethanechol (Urecholine®)

This is a synthetic choline ester that has a longer duration of action than methacholine. It primarily stimulates muscarinic receptors. *Therapeutic uses*: to treat urinary retention, but is rarely used today. *Adverse effects*: abdominal cramps, bronchoconstriction, and miosis.

Pilocarpine (Salagen®)

This is a naturally occurring alkaloid that stimulates muscarinic receptors. *Therapeutic uses*: topical administration in the eye to treat glaucoma by causing miosis and given orally to treat severe dry mouth by increasing saliva production. *Adverse effects*: myopia, blurred vision, hypertension, and bradycardia.

Anticholinesterase Drugs/Cholinesterase Inhibitors

As the name implies, this group of drugs inhibits the effects of ACHE at receptor sites in synapses and effector sites throughout the CNS as well as the peripheral nervous system. This leads to prolonged and intensified effects of ACh. This may lead to increased contraction of skeletal muscles due to the effects of ACh on the skeletal neuromuscular effector site and are effective in treating myasthenia gravis, a disease that causes muscular weakness. The unwanted effects of these agents result from parasympathetic stimulation in the heart, bradycardia, and decreased cardiac contractility. Long-term use or excess doses may cause muscle weakness, diarrhea, excess salivation, and excess bronchial secretions. If these adverse effects are intolerable, an anticholinergic agent may be used in conjunction. Because these drugs are not very selective, their therapeutic use is limited (**Table 3-11**); they should only be used by medical specialists such as anesthesiologists and neurologists. The major therapeutic uses of these drugs are for treating myasthenia gravis, antagonizing the effects of neuromuscular blocking agents, and treating toxic overdose of anticholinergic drugs.

TABLE 3-11
Anticholinesterases

Drug	Clinical Use
Edrophonium (Enlon®)	Diagnosis of myasthenia gravis due to short duration of action
Neostigmine	Myasthenia gravis, reversal of nondepolarizing neuromuscular blockade after surgery
Pyridostigmine (Mestinon®)	
Physostigmine	Antidote to anticholinergic overdose

Edrophonium (Tensilon®), Neostigmine, Pyridostigmine (Mestinon®), and Physostigmine

All of these agents are considered reversible cholinesterase inhibitors. Edrophonium, neostigmine, and pyridostigmine do not penetrate the blood–brain barrier and thus have few CNS effects. Physostigmine is well absorbed into many sites, including the CNS. *Therapeutic uses*: in diagnosing myasthenia gravis; neostigmine and pyridostigmine are also used to reverse neuromuscular blockade. Pyridostigmine is available as an oral tablet and is used in the treatment of myasthenia gravis. Physostigmine is used to reverse toxic effects of an anticholinergic overdose. *Adverse effects*: causes excessive parasympathetic response (e.g., diarrhea, bronchial secretions, salivation), hypotension, bradycardia, and miosis.

NEED TO KNOW

Edrophonium, neostigmine, and pyridostigmine are used in the diagnosis and treatment of myasthenia gravis.

Anticholinergic Drugs

These drugs block the muscarinic receptors throughout the body and can also affect the nicotinic receptors if given in high enough doses. As a group, these drugs are used as a pupil dilator in ophthalmology, as a preanesthetic medication to inhibit secretions, as a bronchodilator, in treating diarrhea and urinary incontinence, and in treating motion sickness (**Table 3-12**). The indication of each agent depends on the specific receptors it acts on. There are five different terms that can be used to describe these drugs: antimuscarinic, anticholinergic, atropinic, antiparasympathetic, and **parasympatholytic**. The following drugs are those that are clinically significant.

TABLE 3-12
Anticholinergic Drugs

Drug	Clinical Use
Atropine	Cardiac stimulant to treat acute bradycardia and before anesthesia to decrease secretions
Ipratropium (Atrovent®)	Treatment of acute bronchospasms in chronic obstructive lung disease and asthma
Scopolamine	Treatment and prevention of motion sickness
Aclidinium (Tudorza), glycopyrrolate (Seebri), tiotropium (Spiriva®), umeclidinium (Incruse Ellipta)	Long-acting bronchodilators used for the chronic treatment of chronic obstructive lung disease
Tropicamide (Mydriacyl®)	Short-acting pupil dilator used in routine eye examinations
Dicyclomine (Bentyl®)	Decreases gastrointestinal motility, treatment of ulcers
Propantheline (Pro-Banthine®)	Decreases gastrointestinal motility, treatment of ulcers

Atropine

Atropine is the prototypic anticholinergic agent and can be used for a number of clinical situations. In low doses, it mainly affects all subtypes of muscarinic receptors, but in higher doses, it can block nicotinic receptors. *Therapeutic uses*: as a preanesthetic agent to decrease salivary and respiratory secretions, as an agent to increase heart rate in bradycardia, and topically for pupillary dilation (rarely due to longer duration of action). *Adverse effects*: dry mouth, constipation, mental confusion, palpitations, tachycardia, urinary retention, and decrease in sweating.

Dicyclomine (Bentyl®) and Propantheline

This agent has a strong affinity for the muscarinic receptors in the GI tract. Owing to more specific acting agents with less adverse effects, these drugs are very rarely used. *Therapeutic uses*: to reduce GI motility in patients with irritable bowel, and in the past has been used to heal gastric ulcers, but is no longer used for this condition. *Adverse effects*: same as with atropine.

Ipratropium Bromide (Atrovent®)

Short-acting anticholinergic bronchodilator administered only as an inhaled aerosol. This agent blocks the muscarinic receptors in the bronchial smooth muscle, causing bronchodilation. *Therapeutic uses*: commonly used in the management of chronic obstructive lung disease (COPD) and may be combined with β-agonists in severe asthma to treat acute bronchospasms. *Adverse effects*: limited to dry mouth or cough. (Ipratropium is described in detail in Chapter 6.)

Scopolamine

This drug is similar to atropine but is more readily absorbed by the CNS. This fact makes it useful as an antimotion sickness drug. *Therapeutic uses*: mainly as a preventive for motion sickness (available as a transdermal patch). *Adverse effects*: same as with

atropine, including drowsiness and amnesia due to its absorption into the CNS.

Aclidinium (Tudorza Pressair), Glycopyrrolate (Seebri Neohaler), Tiotropium (Spiriva®), and Umeclidinium (Incruse Ellipta)

These drugs are long-acting anticholinergic bronchodilators administered by inhalation only. These agents block the muscarinic receptors in the bronchial smooth muscle, causing bronchodilation. *Therapeutic uses*: commonly used in the management of COPD, and some are indicated in the chronic treatment of asthma as well. *Adverse effects*: dry mouth, pharyngitis, dyspepsia, or cough. (These agents are described in detail in Chapter 6.)

Tropicamide (Mydriacyl®)

This agent is instilled into the eye to cause mydriasis. *Therapeutic uses*: commonly used as a dilator before a routine eye examination due to short duration of action compared with atropine. *Adverse effects*: blurred vision, drowsiness, and stinging of the eyes.

Review Questions

1. Compare the difference in function among the somatic, sympathetic, and parasympathetic nervous systems.
   Somatic nervous system:
   Sympathetic nervous system:
   Parasympathetic nervous system:
2. Define the term neurotransmitter.
3. Indicate the neurotransmitter released at the neuroeffector site in the sympathetic and parasympathetic divisions of the ANS.
   Sympathetic division:
   Parasympathetic division:
4. List the overall effects of the sympathetic nervous system on the following:
   a. Arteries:
   b. Heart:
   c. GI tract:
   d. Pupil of the eye:
   e. Respiratory tract:
   f. Urinary bladder:
5. List the names of the receptors in the sympathetic division of the ANS and the general locations where these receptors can be found.

Name	Location
a.	a.
b.	b.
c.	c.

6. Describe the overall effects of α-adrenergic drugs. List three examples of these drugs.

7. Describe the overall effects of β-adrenergic drugs. List three examples of these drugs.
8. Describe the overall effects of α-blocking drugs. Give one example of this type of drug.
9. Describe the overall effects of β-blocking drugs. Give three examples of these drugs.
10. List the names of the receptors in the parasympathetic division of the ANS and the general locations where these receptors can be found.

Name	Location
a.	a.
b.	b.
c.	c.

11. Describe the overall effects of the choline esters and explain why ACh is not used in clinical situations. Give two examples of these drugs.
12. Describe the overall effects of the anticholinesterase drugs. Give one example of these drugs.
13. Describe the overall effects of the anticholinergic drugs. Give three examples of these drugs.

Posttest

For each of the following questions, try to select the *one* best answer from the choices given.

1. The overall function of the ANS includes all of the following, except:
   a. controls bladder.
   b. controls heart rate.
   c. controls skeletal muscle.
   d. controls digestion.
2. Stimulation of the sympathetic nervous system causes:
   a. dilation of the pupils, increased rate and contractility of the heart, and decreased GI activity.
   b. constriction of the pupils, increased heart rate and contractility, and increased GI activity.
   c. vasoconstriction of peripheral arteries, decreased heart rate and contractility, and pupillary constriction.
   d. no effect on the pupils or GI activity, but an increase in heart rate and contractility.
3. Neostigmine and pyridostigmine may be used clinically to:
   a. treat severe hypovolemic shock.
   b. diagnose and treat myasthenia gravis.
   c. stimulate bronchospasm for diagnostic pulmonary function testing.
   d. treat hypertension and migraine headaches.
4. Which of the following statements is true about neurotransmitters? (Select all that apply.)
   a. Neurotransmitters are chemical substances.
   b. Neurotransmitters are released into a synapse or neuroeffector junction when an impulse is transmitted along the nerve.
   c. Neurotransmitters are produced in the postsynaptic terminal.
   d. Neurotransmitters interact with receptors in the postsynaptic or postjunctional site.

5. The neurotransmitter at the neuroeffector site of the parasympathetic nervous system is ACh. True or False?
6. The parasympathetic nervous system causes all of the following, except:
   a. increase in heart rate.
   b. increased function in the GI tract.
   c. contraction of the urinary bladder.
   d. pupillary constriction.
7. Stimulation of the β_2-receptors by epinephrine causes:
   a. constriction of the uterus.
   b. bronchoconstriction.
   c. bronchodilation.
   d. vasoconstriction of the blood vessels of the skeletal muscle.
8. Which of the following statements about propranolol are true?
   a. It affects both β_1- and β_2-receptors.
   b. It is safe to use in patients with asthma.
   c. It is used in treating low blood pressure.
   d. It is used in treating anaphylactic shock.
9. Which one of the following are functions of the parasympathetic nervous system? (Select all that apply.)
   a. Increase in cardiovascular activity
   b. Increase in gastric motility
   c. Increase in salivary and respiratory secretions
   d. Decrease in activity of genitourinary system
10. Which of the following agents have activity similar to ACh at the skeletal muscle neuroeffector site?
   a. Ipratropium
   b. Pyridostigmine
   c. Dicyclomine
   d. Pilocarpine

References/Recommended Readings

Broyles BE, Reiss BS, Evans ME. *Pharmacologic Aspects of Nursing Care.* 8th ed. Clifton Park, NY: Delmar, Cengage Learning; 2013.

Brunton LL, Hilal-Dandon R, Knollmann BC, eds. *Goodman and Gilman's: The Pharmacological Basis of Therapeutics.* 13th ed. New York, NY: McGraw-Hill Medical Publishing; 2018.

Mosby's Drug Reference for Health Professionals. 6th ed. St. Louis, MO: Mosby Elsevier; 2018.

Hitner H, Nagle BT. *Pharmacology: An Introduction*. 6th ed. Mission Hills, CA: Glencoe Publishing Co; 2011

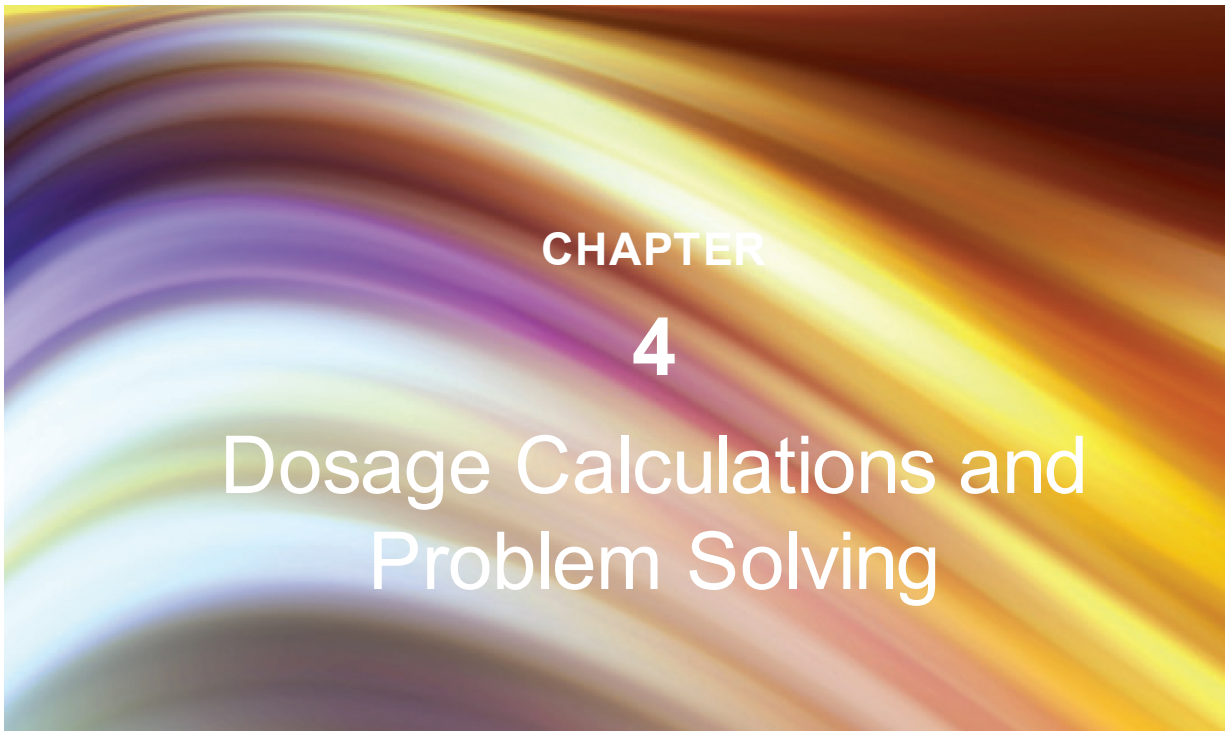
Krinsky DL, Berardi RR, Ferreri SP, et al. *Handbook of Nonprescription Drugs.* 17th ed. Washington, DC: American Pharmaceutical Association; 2012.

McCance KL, Huether SE, Brashers VL. *Pathophysiology: The Biologic Basis for Disease in Adults and Children*. 6th ed. St. Louis, MO: Mosby Elsevier; 2010.

Physicians' Desk Reference for Nonprescription Drugs. 34th ed. Montvale, NJ: PDR Network; 2013.

Rizzo DC. *Fundamentals of Anatomy and Physiology*. 3rd ed. Clifton Park, NY: Delmar Cengage Learning; 2010.

Spratto GR, Woods AL. *Nurses's Drug Handbook*. Clifton Park, NY: Delmar Cengage Learning; 2013.



© Winui/Shutterstock.

OUTLINE

Introduction
Dosage Units
  Systems of Measure
  Dosage Frequencies
  The Joint Commission–Approved Abbreviations
Problem Solving
  Drug Concentration Calculations
Continuous Aerosol Dosages
Other Drug Dosage Calculations
  Solution Strengths
Dosage Guidelines for Infants and Children

OBJECTIVES

After completion of this chapter and its learning activities, you will be able to:

1. Calculate an appropriate dosage of medication in both weight (milligram) and volume (milliliter) and convert medication dosages from one system to the other.
2. Determine dosages of reconstituted medications.

3. Convert metric dosage measures into household units.
4. Determine the appropriate volumes of drugs and diluents for administering continuous bronchodilator aerosol therapy using proportions.
5. Determine drug doses using percentage strength solutions.

KEY TERMS

Concentration
Percent Solution
Ratio Strength
Reconstituted
Solute
Solvent
Strength

Introduction

Respiratory care practitioners (RCPs) must be able to convert medications from volume (milliliter of a certain percent solution) into weight (milligram of the drug), and vice versa. Mastering the concepts of reconstituting and diluting medications for aerosol, instillation, or infusion is necessary in many clinical situations. In the homecare or outpatient settings, it may be necessary to assist patients by converting metric measures to household units (e.g., milliliter to teaspoons, cups to liters). Determining the initial dosage for an infant or child can be accomplished through the use of several generally accepted rules. These concepts, rules, and problem-solving skills are described in this chapter.

Dosage Units

Respiratory therapists commonly receive orders from physicians to administer medications by aerosol, instillation, or infiltration. Medications may be ordered in milliliters, milligrams, or drops. Some medications are administered in their full **concentration** (undiluted), whereas other medications are administered by diluting with a **solvent** (e.g., water, normal saline). Sometimes patients who will be taking medications at home must be able to convert metric units to common household terms, such as teaspoons or cups. **Tables 4-1** and **4-2** provide a quick reference to the most common units needed by the RCP.

TABLE 4-1
Metric Dosage Units and Abbreviations

Symbol or Abbreviation	Unit	Equivalent Measure or Meaning
µ	Micro-	1/1,000,000
µg or mcg	Microgram	1/1,000,000 g (weight)
m	Milli-	1/1000
mg	Milligram	1/1000 g (weight)
g	Gram	1000 mg (weight)
kg	Kilogram	1000 g (weight)
kg	Kilogram	2.2 lb (pounds)
n	Nano-	1/1,000,000
ng	Nanogram	1/1,000,000,000 g (weight)

L or l	Liter	Volume
mL	Milliliter	mL or cc (volume)
cc	Cubic centimeter	ml or mL
m	Meter	Length
cm	Centimeter	1/100 m (length)
cm	Centimeter	2.54 in
mm	Millimeter	1/1000 m (length)

TABLE 4-2
Household and Metric Conversions

Unit	Metric Equivalent	Household Equivalent
gtt		Drop
16 gtts	1 mL or 1 cc	¼ teaspoon
64 gtts	5 mL	1 teaspoon (tsp)
3 teaspoons	15 mL	1 tablespoon (tbsp)
0.24 L	240 mL	1 cup
0.48 L	480 mL	1 pint

Systems of Measure

The two most common units of measure that are used for medication dosages are the metric system (Table 4-1) and the household units of measure (Table 4-2). When using the metric system, the base unit of length is meter, volume is liter, and weight is gram. Measures of weight and volume are used in drug dosing. Most drugs are dosed in

milligrams (mg), which is 1/1000 of a gram, and volumes of drugs are measured in milliliters (mL), which is 1/1000 of a liter. The first step in calculating drug dosages is to understand how to convert from different units of weight and volume using the metric system.

Example 4-1

A drug is dosed in grams. How many grams are in one 250-mg tablet?

The easiest method of calculating this answer is to set up a proportion.

Remember: 1 g = 1000 mg

250 mg = _____ g

1. Units $\frac{g}{mg} = \frac{1}{1000} = \frac{X}{250}$ Cross multiply
2. 250 mg(1 g) = 1000 mg (X g)
3. $\frac{250 \text{ mg}(1 \text{ g})}{1000 \text{ mg}} = X \text{ g}$
4. X= 0.25 g

Example 4-2

A child weighs 35 pounds (lb). Most drugs for children are dosed by weight in mg/kg. Convert pounds to kilogram to determine a drug dose for this child.

Remember: 1 kg = 2.2 lb

35 lb = _____ kg

1. Units $\frac{kg}{lb} = \frac{1}{2.2} = \frac{X}{35}$ Cross multiply
2. 35 lb (1 kg) = 2.2 lb (X kg)
3. $\frac{(35 \text{ lb})(1 \text{ kg})}{22 \text{ lb}} = X \text{ kg}$
4. X = 15.9 kg

Dosage Frequencies

To calculate the total dosage of a specific medication administered to a patient each day, it is necessary to determine the dosage per

treatment and the number of treatments per day. **Table 4-3** provides a reference to the most commonly used frequency abbreviations.

TABLE 4-3
Abbreviations in Prescriptions

Abbreviation	Meaning
ā	Before
p	After
c	With
s	Without
PRN	As needed (whenever necessary)
Bid or bid	Two times a day
Tid or tid	Three times a day
Qid or qid	Four times a day
q	Every
Qod or qod	Every other day
Qd or qd	Every day
qh	Every hour (hourly)
Q2h or q2h	Every 2 h
Q3h or q3h	Every 3 h
Q4h or q4h	Every 4 h
Q4 PRN	Every 4 h, if needed
Q4 and PRN	Every 4 h and as needed

Q4h WA	Every 4 h while awake
Qs or qs	Quantity sufficient (as much as required)

The Joint Commission–Approved Abbreviations

Most respiratory therapists will work in an accredited institution; this means that the institution (hospital, skilled nursing facility, clinic, etc.) meets certain standards for the provision of safe and effective patient care. Hospitals in the United States are accredited through the Joint Commission. Charting and other documentation errors may lead to errors in patient care, and using abbreviations or symbols that may be misinterpreted could also result in errors. To avoid or reduce medical errors associated with written communications, the Joint Commission has published a list of abbreviations, acronyms, and symbols that are approved. The Joint Commission also periodically updates this list with tables that provide the approved abbreviations and those abbreviations that should not be used. **Table 4-4** provides a reference to some of the approved and "do not use" abbreviations currently published by the Joint Commission.

TABLE 4-4
The Joint Commission–Approved Abbreviations and Do Not Use Abbreviations

Abbreviation or Symbol	Meaning	Must Use	Do Not Use
U	Unit (in international drug units)	"unit"	U
IU	International unit	International unit	IU
QD or QOD	Every day or every other day	"daily" or "every other day"	QD or QOD
MS or MSO_4/MgO_4	Can mean morphine or magnesium sulfate	Write morphine sulfate or magnesium sulfate	MS
1.0 mg	1 milligram	1 mg (do not place zero after decimal point; "trailing zero")	1.0 mg
.5 mg	One-half milligram	0.5 mg (always place a zero before the decimal point for dosages less than 1; "missing of the leading zero")	.5 mg

Modified from the “Abbreviations Chart” published by Joint Commission on Accreditation of Healthcare Organizations, updated September 2018.
© Joint Commission Resources. Oakbrook Terrace, IL: Joint Commission on Accreditation of Healthcare Organizations, 2018. Reprinted with permission.

The abbreviations listed in Table 4-4 may be included in charting standards at individual institutions. The “do not use” abbreviations or symbols are recommended because if physician’s orders or patient charting is done by hand (i.e., handwritten), some of these symbols or abbreviations may be mistaken or misread.

Problem Solving

The most common drug administration problem-solving skills needed by the RCP are those that require the conversion of a volume (solution) to a weight, or vice versa. In other words, the practitioner must be able to determine how many milligrams (mg) of a drug are contained in a specific solution with a known concentration or dosage **strength** (mg/mL), such as "how many milligrams of racemic epinephrine are contained in 0.5 mL of Vaponefrin® (epinephrine) 2.25%?" Another application of this concept is calculating how many milliliters (mL) of a drug will be needed to fill a physician's order that is stated in milligrams, such as "how much albuterol (2.5 mg/3 mL) should be given if the physician has ordered 1.5 mg of albuterol per treatment?"

To solve these problems, the practitioner must know two things: (1) the concentration or dosage strength of the drug solution being used and (2) how this concentration is calculated.

Drug Concentration Calculations

Drug concentrations usually describe the strength of the drug preparation. The strength of a drug can be expressed as ratios, fractions, decimals, or percentages. These preparations can be expressed as weight-to-weight (w/w), weight-to-volume (w/v), volume-to-weight (v/w), or volume-to-volume (v/v). In the case of w/w and v/v, the amounts of drug must be expressed in the same units.

Calculating Doses from Prepared Drugs/Solutions

The concentration is the ratio of the amount of drug or ingredient in the product, and many units can be used—mg/mL, g/mL, etc. Calculating drug doses may include determining how much liquid or tablets/capsules should be given to a patient or how much volume of a solution should be given of a specific concentration solution. Certain

drugs are provided in desiccated or powder form and must be reconstituted to a liquid for aerosolization or instillation. **Reconstituted** means using a powder or concentrated form of a drug and adding a solvent to reconstitute (or return) the drug to a liquid form of a specific concentration. Examples of such reconstituted drugs include antibiotics and synthetic surfactants.

The simplest way to calculate doses of these problems is to convert into consistent units and then set up a proportion.

$$\frac{\text{Original dose}}{\text{Per amount}} = \frac{\text{Desired dose}}{\text{Per amount}}$$

Use *X* as the amount or unit you will be solving for.

Problem 4-1

How many milliliters of Coly-Mycin® (colistin) must be given if a treatment is ordered with 100 mg of colistin?
Hint: Coly-Mycin is provided in 150 mg vials, which are reconstituted with 2 mL sterile water.
Solving the problem: Mix the 150 mg powder with 2 mL water.

1. Set up as a proportion:

$$\frac{\text{Original dose}}{\text{Per amount}} = \frac{\text{Desired dose}}{\text{Per amount}}$$

$$\frac{150\text{ mg}}{2\text{ mL}} = \frac{100\text{ mg}}{X\text{ mL}}$$

2. Solve for *X* and cross multiply

$$150\text{ mg }(X\text{ mL}) = 100\text{ mg }(2\text{ mL})$$

3. $\frac{100\text{ mg }(2\text{ mL})}{150\text{ mg}} = X\text{ mL}$

4. $\frac{200}{150} = 1.33\text{ mL}$

Answer: Mix 150 mg vial with 2 mL sterile water and administer 1.33 mL of this solution.

Problem 4-2

You are a homecare therapist and your patient has a prescription for azithromycin because he has developed otitis media. The dosage is specified at 10 mg/kg on the first day and then 5 mg/kg for another 4 days (five total days of antibiotic). The patient weighs 66 lb. After you have reconstituted the antibiotic into a suspension (like a syrup), the suspension will contain 100 mg/5 mL. You need to determine how much of the suspension should be taken on the first day and on each following day (days 2–5). You should also be able to tell the patient what his dosages are in household units (such as teaspoons).

Step 1: How much does your patient weigh in kg (kilograms)?

a. $\frac{1\text{ kg}}{2.2\text{ lb}} = \frac{X\text{ kg}}{66\text{ lb}}$

b. 1 kg (66 lb) = 2.2 lb (*X* kg)

c. $\frac{66}{2.2} = X\text{ kg}$

d. *X* = 30 kg

Your patient weighs 30 kg. Now you need to determine how much of the suspension must be given in each dose at the rate of 10 mg/kg (first day) and then 5 mg/kg (from day 2 to day 5).

Step 2: What is the dosage (mg) for the first day?

$$\frac{10\text{ mg}}{\text{kg}} \times 30\text{ kg} = 300\text{ mg}$$

Step 3: What is the dosage (mg) for days 2–5?

$$\frac{5\text{ mg}}{\text{kg}} \times 30\text{ kg} = 150\text{ mg}$$

Step 4: What is the volume (mL) of suspension for each dosage?

Hint: The suspension strength is 100 mg/5 mL

300 mg dose for day 1:

$$\frac{100\text{ mg}}{5\text{ mL}} = \frac{300\text{ mg}}{X\text{ mL}}$$

$$100\text{ mg } (X\text{ mL}) = 300\text{ mg } (5\text{ mL})$$

$$\frac{1500}{100} = X\text{ mL}$$

$$X = 15\text{ mL}$$

150 mg dose for days 2–5:

$$\frac{100\text{ mg}}{5\text{ mL}} = \frac{150\text{ mg}}{X\text{ mL}}$$

$$100\text{ mg}\ (X\text{ mL}) = 150\text{ mg}\ (5\text{ mL})$$

$$\frac{750}{100} = X\text{ mL}$$

$$X = 7.5\text{ mL}$$

Step 5: What is the patient's dosage in household units (teaspoons)?
Hint: 5 mL = 1 tsp (teaspoon) × 15 mL = 1 tbsp (tablespoon)
Day 1: 300 mg = 15 mL

$$\frac{5\text{ mL}}{1\text{ tsp}} = \frac{15\text{ mL}}{X\text{ tsp}}$$

$$X = 3\text{ tsp}$$

Days 2–5: 150 mg = 7.5 mL

$$\frac{5\text{ mL}}{1\text{ tsp}} = \frac{7.5\text{ mL}}{X\text{ tsp}}$$

$$X = 1.5\text{ tsp}$$

Answer: The patient needs 3 tsp on the first day, and 1.5 tsp on days 2–5.

Percentage Strengths

The **percent solution** is the amount of the active ingredient in 100 parts of the product. This is found on the label or in the product information. Drugs can be expressed in percent weight (w/w), weight-to-volume (w/v), or volume-to-volume (v/v). A 1% drug preparation means that 1 g or mL of the **solute** (active drug) is dissolved in 100 parts of the mixture.

w/w: grams per 100 g of product
w/v: grams per 100 mL of product
v/v: milliliters per 100 mL of product

This information can be used to set up a simple mathematical relationship or algebraic formula. Because most of the drugs administered by RCPs are given in small dosages (milligrams rather than grams), the first conversion should be from grams to milligrams.

1 g = 1000 mg

Problem 4-3

How many milligrams of salt are contained in 3 mL of 0.9% saline (normal saline)? To solve this problem, set up a series of easily solved steps:
Step 1: What is the percent concentration of normal saline?
Answer: 0.9% saline.
Because 0.9% saline is salt dissolved in a solution, this is a w/v percentage strength. This means that 0.9% constitutes 0.9 g of salt (NaCl) per 100 mL of solution. This can be stated mathematically as: $\frac{0.9\text{ g}}{100\text{ mL}}$

Step 2: Convert grams to milligrams because milligram is the unit that you want to answer in.

$$\frac{0.9\text{ g}}{X\text{ mg}} = \frac{1\text{ g}}{1000\text{ mg}}$$
$$X = 900\text{ mg}$$

Step 3: Use concentration of 900 mg/100 mL to determine how much salt is in 3 mL.

Set up as a proportion:

$$\frac{\text{Original dose}}{\text{Per amount}} = \frac{\text{Desired dose}}{\text{Per amount}}$$
$$\frac{900\text{ mg}}{100\text{ mL}} = \frac{X\text{ mg}}{3\text{ mL}}$$
$$900\text{ mg (3 mL)} = 100\text{ mL } (X\text{ mg})$$
$$\frac{2700}{100} = X\text{ mg}$$
$$X = 27\text{ mg}$$

Thus, 3 mL of normal saline contains 27 mg of NaCl.

Problem 4-4

How many milliliters of a 5% solution must be given if the physician has ordered 10 mg of the drug per treatment?
Step 1: What is the concentration of the drug?
Answer: A 5% solution, which is 5 g of the drug per 100 mL of solution.
Step 2: How many milligrams of the drug are contained in 1 mL of the solution?
This can be stated mathematically as:

$$\frac{5\text{ g}}{100\text{ mL}} = \frac{5000\text{ mg}}{100\text{ mL}} = \frac{50\text{ mg}}{\text{mL}}$$

Step 3: If 1 mL contains 50 mg of drug, how much is needed to provide 10 mg? Set up a proportion and solve for milliliters.

$$\frac{50\text{ mg}}{\text{mL}} = \frac{10\text{ mg}}{X\text{ mL}}$$

$$X = 0.2\text{ mL}$$

Thus, 0.20 mL of solution contains 10 mg of drug.

Problem 4-5

How many vials of 0.1% terbutaline must be used for a 1.5-mg dose? Each vial contains 1 mL of terbutaline.
Hint: Calculate how many milligrams of terbutaline are present in each milliliter of solution.
Step 1:

$$\frac{0.1\text{ g}}{100\text{ mL}} \times \frac{1000\text{ mg}}{1\text{ g}} = 100\text{ mg} / 100\text{ mL}$$

Step 2:

$$\frac{100\text{ mg}}{100\text{ mL}} = \frac{1\text{ mg}}{\text{mL}}$$

Step 3: Use a proportion.

$$\frac{1\text{ mg}}{1\text{ mL}} = \frac{1.5\text{ mg}}{X\text{ mL}}$$

$$X = 1.5\text{ mL}$$

Step 4: Calculate how many vials are needed.

$$\frac{1\text{ vial}}{1\text{ mL}} = \frac{X\text{ vials}}{1.5\text{ mL}}$$

$$X = 1.5\text{ vials}$$

Answer: 1.5 vials are needed to make a 1.5-mg dose of terbutaline.

Ratio Strengths

The strength of drug products may also be represented as **ratio strength**. Ratio strength can be thought of as a ratio of 1 to another quantity that is larger than 1 and may be easier to understand if changed into a percentage. For example, ratio strength of 1:1000 is one part into 1000 parts or 1/1000, which is 0.001 or 0.1%. For every 100 parts, there is 0.1 part of that drug in that ratio strength.

Problem 4-6

How many milligrams of isoproterenol are contained in 0.25 mL of Isuprel® (isoproterenol) 1:100?

Step 1: What is the concentration of Isuprel 1:100?

Answer: 1:100 means 1/100, which is equal to 0.01, and if you multiply by 100, you get a percent: 0.01 × 100 = 1%.

Step 2: How many milligrams of isoproterenol are contained in 1 mL of Isuprel 1:100?

Answer: 1% means that there is 1 g of isoproterenol per 100 mL of solution. This can be stated mathematically as:

$$\frac{1\text{ g}}{100\text{ mL}} = \frac{1000\text{ mg}}{100\text{ mL}} = 10\text{ mg / mL}$$

Step 3: If 1 mL contains 10 mg of isoproterenol, how much is contained in 0.25 mL?

$$\frac{1\text{ mL}}{10\text{ mg}} = \frac{0.25\text{ mL}}{X\text{ mg}}$$

$$10\text{ mg } (0.25\text{ mL}) = 1\text{ mL } (X\text{ mg})$$

$$X = \frac{2.5}{1}$$

$$X = 2.5\text{ mg}$$

Thus, 0.25 mL of Isuprel 1:100 contains 2.5 mg of isoproterenol.

Continuous Aerosol Dosages

Continuous aerosolization of bronchodilators has been used with some success in the treatment of status asthmaticus and other conditions of refractory bronchospasm. It is necessary to determine how much medication is to be given on a per-minute or per-hour basis in these situations.

Problem 4-7

What is the dosage per hour and how much bronchodilator is delivered if 300 mL of a 2% solution is nebulized over a 12-hour period?
Hint: Calculate how many milligrams of the bronchodilator are present in each milliliter of solution.

$$\frac{2\text{ g}}{100\text{ mL}} \times \frac{1000\text{ mg}}{1\text{ g}} = \frac{2000\text{ mg}}{100\text{ mL}} = \frac{20\text{ mg}}{\text{mL}}$$

If 300 mL is administered, then how many milligrams would be administered over 12 hours?

$\frac{20\text{ mg}}{1\text{ mL}} = \frac{X\text{ mg}}{300\text{ mL}}$ Cross multiply and solve for X

X = 6000 mg in 12 hours

If total dosage over 12 hours is 6000 mg, then

$$\frac{6000\text{ mg}}{12\text{ h}} = \frac{X\text{ mg}}{1\text{ h}}$$

X = 500 mg will be nebulized per hour

Other Drug Dosage Calculations

Solution Strengths

It is also necessary to convert drug dosages from one solution strength to another. An example of this type of problem is determining the appropriate amount of medication to be given if a physician orders an amount of a given solution, but the RCP has a different solution strength.

Problem 4-8

The physician orders 3 mL of 10% *N*-acetylcysteine (Mucomyst®), but the only available multiple-dose vials of Mucomyst are 20% concentration. How many milliliters of the 20% solution will be needed?

One approach to solving this problem would be to determine what weight (milligrams) is contained in 3 mL of the 10% solution strength and then determine how many milliliters of the 20% solution will be needed to provide the requested dose.

Step 1: 10% solution $= \frac{10\text{ g}}{100\text{ mL}} \times \frac{1000\text{ mg}}{1\text{ g}}$

grams cancel out and you are left with

$$= \frac{10{,}000\text{ mg}}{100\text{ mL}} = \frac{100\text{ mg}}{\text{mL}}$$

Step 2: How many milligrams of *N*-acetylcysteine are in 3 mL of the 10% solution?

$$\frac{100\text{ mg}}{\text{mL}} = \frac{X\text{ mg}}{3\text{ mL}}$$ Cross multiply and solve for X

$$X = 300\text{ mg}$$

Step 3: 20% solution $= \frac{20\text{ g}}{100\text{ mL}} \times \frac{1000\text{ mg}}{1\text{ g}}$ grams cancel out and you are left with

$$= \frac{20{,}000\text{ mg}}{100\text{ mL}} = \frac{200\text{ mg}}{\text{mL}}$$

Step 4: Determine how many milliliters of the 20% solution will give you a 300-mg dose?

$$\frac{200\text{ mg}}{\text{mL}} = \frac{300\text{ mg}}{X\text{ mL}}$$

$$X = 1.5\text{ mL}$$

Answer: If the physician ordered 3 mL of 10% solution, then 300 mg should be given. About 300 mg is contained in 1.5 mL of the 20% solution. Use 1.5 mL of 20% acetylcysteine and 1.5 mL normal saline (or distilled water). A simpler method for this type of problem would be to utilize the general rule of dilution:
A 20% solution diluted 1:1 will yield a 10% solution.

Problem 4-9

You are treating a patient in status asthmaticus and the physician wants to try nebulizing epinephrine to avoid intubating the patient. The doctor wants you to nebulize 0.3 mL of a 1% solution, but the pharmacy only stocks vials of epinephrine in a 1:1000 dilution. How much of the 1:1000 solution must be used to give the equivalent amount of epinephrine?
Step 1: How many milligrams of epinephrine are contained in 1 mL of the 1% solution?

$$1\% = \frac{1\text{ g}}{100\text{ mL}} \times \frac{1000\text{ mg}}{1\text{ g}} = \frac{1000\text{ mg}}{100\text{ mL}} = \frac{10\text{ mg}}{\text{mL}}$$

Step 2: How many milligrams of epinephrine did the doctor order (how many milligrams in 0.3 mL of 1% solution)?

$$\frac{10\text{ mg}}{\text{mL}} = \frac{X\text{ mg}}{0.3\text{ mL}}$$

$$X = 3\text{ mg}$$

Step 3: How many milligrams of epinephrine are contained in 1 mL of a 1:1000 solution? Convert ratio strength 1:1000 into a percentage.

$$1{:}1000 = \frac{1}{1000} = 0.001 \times 100 = 0.1\%$$

$$\frac{0.1\text{ g}}{100\text{ mL}} \times \frac{1000\text{ mg}}{1\text{ g}} = \frac{100\text{ mg}}{100\text{ mL}} = \frac{1\text{ mg}}{\text{mL}}$$

Step 4: Calculate how many milliliters are needed of the 1 mg/mL solution to administer a 3-mg dose

$$\frac{1\text{ mg}}{\text{mL}} = \frac{3\text{ mg}}{X\text{ mL}}$$

$$X = 0.3\text{ mL}$$

The doctor wants 3 mg of epinephrine (3 mg is contained in 0.3 mL of the 1% solution), so you need to give 3 mL of the 1:1000 solution because it contains 1 mg/mL.

Dosage Guidelines for Infants and Children

There are few authoritative definitions of infant or child. The American Heart Association defines an infant as newborn to 1 year of age and a child as 1–8 years of age. These are arbitrary definitions, but are useful for the purpose of making initial treatment decisions. Because only 25% of all drugs approved by the Food and Drug Administration (FDA) are labeled “safe and effective for children,” considerable care must be taken when determining the appropriate dosage of a specific drug for use by the pediatric patient. In clinical practice, treatment decisions are on the basis of the same criteria as for adults: What is the best drug for this patient under these circumstances? The drug of choice in all treatment decisions is the drug that produces the maximum benefit with the fewest adverse reactions and (where possible) at the least expense.

Dosage of drugs given by instillation or aerosol generally is determined by the patient’s response to an initial conservative dosage. In the infant or child, as a general rule, indications, contraindications, and hazards of specific drugs are comparable to those in the adult. Dosage is reduced in the pediatric patient, and careful monitoring during the initial administration provides a useful guide for future treatments. Although drug dosages are determined on the basis of body weight, it is also affected by metabolic rate. Infants and children are given lower doses because of their smaller body weight, but side effects may be enhanced because of changes in the way they clear the drug from their body. Most drugs are dosed on the basis of body weight in milligrams per kilogram per day (mg/kg/day) or on the basis of body surface area (mg/m^2) in infants, children, and adolescents. A general rule is that the pediatric dose should never exceed the dose indicated for an adult.

Once an appropriate dosage range has been determined, treatment should be given under close supervision and monitoring. Dosage adjustments may be made after the initial treatment, on the

basis of the child's therapeutic response and the severity of side effects.

Dosage frequency in infants and children is also adjusted according to therapeutic response and the presence and severity of side effects. In many cases, a drug that is given every 4 hours for an adult patient can also be given every 4 hours for a child. Some drugs may be given more frequently than for adults. Neonates, infants, and children may clear some drugs quicker from the body, and therefore may require it more frequently.

The American Academy of Pediatrics is working actively with the FDA for the provision of better drug dosage guidelines for infants and children. In 2002 and 2003, Congress passed two laws that have increased the number of studies conducted in pediatric patients and requires testing of new drugs in pediatric patients. In the future, you will most likely see more definitive dosing guidelines for medications in pediatric patients.

Case Study 4-1

Respiratory syncytial virus

Jerry M, a 5-month-old male, weighing 7 kg, was admitted with a chief complaint of respiratory distress. The infant was in good health until 3 days ago, when he developed fever, cough, and runny nose. He was treated by his doctor with PO erythromycin. The infant's cough worsened and he was taken to the hospital's Emergency Department by his parents. On admission, the baby was actively wheezing and retracting. His SaO_2 was 75% on oxygen at 5 L/min by facemask. Patient appears to be a well-developed, well-nourished, white male infant in severe respiratory distress.

Physical Examination

Vital signs: Temperature 38.8°C, heart rate 200 beats/min, and respiratory rate 80–90 breaths/min.
Cardiovascular: Tachycardia, normal rhythm.
Respiratory: Diffuse wheezes bilaterally, tachypnea, nasal flaring, and subcostal retractions.

Laboratory Values

Chest radiograph: Hyperinflation with right upper lobe infiltrates.
Arterial blood gases:

	pH	pCO_2 (torr)	pO_2 (torr)	Oxygen
Day 1	7.41	33	54	10 L/min, facemask (ER)
	7.39	30	65	60%, hood
Day 2	7.42	34	60	40%, hood

Electrolytes: Within normal limits.
Hematology: Hgb = 10.2 g/dL, WBC count = 10,700/mm^3, RBC count = 3.81 m/mm^3.

Hospital Orders

Respiratory care:

1. Continuous albuterol 0.083% at 2 mL/h
2. Oxygen hood on 60%, wean for SaO_2 greater than 90%
3. Continuous pulse oximetry and transcutaneous monitor

Other medications

Intravenous (IV) Solu-Medrol®	Acetaminophen
Cefuroxime	IV fluids

Hospital Course

Day 1: The patient was admitted to the pediatric intensive care unit in respiratory distress. He was put in an oxygen hood at 60% oxygen with continuous aerosolized albuterol therapy. A secretion sample was obtained for respiratory syncytial virus culture.

Day 2: After the arterial blood gases on FiO_2 of 0.6, the FiO_2 was decreased to 0.4 in early morning. Continuous aerosolized albuterol will be changed every 2 hours when baby improves. The patient's respiratory rate and breathing effort have decreased.

Day 3: The baby has improved. Continuous aerosol therapy is discontinued, and the baby was started on albuterol treatments 1.25 mg every 2 hours.

Questions

1. While the infant was receiving continuous aerosolized albuterol, what dose of albuterol was the infant receiving each hour?
2. When the baby's bronchodilator therapy was changed from continuous administration to every 2 hours, how many milliliters of albuterol should the infant receive during each treatment?

Review Questions

Dosage Calculation Problems

1. How many milligrams of 2.25% racemic epinephrine does a patient receive if the treatment is given with 0.25 mL Vaponefrin?
2. How many milligrams of 0.5% albuterol does a patient receive if the treatment is given with 0.3 mL?
3. How much active drug does the patient receive if a treatment is given with 0.5 mL of a 1% solution?
4. How many milliliters of isoproterenol 1:100 solution is needed to give a dose of 5 mg to a patient?
5. How many milliliters of isoproterenol 1:200 must be given if a patient in status asthmaticus has an order to receive 2.5 mg of isoproterenol diluted with 1.5 mL normal saline?
6. How many milligrams of lidocaine are contained in 10 mL of a 2% IV solution?
7. A 12-kg infant is written a prescription for amoxicillin suspension of 200 mg/5 mL. The dosage is 15 mg/kg/dose. How many milliliters should the infant receive with each dose?

Posttest

For each of the following questions, try to select the one best answer from the choices given.

1. A 1% solution has:
   a. 1 mg solute per mL solution.
   b. 10 mg solute per mL solution.
   c. 100 mg solute per mL solution.
   d. 1 g solute per mL solution.
2. Epinephrine in a 1:1000 solution strength is what concentration?
   a. 10%
   b. 1%
   c. 0.1%
   d. 0.01%
3. If a solution contains 5 mg of solute per mL of solution, the concentration is:
   a. 0.5%.
   b. 1%.
   c. 2.25%.
   d. 5%.
4. A patient must take 10 mL of albuterol syrup. How many teaspoons should he take?
   a. 2 teaspoons
   b. 1 teaspoon
   c. 2/3 teaspoon
   d. 1/2 teaspoon
5. Mucomyst (acetylcysteine) is supplied in a 20% solution. How many milligrams of acetylcysteine are contained in 4 mL of the 20% solution?
   a. 200 mg
   b. 400 mg
   c. 600 mg
   d. 800 mg

6. A 154-lb patient must take an antibiotic that is prescribed at 0.5 mg/kg for each dose. How many milligrams must be taken each time?
   a. 35 mg
   b. 50 mg
   c. 70 mg
   d. 77 mg
7. Racemic epinephrine is supplied as a 2.25% concentration solution. How many milliliters must be given to provide 11.25 mg of racemic epinephrine?
   a. 0.30 mL
   b. 0.5 mL
   c. 1.0 mL
   d. 5 mL
8. Albuterol (0.5% solution) has been ordered via continuous nebulization. The physician wants to provide 7.5 mg/h. How much albuterol will be needed for 8 hours of nebulized therapy?
   a. 8 mL
   b. 12 mL
   c. 24 mL
   d. 32 mL

References/Recommended Readings

Ansel H, Stockton S. *Pharmaceutical Calculations*. 15th ed. Philadelphia, PA: Wolters Kluwer; 2017.

Broyles BE, Reiss BS, Evans ME. *Pharmacological Aspects of Nursing Care*. Clifton Park, NY: Delmar Cengage Learning; 2013.

Clarke PE. FDA encourages pediatric information in drug labeling. https://www.fda.gov/Drugs/ResourcesForYou/SpecialFeatures/ucm254072.htm. Accessed November 2, 2017.

Hochadel MA, Schroeder S, Smith JJ. *Mosby's Drug Reference for Health Professions*. 6th ed. St. Louis, MO: Elsevier; 2018.

Paul IM, Neville K, Galinkin J, et al. Metric units and the preferred dosing of orally administered liquid medications. *Pediatrics*. 2015;135(4):784-787. doi:10.1542/peds.2015-0072.

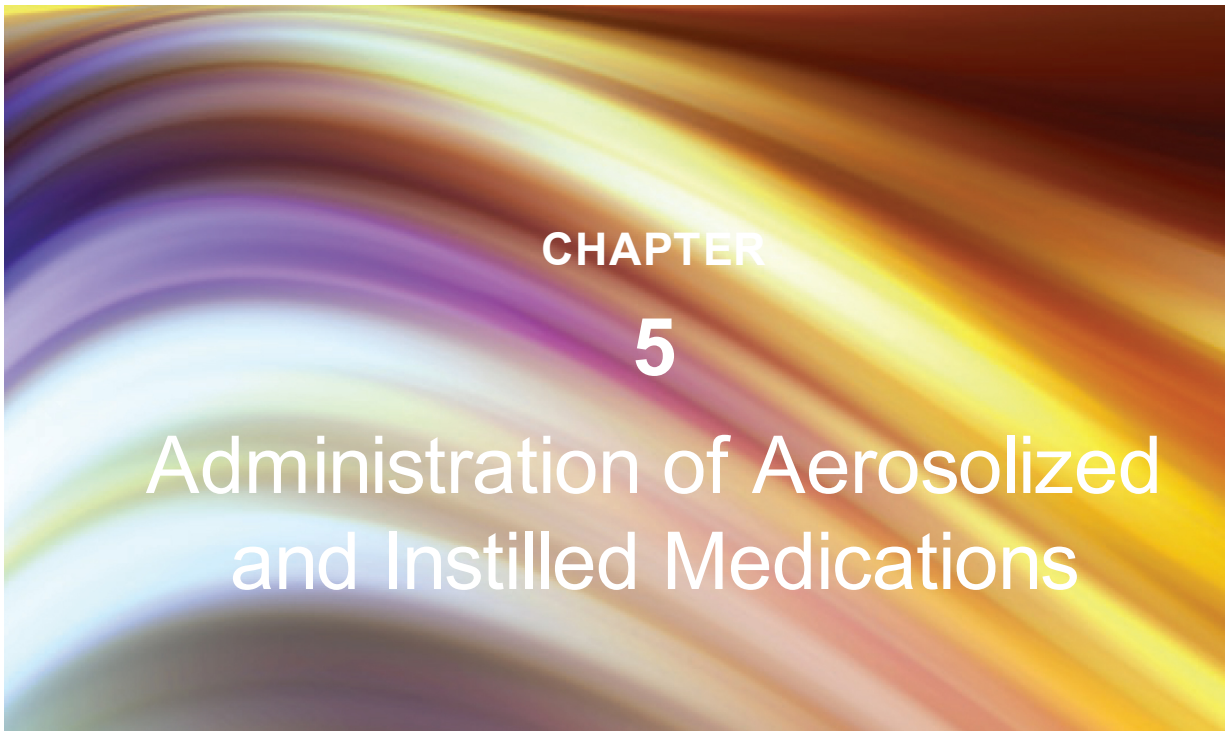
Spratto GR, Woods AL. *Nurse's Drug Handbook*. Clifton Park, NY: Delmar Cengage Learning; 2013.

Whitaker K. *Neonatal and Pediatric Respiratory Care*. 3rd ed. Clifton Park, NY: Delmar Cengage Learning; 2001.

White GC. *Respiratory Notes, Respiratory Therapist's Pocket Guide*. Philadelphia, PA: F.A. Davis Co; 2008.

Part 2
Respiratory Care Pharmacology

© Anna RubaK/ShutterStock, Inc.



© Anna RubaK/ShutterStock, Inc.

OUTLINE

Introduction
Aerosolized Medications
  Disadvantages and Limitations of Aerosol Drug Delivery
  Adverse Effects of Aerosolized Drug Delivery
Devices Used in Aerosolized Drug Delivery
  Liquid Nebulizers
  Metered-Dose Inhalers
  Spacers and Holding Chambers
  Dry Powder Aerosols
  Multiple MDI Medications
SVN and MDI During Mechanical Ventilation
  SVN During Mechanical Ventilation
  MDI During Mechanical Ventilation
  Ventilator Parameters During SVN Treatments
Instilled Medications
  Disadvantages and Limitations of Drug Delivery by Instillation

OBJECTIVES

After completion of this chapter and its learning activities, you will be able to:

1. Discuss the characteristics of an aerosol solution that leads to more effective drug delivery into the lung tissue.
2. List the advantages and disadvantages of drug administration by the aerosol route.
3. Describe the equipment used for aerosol administration of drugs by small-volume nebulizer (SVN) and the procedure that should be followed.
4. Describe patient instructions for taking an effective SVN treatment.
5. Describe the purpose of a spacer or valved holding chamber device for aerosol administration of drugs by metered-dose inhaler (MDI).
6. Describe patient instructions for taking an effective dose of medication by MDI, including the use of a spacer or holding chamber.
7. Describe the use of SVN and MDI aerosol medications during continuous mechanical ventilation, including placement of these devices in the ventilator circuit.
8. List the drugs that are currently administered by powder aerosol (dry powder inhaler), including the devices used for this administration.
9. List the indications (or clinical settings) for drug administration by instillation and the disadvantages or hazards of drug administration by instillation.
10. Compare and contrast nebulizers, MDI, and dry powder inhalers for aerosol drug delivery.
11. Recommend the appropriate method for medication delivery, when given a patient case study.

KEY TERMS

Aerosol
Chamber
Chlorofluorocarbon (CFC)
Deposition
Dry powder inhaler (DPI)
Hydrofluoroalkane (HFA)
Instillation
Mass median aerodynamic diameter (MMAD)
Metered-dose inhaler (MDI)
Nebulizer
Particle size
Priming
Small-volume nebulizer (SVN)
Spacer

Introduction

Respiratory care practitioners (RCPs) are one of the most highly trained healthcare professionals in the administration and knowledge of devices for aerosolized drug administration. RCPs deliver medications by two primary routes: aerosolization and **instillation**. Each route has its advantages, disadvantages, and limitations. State licensure for RCPs may allow drug administration by other routes or may allow infiltration for procedures such as local anesthesia for the insertion of indwelling arterial catheters. This chapter discusses the rationale for administering medications by aerosol or instillation, as well as the appropriate equipment and techniques to optimize these routes of delivery.

Aerosolized Medications

An **aerosol** is a suspension of liquid or solid particles in air or a gas that is generated by a device. Aerosols that will be discussed in this text are related to medication therapies that are intended to be inhaled into the lungs to treat respiratory disease. Aerosolized agents may be deposited into any area of the respiratory tract (e.g., nose, oropharynx, conducting airways, lung tissue). The sites of aerosol **deposition** depend upon certain factors such as **particle size**, the device used to deliver the medication, patient effort, and patient disease. A major determinant of lung deposition or the means of particles distributed in the lungs is the **mass median aerodynamic diameter (MMAD)**. MMAD is the particle size above and below which 50% of the mass of the particles is contained. The higher the MMAD, the more larger particles are contained in the aerosol. A particle size of 1–5 μm will reach the lower respiratory tract, and small particles less than 1 μm in diameter will not settle in the airways and will most likely be exhaled by the patient. Larger particles (>5 μm) may deposit in the upper airway and particle of size more than 10 μm will deposit in the nose and oropharynx. Most aerosolized devices will produce particles in a variety of sizes in the aerosol. Different devices deposit different medications into the lung tissue; therefore, doses of the same drug may not be equivalent when using a different device.

There are several advantages to the delivery of medications directly to the mucosal membrane by aerosol:

1. There is immediate onset of drug action at the desired site.
2. There are reduced side effects from systemic absorption.
3. Smaller doses of potent drugs (e.g., bronchodilators) may provide comparable therapeutic benefits.
4. Patients may be taught to self-administer medications.

Aerosol administration of many drugs provides a convenient and rapidly effective route while minimizing side effects. Drugs that are administered by aerosol include bronchodilators, antibiotics, anti-

inflammatory agents (e.g., steroids), mucolytics, wetting agents, surface-active agents (e.g., surfactants), and antiasthmatic agents (e.g., cromolyn sodium). Chapters 6–9 will provide specific information about drugs in each of these categories.

Recent studies have investigated the use of aerosol delivery of other drugs to take advantage of its noninvasive route, ease of self-administration, and broad mucosal membrane surface for drug absorption. Aerosolized insulin demonstrates excellent deposition and absorption of the insulin, with good therapeutic blood levels achieved in diabetics. Continued study will have broad implications for the future use of aerosolized medications and the role of the RCP in drug administration to treat respiratory and nonrespiratory diseases.

Disadvantages and Limitations of Aerosol Drug Delivery

The primary disadvantage of drug administration by the aerosol route is the inability to determine the absolute amount of the drug that is deposited in the lungs. When a drug is inhaled, some inevitably rains out in the oropharynx and upper airway, some is swallowed, some is deposited on the mucosal membrane, and some is exhaled. Studies have shown that as little as 10–15% of the drug may actually be deposited in the lungs, although the proportion increases when the variables mentioned below are controlled as well as with newer inhaled medications and devices. Variables that affect pulmonary drug deposition include the breathing pattern of the patient and the type of **nebulizer** used to aerosolize the drug. If the nebulizer operates continuously, rather than during inspiration only, much of the drug may be lost during exhalation and the pause between respiratory cycles. If the patient is unable to perform an optimal breathing pattern during the treatment (i.e., slow, deep inspiration with an end-inspiratory pause), very little of the drug is deposited in the smaller airways and lung periphery. If the type of nebulizer used to aerosolize the drug produces a particle size that is outside the therapeutic range, the aerosol may be unstable (i.e., rains out in the upper airway/pharynx)

or too stable (i.e., very little of the drug deposits). When a drug is swallowed rather than being deposited on the mucosal membrane, it typically is broken down and metabolized instead of providing its intended therapeutic effect.

Another disadvantage of aerosolized medication delivery is that the efficacy is also dependent on the patients' knowledge, coordination, and correct use of the aerosol device. There are many devices available, and it is important for the RCP to remain knowledgeable on the accurate use of each of these devices.

Adverse Effects of Aerosolized Drug Delivery

Although very little inhaled medication is systemically absorbed into a patient, there are some hazards of aerosolized therapy that is important to be aware of. Bronchospasm, eye irritation, and infection are risks of aerosolized therapy to a patient. If nebulized solution is either too warm or cold, the change in temperature may induce bronchospasm. If this occurs, the therapy should temporarily be discontinued. If nebulized devices are used incorrectly or if delivered via face mask, the risk of medication delivery into the eyes is increased. Eye irritation may occur, and in the case of anticholinergic agents being deposited into the eyes, it may cause blurry vision and can worsen glaucoma. Liquids that remain in nebulizers provide a medium for bacterial growth and contamination. Delivery of contaminated liquids can increase the risk of pulmonary infection to patients. Proper sterilization of nebulizer devices and handling of medications is critical to preventing infection. Occupational or bystander exposure to inhaled medications may also pose a problem with this type of therapy. There have been reports of detectable drug concentrations due to occupational exposure as well as asthma-like symptoms or occupational asthma. Development and implementation of policies and procedures can help limit occupational exposure to inhaled medications.

Devices Used in Aerosolized Drug Delivery

Medications for aerosol delivery typically are nebulized in **small-volume nebulizers (SVNs)** (maximum volume about 10 mL) or by pressurized **metered-dose inhalers (MDIs)** or **dry powder inhaler (DPI)**. If used correctly, these devices are equally effective.

Liquid Nebulizers

Liquid nebulizers create an aerosol from a liquid or suspension. There are multiple types of nebulizers. These include jet nebulizers, ultrasonic nebulizers, and mesh nebulizers that may hold large or small volumes. Different medications may be approved for use in all or specific nebulizer devices. Jet nebulizers are the cheapest and most common type of SVN that is gas-powered by high-pressure air or oxygen by a portable compressor through a jet, causing negative pressure. The solution to be nebulized enters the gas stream and breaks into aerosolized particles. Ultrasonic nebulization of medications can also be accomplished with the use of specially designed equipment such as the MicroAir Omron and Mabis Mist II. Ultrasonic nebulizers press a crystal with enough force to generate electric energy (piezoelectricity). This causes sound vibrations that break up the liquid into an aerosol. Large-volume ultrasonic nebulizers are used for bland aerosol therapy or to induce sputum. Small-volume ultrasonic nebulizers are available for bronchodilators and antibiotics but should not be used for medications in a suspension form (budesonide). Vibrating mesh nebulizers are technology developed for aerosolizing liquid medications. They use electricity to vibrate, which pushes the liquid medication through a fine mesh or plate to create an aerosol. They are battery-powered, portable, and rapidly deliver medication with low residual volume, but are expensive.

Newer technologic approaches to aerosol delivery have resulted in the development of several devices that have been shown to deliver between 40 and 60% of the medication to the lung. Circulaire II™ is a

system that incorporates a one-way valve, a distensible reservoir, and inspiratory retard in conjunction with a standard SVN. This system has better aerosol deposition than the simple SVN or MDI, and it captures most of the exhaled medication in the attached reservoir. The reservoir reduces the amount of medication released to ambient air during patient exhalation. The inspiratory retard feature apparently encourages a more effective patient breathing pattern, and the reservoir system has been shown to utilize medication more efficiently so that treatment times may be reduced from 10 to 4 minutes. This device is illustrated in **Figure 5-1**.

FIGURE 5-1 Nebulizer with reservoir bag to capture aerosol during the expiratory phase.

Courtesy of Dr. Dean Hess.

The single most important variable in providing effective aerosol administration of medications is the patient's breathing pattern. Often the practitioner is in a position to improve the outcome of a course of therapy by exercising good clinical assessment skills. Most institutions establish some appropriateness criteria for the selection of patients who can benefit from aerosol administration of drugs (in

addition to or instead of some other route). These criteria usually are on the basis of several patient factors:

1. the patient's willingness and ability to cooperate with the treatment
2. the patient's ability to generate a slow, deep breath and perform a brief "breath-hold" (3–5 seconds) at end-inspiration
3. the responsiveness of the patient's pulmonary disease to the drug being used

Standardizing such criteria improves patient selection and ultimately improves the cost-effectiveness of therapy. The American Association for Respiratory Care (AARC) has developed Clinical Practice Guidelines (CPGs) with input from practitioners and physicians. The most current CPG regarding aerosol therapy was published in 2012. The AARC also publishes an online educational pamphlet, A Guide to Aerosol Delivery Devices for the Respiratory Therapist, which provides a comprehensive and illustrated overview of all aspects of medicated aerosol therapy. This pamphlet includes an updated reference to the costs of many MDIs and DPIs, as well as color photos of these devices.

There continues to be controversy regarding whether the most appropriate vehicle for delivering aerosolized medication is the SVN or the MDI. Some studies have shown equivalent therapeutic outcomes with both devices, suggesting that the more cost-effective method (MDI) should be adopted for routine use. Other studies have demonstrated that, because SVN treatments require more time (and more respiratory cycles), drug delivery to the lung may be enhanced. It is likely that some balance between the two methods will emerge, perhaps establishing MDI as the primary method and allowing practitioner discretion when specific patients do not respond to therapy or are unable to master the coordination to take an effective treatment by MDI.

There is also significant evidence that currently used disposable SVNs may vary widely in the quality of aerosol produced. The selection of SVNs to be purchased for an institution ideally should be

on the basis of both cost-effectiveness and the quality and consistency of aerosol produced.

Technique for SVN Treatment

Taking into account all of the factors mentioned and the results of recent studies about aerosol therapy, the following general guidelines should be observed when administering SVN treatment using a jet nebulizer:

1. Assemble the equipment (e.g., tubing, cup, and mouthpiece/mask).
2. Place the medicine into the nebulizer cup, using a range of 4–5 mL of solution (e.g., 0.5 mL of medication and 3.5–4.5 mL of diluent).
3. Connect to a power source; flow rates of 6–8 L/min have been shown to produce the optimal particle size for most disposable SVNs.
4. The patient should be instructed to breathe normally with occasional deep breaths, or they can also be instructed and monitored to breathe more slowly and more deeply.
5. The patient should keep breathing until they hear sputter (signifies the treatment is complete) or no more aerosol is produced.
6. Rinse nebulizer with sterile water and allow to air-dry.

NEED TO KNOW

Light-headedness or numbness and tingling are common signs of hyperventilation. If a patient develops these symptoms during an aerosol treatment, interrupt the treatment and allow the patient to rest. Coach the patient to take slow breaths.

Metered-Dose Inhalers

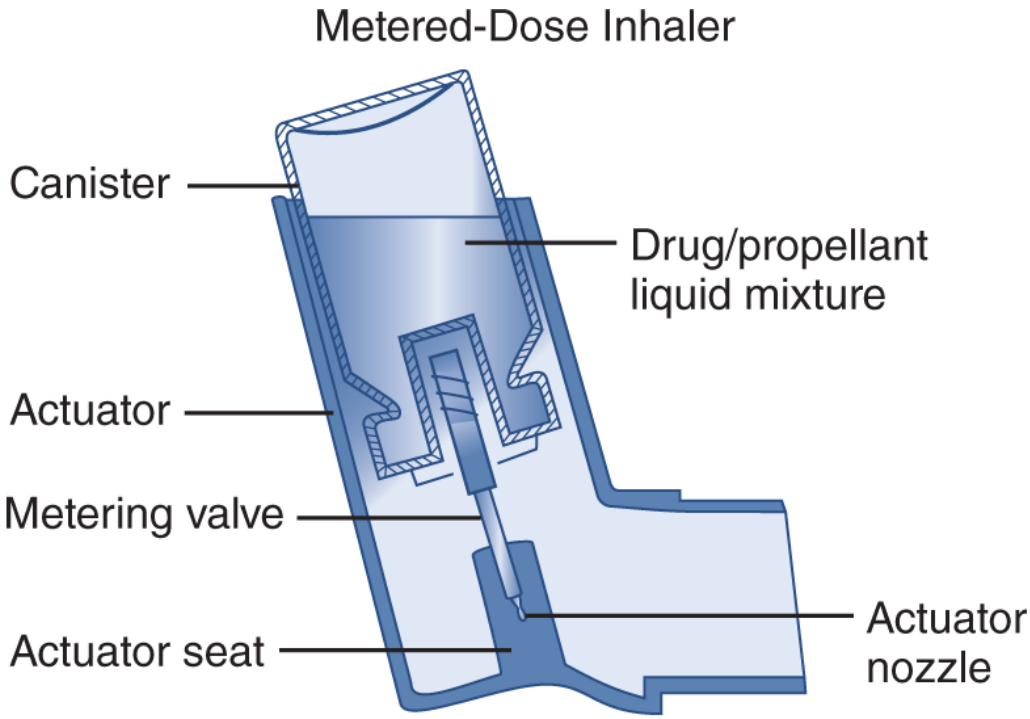
Pressurized metered-dose inhalers (pMDIs) and DPIs are frequently used by patients at home and are becoming increasingly common as

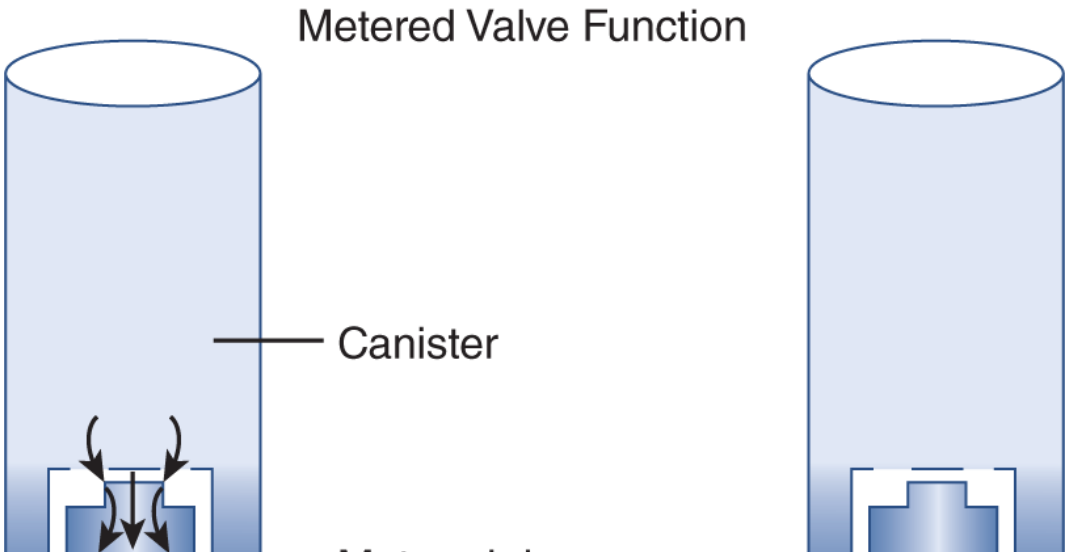
part of the inpatient care provided in many hospitals. There are numerous inhaler designs available, and instructions vary for each device. However, proper use of these devices (to achieve the desired results) requires a cooperative and coordinated patient and conscientious instruction and supervision by a practitioner. Because MDI aerosols have been available as over-the-counter drugs for decades, the critical nature of proper patient use and instruction has not been appreciated until recent studies showed the variability in medication delivery by this method. Studies have shown that up to 75% of patients using MDIs use them incorrectly, and half of the healthcare professionals do not completely understand their proper use. As pressure to reduce healthcare costs increases, the importance of appropriate and effective patient education will become even more critical.

Pressurized Metered-Dose Inhalers

A pMDI is a convenient way to deliver aerosolized medication therapy. The device contains a pressurized canister with a drug in a powder or a solution that is suspended in a propellant displayed in **Figure 5-2**. In the past, the propellant that was used was a **chlorofluorocarbon (CFC)**. The Food and Drug Administration banned the use of CFCs after the year 2008 owing to potential harm of CFCs to the ozone layer. MDIs have now converted to a **hydrofluoroalkane (HFA)** propellant to replace CFC-driven MDIs (these medications are discussed in detail in Chapters 6 and 7). Although part of the reason to convert from CFC-driven MDIs is to reduce their effect on the ozone layer, most HFA-driven MDIs have significantly higher lung deposition of the active drug compared with CFC-containing devices. Proventil® HFA™, Ventolin® HFA, Atrovent® HFA, and Flovent® HFA are pMDIs utilizing the standard dosage of the active ingredient medications but incorporating a carrier gas that contains no CFCs. HFAs deliver a warmer aerosolized mist than CFC-driven pMDIs, which may be more comfortable for the patient. CFC-driven pMDIs produce a cold mist and have been shown to contribute to bronchospasm. CFC-driven pMDIs deliver varying

dosages of medication, depending on canister contents and ambient temperature. HFA-driven pMDIs deliver a more stable medication dosage when ambient temperature is less than 40°F and as canister contents change. The jet system of these pMDIs has also been modified to soften the medication plume, thus reducing impaction of the medication in the oropharynx and increasing pulmonary deposition.





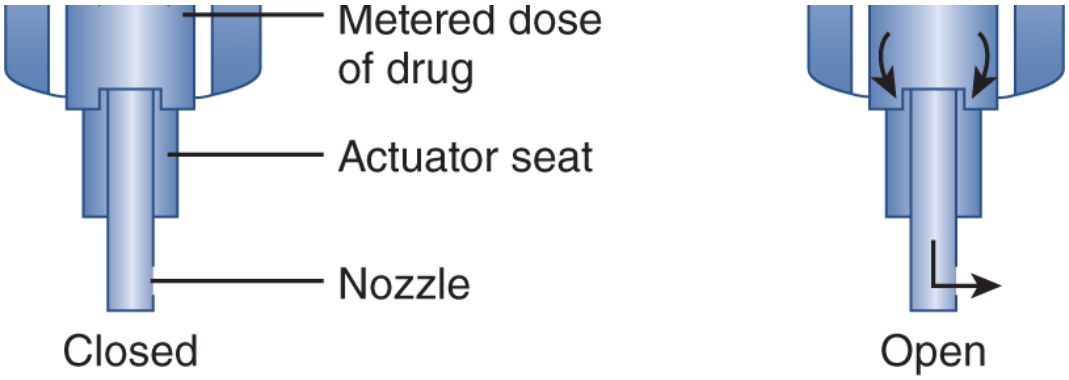


FIGURE 5-2 Schematic drawing of metered-dose inhaler.

Data from Rau JL Jr. *Respiratory Care Pharmacology.* 5th ed. St. Louis, MO: Mosby; 1998.

Description

NEED TO KNOW

HFA-driven MDIs have a softer plume with better deposition than CFC-driven MDIs. Patients who had been using CFC-driven MDIs may need to be instructed about the difference in the medication plume.

Developments in MDI technology include breath-actuated MDIs (e.g., Maxair™ Autohaler™). The Autohaler is breath-actuated, assuring proper inspiratory flow and breathing pattern when the medication is released from the canister. This device eliminates the need for hand–breath coordination during administration and triggers in response to the patient's inspiratory effort. It should be mentioned that Maxair Autohaler has been removed from the market in the United States.

The Respimat™ soft-mist inhaler (**Figure 5-3**) is a new technology that delivers a metered dose of medication as a fine mist in a spring-loaded propellant-free nebulizer that delivers a single dose of fine aerosol in the 1–2 μm range and is currently marketed to provide Combivent® and Spiriva® (bronchodilators that are further described in Chapter 6). The soft mist has a slower spray lasting about 1.5 seconds compared with traditional pMDIs. Because this is propellant-free, there is no need to shake this device before use. This

device is intended to replace the current MDI for Combivent and has demonstrated lung deposition of up to 40%.

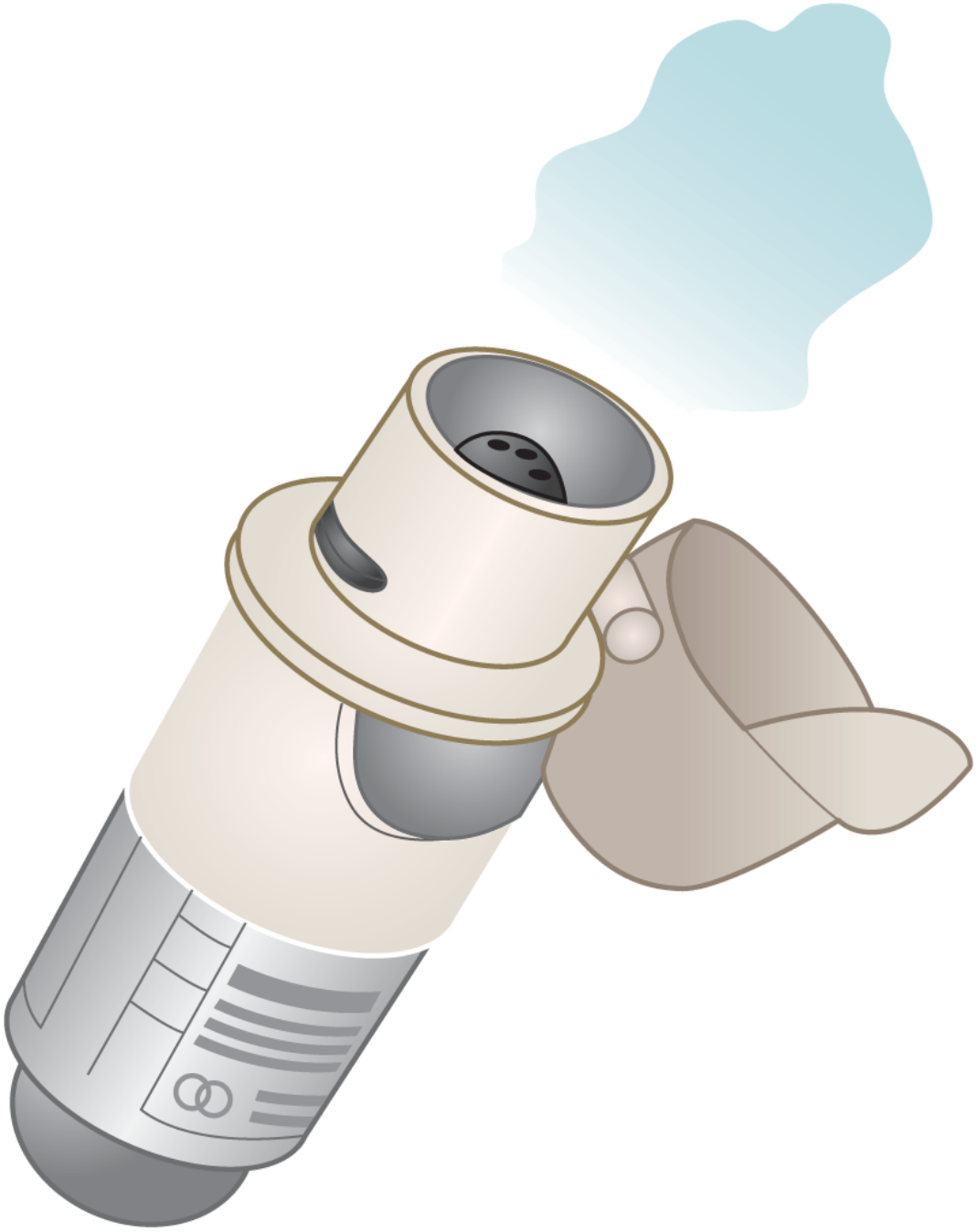


FIGURE 5-3 Respimat™ soft-mist inhaler.

Priming of MDIs

All HFA-driven pMDIs and Combivent Respimat (which is a propellant-free MDI) require **priming** before their first patient use. Priming the MDI consists of discharging one or more doses to assure the medication is ready for patient inhalation. Many require priming if they have not been used for a specified length of time. The manufacturer's information insert in the packaging is very specific with respect to the recommended priming and/or repriming required for each type of medication.

Technique for MDI Treatment

Important factors that affect the delivery of drug in MDIs include shaking of the canister with each use to disperse the drug and propellant, cleanliness of nozzle, pausing for 1 minute in between actuations of the same medication, and appropriate priming.

Ideal medication deposition by pMDI occurs when the patient uses the following procedure:

1. Remove cap and vigorously shake the canister to evenly distribute the medication. If the MDI has not been recently used, a priming dose should be discharged on the basis of the package insert instructions.
2. Hold the inhaler with the mouthpiece down.
3. Breathe out through your mouth and push as much air from your lungs as possible.
4. Put the mouthpiece in your mouth and close your lips around it.
5. Push the top of the canister all the way down at the beginning of a slow, deep inspiration. Take a slow deep breath as you push down the canister.
6. Close your mouth, inhale fully, and hold breath for up to 10 seconds or as long as possible.
7. Exhale normally, wait at least 60 seconds, and repeat procedure for second inhalation if needed.
8. Put the cap back on the mouthpiece after each use.

Although these instructions seem rather simple, many patients have difficulty in successfully following them. Studies have shown that

patients frequently squeeze the canister at the wrong time (at end-inspiration or during exhalation), they interrupt or stop inhalation when the canister is squeezed (causing most of the medication to impact in the mouth and be swallowed), they inhale too rapidly, or they fail to hold their breath when their lungs are fully inflated.

Spacers and Holding Chambers

Because of the factors affecting proper pMDI use, devices (e.g., **spacers** or **chambers**) have been developed to provide a reservoir of aerosol to improve medication delivery by pMDI. A wide variety of spacers and chambers are available, with their primary purpose being to hold the aerosol in suspension for a longer period while giving the patient time to inhale when ready. These devices are especially effective for patients that have difficulty coordinating breaths with an MDI. Spacers merely hold the aerosol in a tube-like device while the patient inhales and provide space and volume between the MDI and the patient's mouth. **Figure 5-4** illustrates a simple MDI with spacer. These devices also decrease the deposition of the particles in the oropharynx. Because both spacers and chambers are somewhat bulky, many patients do not use them on a regular basis when not hospitalized. Patients should be encouraged to use a spacer or chamber whenever using a pressurized MDI.

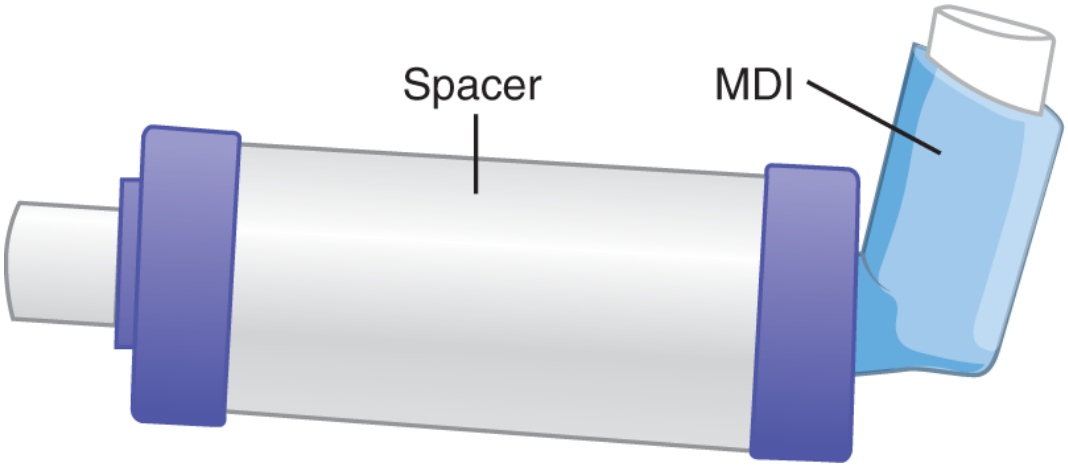


FIGURE 5-4 Metered-dose inhaler (MDI) with spacer chamber.

A valved holding chamber (**Figure 5-5**) includes a one-way valve and allows the patient to inhale when ready and exhale through the device without affecting the aerosol. The valve opens when it senses an inspiratory effort. Optimal use still depends on taking a slow deep breath as close to actuating the MDI as possible. Some devices may whistle or signal if the inspiration is too rapid. These devices are particularly helpful for patients who have difficulty coordinating the pMDI and their breathing patterns, and they have become the standard for most inpatient pMDI therapy. MDI use has not been considered appropriate for infants and pediatric patients, but the valved holding chamber with an infant mask currently is recommended for infant MDI therapy. It is still essential, however, that a patient (or family member) receive good instructions and practice while supervised by a practitioner until the procedure has been mastered. **Figure 5-6** illustrates a pediatric patient using an MDI with a valved holding chamber and mask.

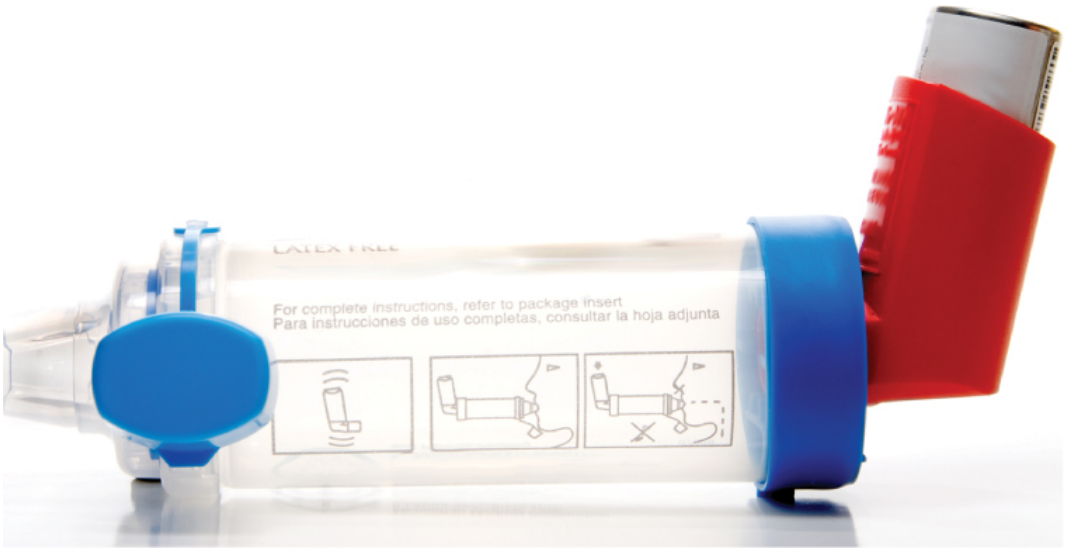


FIGURE 5-5 Valved holding chamber.

© Rob Byron/Shutterstock.

NEED TO KNOW

Valved holding chambers should always be used for MDI therapy for infants and children.

Dry Powder Aerosols

DPIs are inspiratory flow-driven inhalers that deliver a dry powder into the lungs. The powder contains drug particles that are less than 5 μm in size with either a lactose or glucose filler that acts as a carrier. Many drugs frequently administered by RCPs are available in this formulation, such as the Diskus, Ellipta, Flexhaler, Diskhaler, HandiHaler, Neohaler, and Pressair (**Figure 5-6**). Single-dose DPIs contain individually wrapped capsules that contain one dose of medication. Multiple-dose DPIs contain multiple doses of dry powder within the device. One dose is administered with each actuation. All these drugs are described in detail in Chapters 6 and 7. Manufacturers of DPI devices have patient information available on their websites and many provide online video instructions for patient use.

FIGURE 5-6 Multiple-dose dry powder inhalers: (**A**) Diskus. (**B**) Flexhaler. (**C**) Diskhaler. Single-dose dry powder inhalers: (**D**) HandiHaler. (**E**) Aerolizer.

(**B**) © Denis Mironov/Shutterstock. (**C**) © Marjanneke de Jong/Shutterstock. (**D**) © mayer kleinostheim/Shutterstock. (**E**) © Silentiger/Dreamstime.com

Description

Administration of a drug by powder aerosol has two primary advantages: (1) proper breathing pattern is required to activate the device, and therefore better deposition of aerosol is likely, and (2) no propellant gas is used. The advantage of breath-actuated devices is also one of the disadvantages because many chronic obstructive lung disease (COPD) patients cannot generate the required inspiratory flow to create the aerosol. An inspiratory flow rate of 40–120 L/min is required to generate adequate flow when using a DPI; many institutions are now using inspiratory flow meters to assess a patient's ability to generate adequate flow before utilizing these devices.

Multiple MDI Medications

If a patient is receiving more than one type of medication by MDI (e.g., an asthmatic who may take both a bronchodilator and an anti-inflammatory agent), the bronchodilator always should be taken first. It is also suggested that for administration of corticosteroid drugs such as fluticasone (Flovent), which may make the patient more vulnerable to oral infections such as candidiasis, the technique should be slightly modified. For MDI treatment with corticosteroids, the patient should be instructed to wait 1–2 minutes after taking the bronchodilator and then hyperextend the neck when inhaling. This modification (having the patient look toward the ceiling during inhalation) may reduce the amount of the drug that is deposited in the mouth and pharynx. It is also important to have the patient rinse the mouth after inhaling a corticosteroid.

Case Study 5-1

Aerosol Techniques

Martha G is an 83-year-old female (66 kg, 5′4″) with COPD, hypertension, and diabetes. She is brought to the emergency room by her daughter for shortness of breath, worsening cough, and sputum production.

History and Physical Examination

History: Patient has a history of COPD, hypertension, diabetes, and has had an appendectomy. Tobacco use 1 PPD × 50 years. No history of alcohol use.
Vital signs: Heart rate, 118 beats/min; respiratory rate, 26 breaths/min; blood pressure, 151/100 mm Hg; and temperature, 35°C.
Neurologic: Decreased alertness and slow to answer questions.
Respiratory: Bilateral inspiratory and expiratory wheezes, minimal air movement, and moderate amount of thick secretions.

Laboratory Values

Chest radiograph: Hyperaeration.

Diagnosis

COPD exacerbation.

Hospital Orders

Questions

1. Inhaled albuterol is ordered every 20 minutes for three doses. Why would albuterol administered via a nebulizer be the most appropriate route of administration and type of inhaled device for this patient?
2. The patient's family does not understand why she is receiving only inhaled therapy to treat her condition. Explain the advantages and disadvantages of giving inhaled therapy to this patient.
3. The patient's condition responded quickly to therapy and it was decided to discharge her home with inhaled therapy and systemic steroids. She is still weak and has a poor inspiratory effort/force. Which inhaled device would be appropriate for her to take her inhaled bronchodilators and inhaled corticosteroids? Which should be avoided and why?

SVN and MDI During Mechanical Ventilation

Aerosolized medications, for example, bronchodilators, mucolytics, antibiotics, and corticosteroids, are commonly administered to hospitalized mechanically ventilated patients. Aerosol medications may be delivered during mechanical ventilation by either SVN or pMDI. These aerosols tend to deposit in ventilator tubing and are baffled by the reduced airway diameter of the artificial airway (endotracheal [ET] or tracheostomy tube). These factors significantly reduce the amount of medication delivered to the patient being mechanically ventilated. Drug dosage and placement of nebulizing devices in the ventilator circuit are important considerations when providing aerosol to the patient on a ventilator. Other factors, for example, patients lying in the supine position, using humidified air/oxygen, and breaths being controlled by the ventilator, make administration in this setting challenging.

SVN During Mechanical Ventilation

Jet nebulizers, ultrasonic nebulizers, and vibrating mesh nebulizers are used to deliver medications in mechanically ventilated patients. Studies have found that as little as 1.5–3% of a drug being nebulized in-line with a ventilator is delivered to the patient's airway. Medication delivery has significantly improved in mechanically ventilated patients due to the increased knowledge of aerosol therapy and development of improved techniques. If the nebulizer is placed between the patient wye and the patient, the percentage delivered is even less (because the drug nebulized during exhalation is lost). Optimal delivery using the SVN during mechanical ventilation occurs when the SVN is placed in the inspiratory limb of the circuit, within 12 in (30 cm) of the patient Y-piece. The flow through the nebulizer should be 6–8 L/min or continuous gas flow can be used. Dosage of medication should be adjusted until a therapeutic response is noted. Often this requires doubling the usual aerosol dosage. Nebulizers placed in-line with the

ventilator circuit can become contaminated with bacteria and increase the risk of ventilator-associated pneumonia. When a chamber remains in the ventilator circuit between treatments, liquid condensate may accumulate and serve as a medium for bacterial growth. Condensate must be removed promptly to avoid bacterial growth. Nebulizers should be thoroughly cleaned and disinfected, rinsed with sterile water, and dried between treatments. If possible, single unit-dose medications should be used for nebulizer treatments. Multidose containers have been responsible for contaminating nebulizers, which can result in the spread of nosocomial infection.

MDI During Mechanical Ventilation

Administration of pMDIs during mechanical ventilation is convenient and safe, but the actuator mouthpiece on a pMDI does not function with the ventilator unit. Numerous adaptors have been developed for use of MDIs for medication administration during mechanical ventilation. These adaptors include elbow-type, Tee-types, in-line types, and a variety of chambers that act as spacers. Placement of the MDI adaptor system, dosage, and timing of MDI actuation are key factors during mechanical ventilation. The spacer-type adaptors generally have the most effective drug deposition. Connecting the pMDI to a spacer chamber placed 15 cm from the ET tube or Y-piece may also increase disposition in the lungs. If possible, a heat-and-moisture exchanger that is adapted for aerosol delivery should be used so that the aerosol will bypass the heat-and-moisture exchanger for delivery of aerosols during mechanical ventilation. Otherwise, the heat and moisture will change the particle size and decrease disposition of aerosolized medications.

When administering MDI dosages during mechanical ventilation, the MDI adaptor should be as close to the patient’s airway as possible. If a chamber-type adaptor is used, the MDI should be actuated at the beginning of inspiration. Dosage of the MDI should be adjusted to achieve therapeutic results. Most studies have found a

minimum of four to eight puffs will be required to deliver an effective dose. A 15-second pause between each actuation is recommended.

Ventilator Parameters During SVN Treatments

Depending on the ventilation mode and patient parameters during mechanical ventilation, significant volume changes may occur from the additional gases being introduced into the ventilator circuit during SVN treatments. This is most critical during mechanical ventilation of neonates; it is less dramatic when ventilating adults. If this method of nebulization is preferred to an MDI for a ventilated patient, some RCPs prefer using a vibrating mesh nebulizer to avoid affecting the total flow rate. With an SVN, the FiO_2 of the nebulizing gas may be important; this should be taken into account by the RCP administering the treatment. Flow-by or continuous flow ventilator modes should be turned off during SVN treatments, with ventilator settings restored after therapy.

Instilled Medications

Another route of administration used by RCPs is direct instillation of drugs through an ET tube or intratracheal catheter. Instillation consists of injecting a bolus (3–5 mL) of a drug directly into the tracheobronchial tree via a tube or catheter. This route typically is used for the administration of wetting agents or mucolytics, surface-active agents (e.g., surfactant replacement), and advanced cardiac life-support drugs during cardiac resuscitation.

Instillation of wetting agents (e.g., normal saline) may be used as part of the airway management protocol for intubated or tracheotomized patients when mucus plugging or retention of secretions has developed. Routine instillation of saline into ET tubes of patients on mechanical ventilation is not recommended and may decrease oxygenation and cause nosocomial infection.

Current surfactant replacement therapy requires direct instillation of the synthetic surfactant into an ET tube and vigorous ventilation of the infant for distribution. (These agents and specific dosage recommendations are discussed in Chapter 9.)

Instillation of cardiac resuscitation drugs through the ET tube has long been known to be a satisfactory route when cardiac output is reduced and/or intravenous routes have not been established. Drugs administered directly to the pulmonary mucosal surface may be effectively absorbed (similar to sublingual administration) in situations in which cardiac output and perfusion are reduced. Resuscitation drugs and dosages are discussed in Chapter 12.

Instillation of medications via bronchoscope is a common practice during the bronchoscopy procedure. Depending on the bronchoscopic findings, the physician may request a wetting agent, mucolytic, or antibiotic for instillation during the procedure. Lidocaine is frequently used during bronchoscopy for its local anesthetic and antitussive properties. (Bronchoscopy and dosage recommendations for lidocaine are discussed in Chapter 11.)

Disadvantages and Limitations of Drug Delivery by Instillation

The primary disadvantage of this method of drug delivery is its tendency to stimulate bronchospasm and a violent cough reflex. In patients with retained secretions, the cough is a necessary part of secretion removal, but special care must be taken to protect the artificial airway and/or the stoma site.

When this method of drug delivery is used during cardiac resuscitation, the dosage of drug retained cannot be determined absolutely because some may be suctioned from the airway. Coughing typically is not a consideration for the patient in full cardiac arrest.

Transient hypoxemia secondary to airway obstruction has been associated with the instillation of artificial surfactant. Monitoring of cardiac rhythms and pulse oximetry during such therapy is strongly recommended and is usually part of the treatment protocol.

Review Questions

1. List at least four advantages and disadvantages of administering medications by aerosol.
2. Define the appropriate particle size for deposition in smaller airways and lung periphery.
3. Describe the proper procedure for taking an effective SVN treatment. (*Note:* Try to write patient instructions as if you were giving a patient his or her first SVN treatment.)
4. Describe the proper procedure for taking an effective MDI medication. (*Note*: Try to write patient instructions as if you were giving a patient his or her first MDI dosage.)
5. Describe the function of spaces or chambers when used with MDI therapy and list the patient circumstances when a spacer or chamber should be used for pMDI therapy.
6. Describe the proper placement of SVN and MDI in the ventilator circuit for providing in-line aerosol therapy during continuous mechanical ventilation. When should the MDI be actuated for in-line MDI therapy?
7. Define drug administration by instillation and describe three indications for this route.
   a.
   b.
   c.
8. Describe the disadvantages and hazards of drug administration by instillation.

Posttest

For each of the following questions, try to select the one best answer from the choices given.

1. Which of the following statements is true regarding the use of a DPI for medication administration?
   a. DPI is the preferred method of aerosol medication for infants and children under 5 years old.
   b. Inspiratory flow rate of 40–120 L/min is needed for effective powder aerosol deposition.
   c. Breathing pattern and patient cooperation are not important for an effective treatment.
   d. Use of a spacer or valved holding chamber is recommended when using a DPI.
2. Which of the following is the recommended breathing pattern for maximal deposition of medication by aerosol?
   a. Normal breathing
   b. Normal breathing with a 3-second pause at end-inspiration
   c. Slow, deep breathing with a 10-second pause at end-inspiration
   d. Rapid inspiration with a 3- to 5-second pause at end-inspiration
3. Which of the following are advantages of drug administration by aerosol?
   1) Fewer systemic side effects than other routes
   2) Rapid onset of therapeutic effects of drug
   3) Precise amount of drug is given only to target organ
   4) Technique is cost-effective because patient effort is not required
   a. 1 and 2 only
   b. 2 and 4 only
   c. 1, 2, and 3 only
   d. 1, 2, 3, and 4

4. Which of the following is the recommended flow rate to be used to power an SVN?
   a. 1–4 L/min
   b. 4–6 L/min
   c. 6–8 L/min
   d. 15 L/min
5. When taking a drug by pMDI, a spacer is used to:
   a. concentrate the medication.
   b. capture the patient's exhaled air.
   c. provide a reservoir and improve drug delivery.
   d. eliminate the need for the patient to inhale deeply.
6. When an aerosol device produces particle sizes that are very large (>5 μm), the aerosol would most likely:
   a. deposit in the oropharynx.
   b. deposit in the large upper airways (trachea and bronchi).
   c. be exhaled.
   d. deposit in the small airways and lung periphery.
7. The purpose of a brief breath-hold at end-inspiration during an aerosol treatment is to:
   a. improve treatment effectiveness and drug deposition.
   b. prevent hyperventilation during treatment.
   c. assure proper drug mixing in nebulizer.
   d. assure appropriate treatment length.
8. Drugs are instilled into an artificial airway for which of the following reasons?
   1) Provide precise amount of desired drug
   2) Utilize pulmonary mucosa for drug absorption in low cardiac output state (i.e., cardiac resuscitation)
   3) Minimize systemic effects of drugs
   4) Assure drug is not swallowed
      a. 1 only
      b. 2 only
      c. 2 and 3 only
      d. 2, 3, and 4 only
9. When using a pMDI without a spacer or chamber, the patient should be instructed to squeeze the canister:

a. at end-inspiration.
b. at end-exhalation.
c. during the middle of inspiration.
d. at the beginning of inspiration.

10. When using pMDI treatments for pediatric patients:
    a. a spacer or valved holding chamber is not recommended.
    b. a valved-holding chamber is recommended.
    c. the breathing pattern is not important.
    d. a DPI is preferred.

References/Recommended Readings

AARC Clinical Practice Guideline. Endotracheal suctioning of mechanically ventilated patients with artificial airways 2010. *Respir Care*. 2010;55(6):758-764.

Alvine GF, Rodgers P, Fitzsimmons KM, et al. Disposable jet nebulizers: how reliable are they? *Chest*. 1992;101:316.

Ari A. Aerosol therapy in pulmonary critical care. *Respir Care*. 2015;60(6):858-879.

Ari A, Restrepo RD. Aerosol delivery device selection for spontaneously breathing patients. *Respir Care*. 2012;57(4):613-626.

Arunthari V, Bruinsma R, Lee A, et al. A prospective, comparative trial of standard and breath-actuated nebulizer: efficacy, safety, and satisfaction. *Respir Care*. 2012;57(8):1242-1247.

Barrons R, Pegram A, Borries A. Inhaler device selection: special considerations in elderly patients with chronic obstructive pulmonary disease. *Am J Health Sys Pharm*. 2011;68:1221-1232.

Bills G. Balancing aerosol therapy: selecting drugs, patients, and delivery methods. *J Respir Care Pract*. 1993;6:66-74.

Brand P, Hederer B, Austen G, et al. Higher lung deposition with Respimat Soft Mist inhaler than HFA-MDI in COPD patients with poor technique. *Int J Chron Obstruct Pulmon Dis*. 2008;3(4):763-770.

Dal Negro RW. Dry powder inhalers and the right things to remember: a concept review. *Multidiscip Respir Med*. 2015;10(1):13.

Dhand R. How should aerosols be delivered during invasive mechanical ventilation? *Respir Care*. 2017;62(10):1343-1367.

Dhand R. Nebulizers that use a vibrating mesh or plate with multiple apertures to generate aerosol. *Respir Care*. 2002;47(12):1406-1416.

Diot P, Morra L, Smaldone GC. Albuterol delivery in a model of mechanical ventilation: comparison of metered dose inhaler and nebulizer efficiency. *Am J Respir Crit Care Med*. 1995;152:1391.

Dolovich M. Clinical aspects of aerosol physics. *Respir Care*. 1991;36:931-938.

Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest*. 2005;127(1):335-371.

Ebert J, Adams AB, Green-Eide B. An evaluation of MDI spacers and adaptors: their effect on the respirable volume of medication. *Respir Care*. 1992;37:862-868.

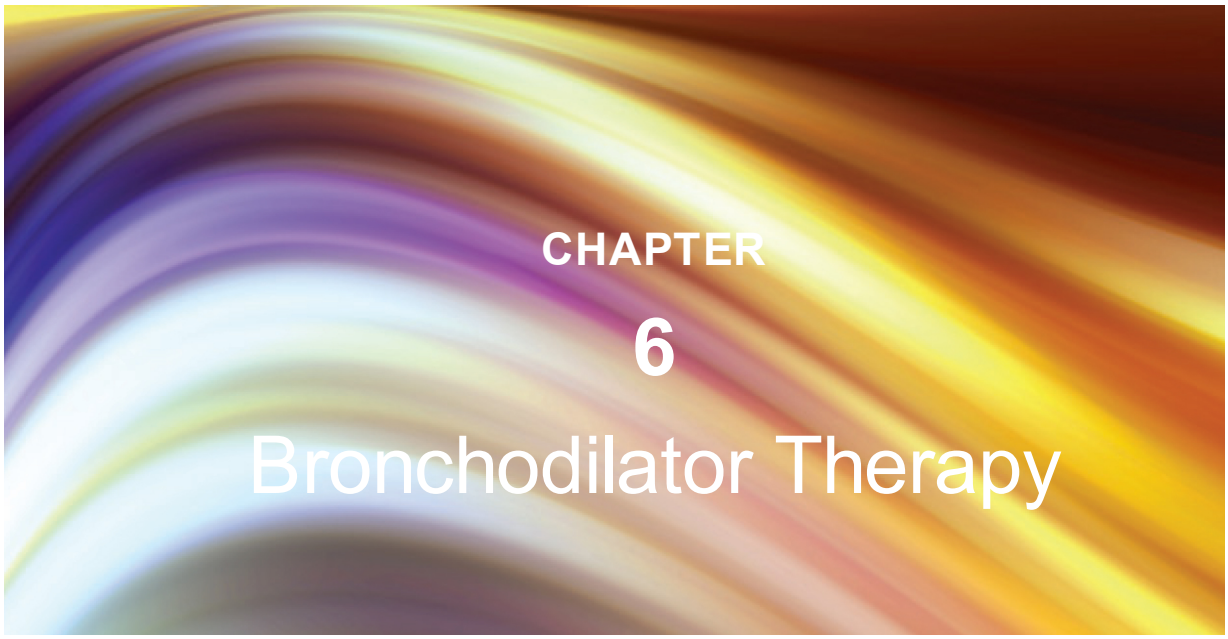
Fink JB, Rubin BK. Problems with inhaler use: a call for improved clinician and patient education. *Respir Care*. 2001;50:1360-1375.

Gardenhire DS, Ari A, Hess D, et al. *AARC: A Guide to Aerosol Delivery Devices for Respiratory Therapists (2017)*. 4th ed. Irving, TX: American Association of Respiratory Care. https://www.aarc.org/wp-content/uploads/2015/04/aerosol_guide_rt.pdf. Accessed February 15, 2019.

Guidry GG, Brown WD, Stogner SW, et al. Incorrect use of metered dose inhalers by medical personnel. *Chest*. 1992;101:31.

Janssens HM, Tiddens HA. Facemasks and aerosol delivery by metered dose inhaler-valved holding chamber in young children: a tight seal makes the difference. *J Aerosol Med*. 2007;20(suppl 1):S59-S63.

Jendle J, Karlberg BE, Persliden J, et al. Delivery and retention of an insulin aerosol produced by a new jet nebulizer. *J Aerosol Med.* 1995;8(3):243.
Laube BL, Georgopoulos A, Adams GK. Preliminary study of the efficacy of insulin aerosol delivered by oral inhalation in diabetic patients. *JAMA.* 1993;269:2106.
Lavorini F, Levy ML, Corrigan C, et al; ADMIT Working Group. The ADMIT series: issues in inhalation therapy. 6) Training tools for inhalation devices. *Prim Care Respir J*. 2010;19:335-341.
Li JT, Reed CE. Proper use of aerosol corticosteroids to control asthma. *Mayo Clin Proc*. 1989;64(2):205-210.
Mahon J, Fitzgerald A, Glanville J, et al. Misuse and/or treatment delivery failure of inhalers among patients with asthma or COPD: a review and recommendations for the conduct of future research. *Respir Med*. 2017;129:98-116.
Mason JW, Miller WC, Small S. Comparison of aerosol delivery via Circulaire system vs. conventional small volume nebulizer. *Respir Care*. 1994;39:1157-1161.
Mitchell JP, Nagel MW. Valved holding chambers (VHCs) for use with pressurized metered-dose inhalers (MDIs): a review of causes of inconsistent medication delivery. *Prim Respir Care J*. 2007;16(4):207-214.
Newman SP, Busse WW. Evolution of dry powder inhaler design, formulation, and performance. *Respir Med*. 2002;96:293.
Pederson S, Hansen OR, Fugslang G. Influence of inspiratory flow rate upon the effect of a Turbuhaler. *Arch Dis Child*. 1990;65:308-310.
Pierson DJ. Toward international consensus on clinical aerosol administration. *Chest*. 1991;100:1100.
Rau JL. Delivery of aerosolized drugs to neonatal and pediatric patients. *Respir Care*. 1991;36:514.
Rau JL. Practical problems with aerosol therapy in COPD. *Respir Care*. 2006;51(2):158-172.
Ridling D, Martin LD, Bratton SL. Endotracheal suctioning with or without instillation of isotonic sodium chloride in critically ill children. *Am J Crit Care*. 2003;12:212-219.
Rubin B. Pediatric aerosol therapy: new devices and new drugs. *Respir Care*. 2011;56(9):1411-1423.
Rubin DK, Fink JB. Optimizing aerosol delivery be pressurized metered-dose inhalers. *Respir Care*. 2005;50:1191.
Smaldone GC. Assessing new technologies: patient-device interactions and deposition. *Respir Care*. 2005;50(9):1151-1160.
Svedmyr N. Clinical advantages of the aerosol route of drug administration. *Respir Care*. 1991;36:922-930.
van Noord JA, Cornelissen PJ, Aumann JL, et al. The efficacy of tiotropium administered via Respimat Soft Mist inhaler or HandiHaler in COPD patients. *Respir Med*. 2009;103(1):22-29.
Volsko TA, Chatburn RL, El-Khatib MF. *Equipment for Respiratory Care*. Burlington, VA: Jones & Bartlett Learning, LLC; 2016.
Woodcock A. Continuing patient care with metered dose inhalers. *J Aerosol Med*. 1995;8(suppl 2):S5-S10.



© Anna RubaK/ShutterStock, Inc.

OUTLINE

Introduction
Mechanisms of Bronchoconstriction and Bronchodilation
  Neurochemical Mediators in Bronchoconstriction and Bronchodilation
  Relief of Mucosal Edema
  Relief of Bronchospasm
Adrenergic (Sympathomimetic) Bronchodilators
  Nonselective Sympathomimetics
  β_2-Adrenergic Agonists
  Sympathomimetic Drug Interactions
Anticholinergic Bronchodilators
  Short-Acting Antimuscarinic Agents
  Long-Acting Antimuscarinic Agents
  Anticholinergic Drug Interactions
Combination Preparations: Adrenergic/Anticholinergic and Adrenergic/Corticosteroid
  General Bronchodilator Special Considerations
Methylxanthines and PDE Inhibitors
  Mechanism of Methylxanthines and PDE Inhibitors
  Therapeutic Use of Methylxanthines
  Side Effects of Methylxanthines
  Description of Methylxanthines
  Methylxanthine Drug Interactions
Magnesium

Mechanism of Bronchodilation Using Magnesium

OBJECTIVES

After completion of this chapter and its learning activities, you will be able to:

1. Compare and contrast bronchoconstriction and bronchospasm.
2. List the three categories of bronchodilators and describe the mechanism of how each class causes bronchodilation.
3. Describe the common adverse effects and contraindications of sympathomimetic, anticholinergic, and methylxanthine bronchodilators.
4. List the common drugs that interact with sympathomimetic, anticholinergic, and methylxanthine bronchodilators and predict the potential effect of using the drugs concomitantly.
5. Compare the use of adrenergic, anticholinergic, and methylxanthine bronchodilators in clinical practice.
6. Assess the clinical indications for short-acting and long-acting inhaled bronchodilators.
7. Suggest the most appropriate bronchodilator therapy, including the drug of choice and route of administration, given a patient case study.

KEY TERMS

Adrenergic
Anticholinergic
Antimuscarinic
Bronchoconstriction
Bronchospasm
Catecholamine
Cyclic 3′,5′-adenosine monophosphate (cAMP)
Cyclic 3′,5′-guanosine monophosphate (cGMP)
LABA
LAMA
Methylxanthine
Parasympatholytic
Phosphodiesterase (PDE)
SABA
SAMA
Sympathomimetic

Introduction

Bronchodilator therapy may be the most critical and challenging aspect of respiratory care pharmacology. Acute bronchoconstriction is often relieved most effectively by aerosol or inhalation therapy, and the respiratory care practitioner (RCP) may be the most knowledgeable individual regarding the best drug for a specific patient given a clinical scenario.

The RCP may be asked to recommend the most appropriate drug, its dosage (either in solution [mL] or by weight [mg]), and route of administration. Considering the wide range of patients seen by practitioners and the variety of available drugs, it is critical for the RCP to possess a working knowledge of how each bronchodilator achieves its purpose, how much of each agent is appropriate, how often it is safe to administer, and how long until it takes effect and duration of action. An RCP should also be able to identify contraindications to each medication and be aware of the side effects that may occur.

The art of respiratory care utilizes the skill and knowledge of the RCP to recommend or select the best drug for each situation. The challenge is to select the drug with the most beneficial effects, the least negative side effects, and the optimal duration. Because patients often develop a rapidly occurring tolerance (tachyphylaxis) to sympathomimetic drugs, the RCP may be in the best position to notice this phenomenon and recommend a course of therapy with an alternative drug or higher dosage. Combinations of drugs from several categories are frequently used in the management of chronic bronchospasm or severe acute symptoms (i.e., status asthmaticus). Knowledge of the mechanism by which each bronchodilator achieves its goal is a key factor in the safe, effective, and efficient care of patients with reactive airway disease.

Mechanisms of Bronchoconstriction and Bronchodilation

The term **bronchoconstriction** is often used incorrectly as a synonym for **bronchospasm**. A bronchospasm is a reversible contraction of the bronchial smooth muscle leading to decreases in pulmonary function, for example, forced expiratory volume after 1 second (FEV_1) and peak expiratory flow rate (PEFR). Bronchospasm is one of the major triggers of bronchoconstriction, but not the only one. Bronchoconstriction is a condition in which the diameter (lumen) of the airway is reduced or constricted, thereby decreasing expiratory flow. This condition may be due to bronchospasm, airway inflammation/airway wall thickening, mucosal edema, or the presence of secretions (or a combination of these). In the selection of the best bronchodilator for each patient, the RCP must have some knowledge of the pathophysiology of the disease or injury being treated.

Bronchodilators (e.g., β-adrenergics and anticholinergics) achieve relief of bronchoconstriction by reducing the smooth muscle contraction that is causing the constriction. Asthmatics frequently exhibit all three aspects of bronchoconstriction (e.g., bronchospasm, mucosal edema, and excessive secretions), whereas a croup patient may have only mucosal edema. The drug or drugs of choice in treating bronchoconstriction are determined by the mechanism of constriction, as well as patient's history, other medications the patient is receiving, and the acuity (criticalness) of the situation.

Neurochemical Mediators in Bronchoconstriction and Bronchodilation

Research has shown that when nerve endings in the autonomic nervous system are stimulated, they release transmitters (chemicals) that bind to receptor sites on the adjoining nerve ending (or neuroeffector site) to cause an effect. As described in Chapter 3, the

neurotransmitter that stimulates bronchodilation is norepinephrine, which binds to a β_2-receptor and stimulates intracellular production of **cyclic 3′,5′-adenosine monophosphate (cAMP)**. When a sympathetic nerve in the bronchial tree is stimulated, it promotes the conversion of adenosine triphosphate to cAMP, which leads to the relaxation of smooth muscle (**Figure 6-1**).

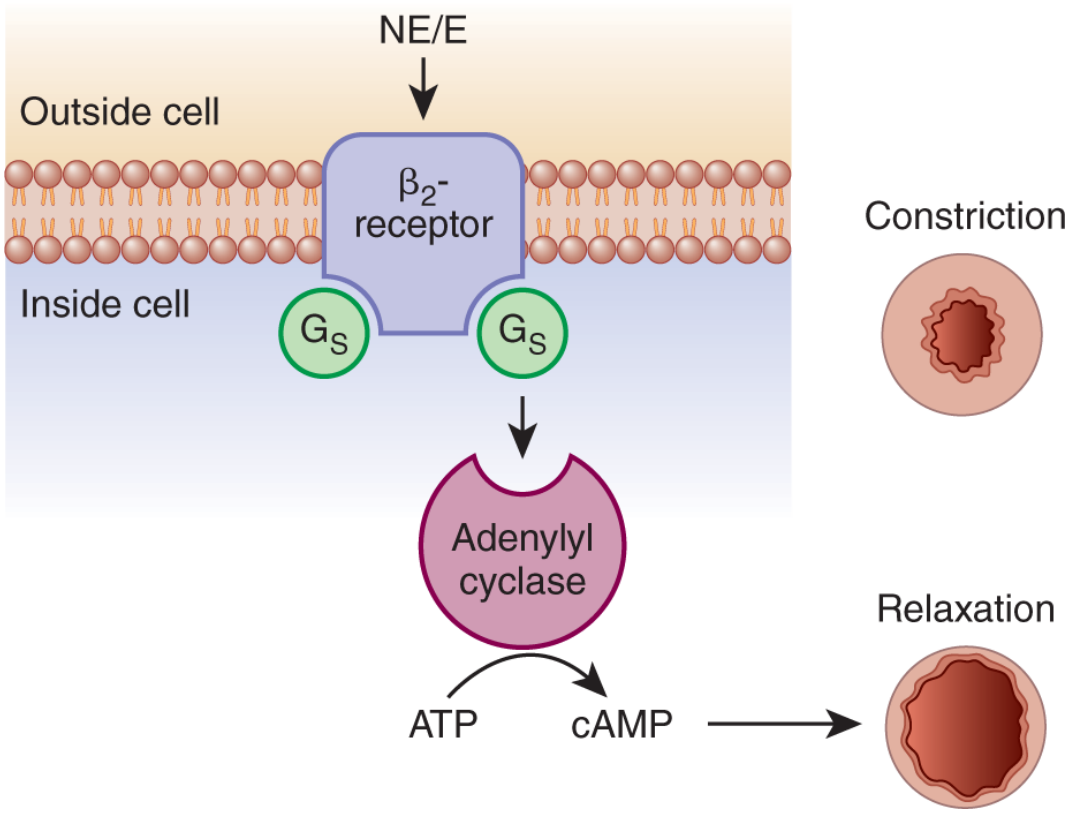


FIGURE 6-1 Sympathetic stimulation of bronchial cells. ATP, adenosine triphosphate; cAMP, cyclic 3',5'-adenosine monophosphate; G_S, stimulatory G protein.

Description

This mediator (cAMP) is constantly broken down into an inactive form (AMP) by the presence of the enzyme **phosphodiesterase (PDE)**. When AMP is present in large quantities, it interferes with the stimulation of bronchodilation. Although the exact mechanism of action of methylxanthines is not known, it is thought that they have some effect on the inhibition of PDE.

Increased bronchial smooth muscle tone (bronchoconstriction) may also be caused by an increase in parasympathetic cholinergic activity. When a parasympathetic nerve in the bronchial tree is stimulated, acetylcholine (ACh) is released to the postganglionic site and promotes the conversion of guanosine triphosphate (GTP) to **cyclic 3′,5′-guanosine monophosphate (cGMP)**. The intracellular levels of cGMP in bronchial smooth muscle cells promote bronchoconstriction (**Figure 6-2**). The primary goal of bronchodilator therapy is to increase the levels of cAMP or decrease the levels of cGMP in the smooth muscle cells in the pulmonary tree. Often, a combination of drugs from these categories is needed in the management of acute or chronic bronchospasm (e.g., asthma or chronic obstructive pulmonary disease [COPD]).

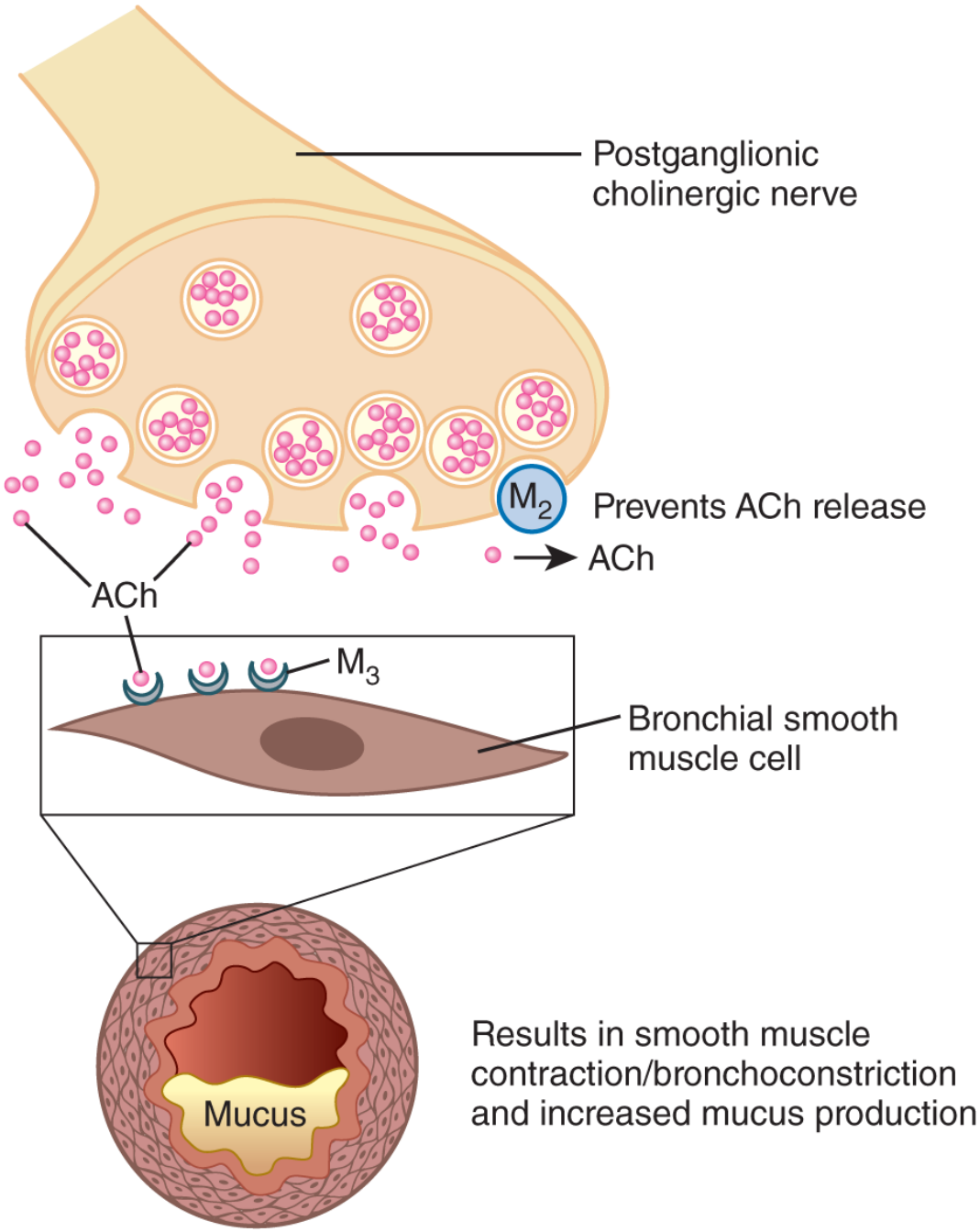


FIGURE 6-2 Effect of parasympathetic stimulation in bronchial cells ACh, acetylcholine.

Description

Relief of Mucosal Edema

Drugs that reduce bronchoconstriction by relief of mucosal edema include both **sympathomimetics** with an α-effect (α-adrenergic), which promotes vasoconstriction (decongestant), and corticosteroids, which have a general anti-inflammatory effect. The α-adrenergics and corticosteroids are discussed in more detail in this chapter and in Chapter 7.

Relief of Bronchospasm

Bronchodilation is a complex process, and bronchodilators are often categorized according to the mechanism by which each achieves relief of bronchospasm. The three categories of bronchodilating drugs are sympathomimetics (β-adrenergics), anticholinergics (**parasympatholytics**), and, the less commonly used, **methylxanthines**. RCPs administer both sympathomimetic and anticholinergic drugs by aerosol or instillation, and although methylxanthines are given systemically, one must be aware of the effects and role in the relief of or prevention of bronchospasm.

Bronchodilation through relief of bronchospasm is achieved in the pulmonary smooth muscle by either directly stimulating bronchodilation (adrenergics or sympathomimetics) or blocking bronchospasm (anticholinergics or methylxanthines). When the sympathetic nervous system is stimulated, its effects in the pulmonary system include bronchodilation and vasoconstriction. Bronchodilators in this category are thus referred to as sympathomimetic, meaning they mimic or imitate the sympathetic nervous system, or as **adrenergic**, meaning they utilize neurotransmitters similar to adrenalin (epinephrine). When the parasympathetic nervous system is stimulated, its effects in the pulmonary system include bronchoconstriction. Bronchodilators in this category are thus referred to as **anticholinergic**, meaning they block the bronchoconstricting effects of the parasympathetic system, or as parasympatholytic, meaning the drug lyses or dissolves the effect of the parasympathetic system.

Table 6-1 provides a quick reference to general information about the categories of bronchodilators.

TABLE 6-1
General Bronchodilator Profiles

	β-Adrenergic	Anticholinergic	α-Adrenergic	Methylxanthine
Mechanism of action	Directly increases cAMP	Inhibits GMP	Vasoconstriction	Unknown, may inhibit phosphodiesterase to maintain the level of cAMP
Effect	Direct bronchodilation	Prevents bronchospasm	Decreases mucosal edema	Promotes or prolongs bronchodilation
Synonyms	Adrenergic, β-agonist, sympathomimetic	Antimuscarinic, parasympatholytic	α-Agonist, sympathomimetic	
Route of administration	Aerosol (solution or DPI); oral (tablets or syrup)	Aerosol (solution or DPI)	Aerosol, IV, IM	Oral, IV (not aerosolized)

cAMP, cyclic 3′,5′-adenosine monophosphate; DPI, dry powder inhaler; GMP, guanosine monophosphate; IM, intramuscular; IV, intravenous.

Adrenergic (Sympathomimetic) Bronchodilators

Bronchodilators in this category have historically been referred to as sympathomimetic amines. This term refers to the chemical composition of the drug (its **catecholamine** properties) but can no longer be used to refer to all drugs in this category. Many of the newer agents in this category have a higher specificity (i.e., they promote bronchodilation with fewer side effects) and are not catecholamines. The advantages of these newer formulations are the reduction in cardiovascular side effects and a prolonged duration of action. It is common to refer to all these drugs as simply adrenergic agents because this term is sufficient to describe the mechanism of action.

When adrenergic (sympathomimetic) drugs are used, there are three potential effects on the cardiovascular and pulmonary systems:

1. α-effects (vasoconstriction)
2. β_1-effects (increase heart rate)
3. β_2-effects (reverse bronchospasm)

A few drugs in this category have both α- and β-effects. The ideal bronchodilators in this category are β_2-specific, meaning they promote bronchodilation while minimizing cardiac-related side effects. The most commonly used agents are inhaled β_2-agonists. This class can be divided into short-acting β_2-agonist (**SABA**) and long-acting β_2-agonist (**LABA**). **Table 6-2** summarizes the α, β_1, and β_2 characteristics of adrenergic bronchodilators that are currently in use in the United States and Canada.

TABLE 6-2
Adrenergic Bronchodilators: Actions and Side Effects

	α (Vasoconstriction)	β_1 (Heart Rate)	β_2 (Bronchodilation)	Other Side Effects (Nausea, Headaches, Tremor)
Short-Acting				
Albuterol (Proventil®, Ventolin®, salbutamol)	None	**	****	**
Levalbuterol (Xopenex®)	None	**	****	*
Epinephrine (systemic)	****	****	****	****
Racemic epinephrine (inhaled) (Micronefrin®, Racepinephrine®)	****	**	**	*
Metaproterenol	None	**	****	***
Terbutaline (Bricanyl®)	None	*	***	***
Long-Acting				
Arformoterol (Brovana®)	None	None	****	*
Formoterol (Foradil®)	None	None	****	*
Salmeterol (Serevent®)	None	None	****	*
Ultra Long-Acting				
Indacaterol (Arcapta®)	None	None	****	*
Olodaterol (Striverdi®)	None	None	****	*
Vilanterol (only available in combination)	None	None	****	*

Estimated effects: *, few or mild; **, mild-to-moderate; ***, moderate; ****, strong.

Nonselective Sympathomimetics

Isoproterenol is a potent nonselective β-agonist, which means that it acts on β_1-receptors in the heart and β_2-receptors in the lungs. It is no longer available as an inhalation solution and is no longer used for the treatment of bronchospasm because of adverse effects and the availability of newer, safer agents that are also effective. Epinephrine is a fast-acting and effective bronchodilator when injected. It causes bronchodilation because of its activity on the β_2-receptor. This stimulates production of cAMP, leading to bronchial smooth muscle relaxation. This agent also affects the α- and β_1-adrenergic receptors. This agent is used as an intramuscular (IM) injection in the treatment of anaphylaxis and may be administered subcutaneously or IM to treat acute bronchospasms caused by refractory asthma or

inhaled to treat upper airway obstruction and croup. The α-receptor activity is responsible for vasoconstriction and reducing mucosal airway edema as well as hypertension when administered by injection. This agent is useful only in the acute setting because of its short duration of effect. Epinephrine is quickly metabolized by catechol-*O*-methyltransferase. Epinephrine's activity on the β_1-receptor is responsible for cardiac stimulation, palpitations, and tachycardia, which may cause or worsen arrhythmias and coronary artery disease. It should be used with caution in patients with preexisting cardiovascular disease. Other significant adverse effects of epinephrine are tremors, headache, and insomnia. IM epinephrine is the first-line treatment for anaphylaxis but is used as an inhaled bronchodilator in severe cases of bronchospasm and upper airway obstruction unresponsive to other therapies. The injectable epinephrine is the naturally occurring formulation. The nebulized formulation is a synthetic racemic mixture of the R-isomer and the S-isomer (inactive form). The adverse effects of both agents have been found to be similar. An epinephrine dose of 0.2–0.5 mg IM is given for anaphylaxis, and 0.25–0.5 mL of a 2.25% epinephrine solution can be administered by nebulizer every 3 hours as needed (**Table 6-3**). Patients must be monitored closely for adverse effects and relief of bronchospasm or airway edema. Patients frequently require another dose for rebound edema or bronchospasm. The injectable preparations are not recommended for the treatment of asthma or any diseases that cause bronchospasm in view of the potential for cardiac adverse effects such as tachycardia, palpitations, and arrhythmias due to activity on β_1-receptors.

TABLE 6-3
Nonselective Sympathomimetics

Drug	Dose	Onset of Action	Duration of Effectiveness	Clinical Indications
Epinephrine	0.2–0.5 mg IM (may be repeated)	Within 3–5 min	Short-acting, 1–3 h (SABA)	Status asthmaticus, anaphylaxis
Racemic epinephrine (Micronefrin®, Racepinephrine®)	0.5 mL nebulized (may use lower doses in pediatrics), may repeat if needed	Rapid onset, 3 min	Ultra-short duration, 30–120 min (SABA)	Fast-acting α-agonist for acute mucosal edema, i.e., croup, laryngeal edema

IM, intramuscular; SABA, short-acting β_2-agonist.

β_2-Adrenergic Agonists

The development of β_2-agonists is based on the modification of the structures, norepinephrine and epinephrine, to allow for development of more β_2-selective drugs. These agents were developed to cause bronchodilation needed for the treatment of asthma and COPD and decreased adverse effects that would likely occur with activity on the β_1-receptor. Activity on the β_2-receptor couples and activates the stimulatory G (Gs) protein, forming GTP. This activates adenylyl cyclase to synthesize cAMP. cAMP causes bronchial smooth muscle relaxation and dilation (**Figure 6-3**). β_2-Agonists may also decrease acute inflammation by preventing mediator release from human lung mast cells and bronchial mucosal edema after exposure to histamines, leukotrienes, and prostaglandin D_2. This effect may benefit patients with acute bronchospasm caused by asthma but does not decrease chronic inflammation. β_2-Adrenergic agonists may also increase mucociliary clearance and reduce ACh release in the airways, thereby preventing bronchoconstriction.

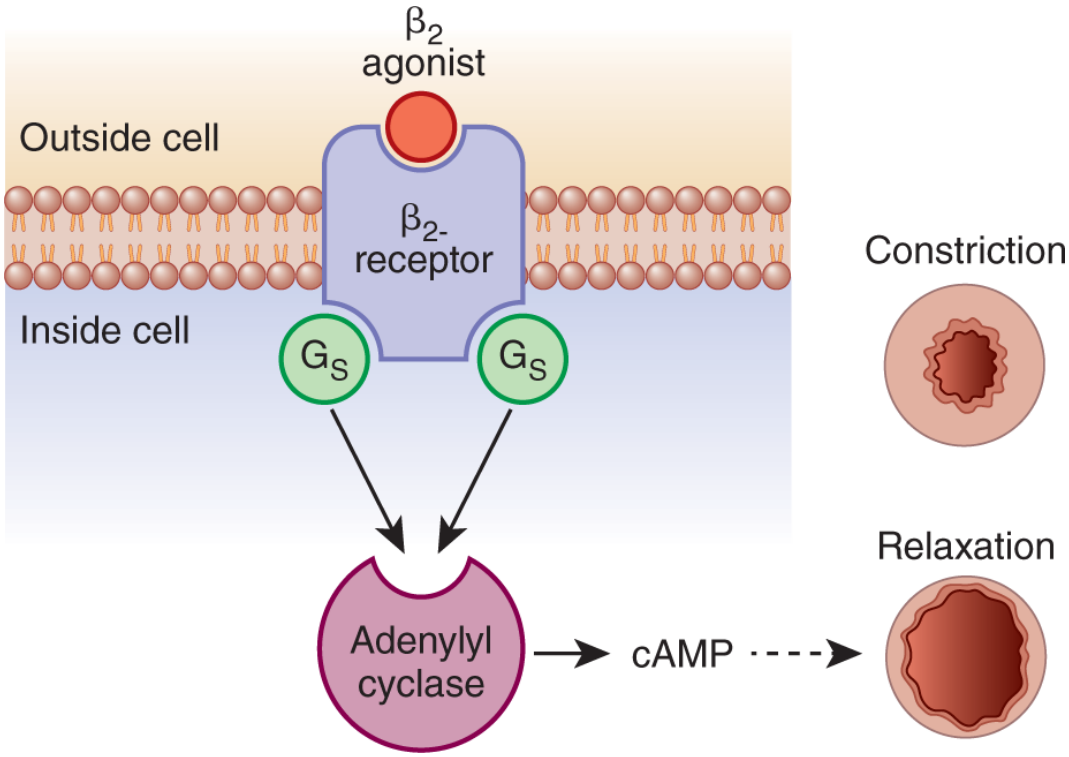


FIGURE 6-3 Mechanism of β_2-adrenergic agonists.

cAMP, cyclic 3',5'-adenosine monophosphate; G_S, stimulatory G protein.

Description

The primary indication for the use of bronchodilators is the relief of bronchoconstriction that is caused by bronchospasm, but some of the newer sympathomimetic agents may also have some beneficial effect in the prevention of bronchospasm (e.g., those associated with asthma, COPD, exercise, or exercise-induced asthma). A key factor in the selection of the appropriate β-agonist is the type of reactive airway disease present, the onset of action (i.e., how quickly the medication will have an effect), and the duration of effectiveness. The β_2-adrenergic agonist class of drugs falls into two therapeutic categories, the short-acting agents and the long-acting agents (**Table 6-4**). The inhaled SABAs are primarily used for the acute treatment of bronchospasms. Albuterol is available in an inhaled formulation and oral tablets/syrup. Terbutaline is available in tablets and an injectable formulation. Oral preparations of β_2-agonists are no longer recommended for use in the treatment of bronchospasms or asthma

because of the higher risk of side effects and longer time to onset of action. Inhaled preparations are used for the management of acute bronchospasms and are first line in the treatment of asthma and COPD exacerbations. LABAs are used in the chronic treatment of COPD and in combination with inhaled corticosteroids (ICSs) in the chronic management of asthma.

TABLE 6-4
Adrenergic Drugs: Dosing, Onset, Duration, and Clinical Uses

Drug	Dose	Onset of Action	Duration of Effectiveness	Clinical Indications
Short-Acting β_2-Adrenergic Agonists				
Albuterol (Proventil®, Ventolin®, ProAir)	HFA: two puffs every 4–6 h NEB: 1.25–5 mg every 4–8 h	Rapid onset, usually <10 min	2–6 h (SABA)	Fast-acting bronchodilator for acute bronchospasm
Albuterol (Proventil Repetabs®, Volmax®)	2–4 mg three to four times daily or extended release tablets: 8 mg every 12 h	Nonaerosol, oral tablets, slower onset (up to 30 min)	Extended duration due to slow-release tablet formulation, may last up to 12 h	No longer used for asthma, inhaled agents are preferred
Levalbuterol (Xopenex®)	HFA: one to two puffs every 4–6 h NEB: 0.63–1.25 mg every 8 h	Within 15 min	3–8 h (SABA)	Fast-acting bronchodilator for acute bronchospasm
Metaproterenol (oral tablets and syrup)	TAB: 20 mg three to four times daily (adults)	Within 30 min	2–6 h (SABA)	No longer recommended in asthma/COPD
Terbutaline	TAB: 2.5–5 mg three times daily SUBQ: 0.25 mg every 30 min (maximum two to three doses)	TAB: 30–45 min SUBQ: 5–15 min	TAB: 4–8 h SUBQ: 1–4 h	Oral: no longer recommended SUBQ: treatment of acute bronchospasm in asthma not responding to inhalation therapy
Long-Acting β_2-Adrenergic Agonists				
Arformoterol (Brovana®)	NEB: 15 μg twice daily	Within 15 min	Long-acting, up to 12 h (LABA)	Maintenance therapy for COPD
Formoterol (Foradil®/ Perforomist)	INH: 12 μg every 12 h NEB: 20 μg every 12 h	Within 15 min	Long-acting, up to 12 h (LABA)	Maintenance therapy for COPD or in combination with ICSs in asthma
Indacaterol (Arcapta®)	INH: 75 μg daily	Within 5 min	Ultra long-acting, up to 24 h (LABA)	Maintenance therapy for COPD
Olodaterol (Striverdi®)	INH: 5 μg (two inhalations) daily	Within 5 min	Ultra long-acting, up to 24 h (LABA)	Maintenance therapy for COPD
Salmeterol (Serevent®)	INH: 50 μg (one inhalation) every 12 h	Delayed onset, >20 min	Long-acting, up to 12 h LABA)	Maintenance therapy for COPD
Vilanterol	Only available in combination with ICS or LAMA	Within 5–15 min	Ultra long-acting, up to 24 h (LABA)	Used in combination with ICS or LAMA for COPD

COPD, chronic obstructive pulmonary disease; HFA, hydrofluoroalkane inhaler; ICH, inhaled corticosteroid; INH, inhaled; LABA, long-acting β_2-adrenergic agonist; LAMA, long-acting antimuscarinic agent; NEB, nebulized; SABA, short-acting β_2-adrenergic agonist; SUBQ, subcutaneous; TAB, tablet.

Short-Acting β_2-Adrenergic Agonists

Inhaled SABAs are the most commonly used bronchodilators. Albuterol is the most commonly used β_2-adrenergic agonist and is the drug of choice for the treatment of acute bronchospasms.

Levalbuterol is the R-isomer, which is the active isomer of albuterol with potent bronchodilating properties. Both albuterol and levalbuterol are available in a metered-dose inhaler (MDI) and nebulizer solution. Both agents may be used intermittently by inhaler device or nebulizer or may be administered as a continuous infusion in patients with severe asthma and COPD exacerbations not responding to intermittent dosing and poor or worsening oxygenation. Albuterol nebulizer solution is available in 0.083% (2.5 mg/3 mL) and 0.5% (2.5 mg/0.5 mL) strengths. The 0.5% solution should be diluted with normal saline to make a total of 3 mL. For example, 2.5 mL of normal saline should be added to a 2.5-mg dose or 0.5 mL of the 0.5% solution. The development of levalbuterol was based on having the advantage of less tachycardia and better tolerability with similar efficacy. When the degree of tachycardia was compared between the two agents, the mean heart rates in patients on levalbuterol were less compared with albuterol. The difference in heart rate was low and potentially only clinically significant in patients with a history of arrhythmias or significant heart disease. The cost of levalbuterol may be significantly more than albuterol with minimal clinical advantages. Therefore, the use of levalbuterol is usually limited to patients not responding to albuterol or to patients with significant tachycardia attributed to albuterol. Metaproterenol is available only as an oral agent, and terbutaline is available in an oral and injectable dosage form. Metaproterenol is no longer recommended or used in the treatment of asthma or bronchospasms. The injectable form of terbutaline may be used in cases of severe acute bronchospasms caused by asthma that are refractory to inhaled SABAs. Because β_2-receptors are also found in the uterus, terbutaline has been used by infusion or subcutaneously to inhibit premature labor contractions. Refer to product literature for dosing guidelines for this application. Both of these systemic agents have an increased potential for adverse effects compared with inhaled SABAs. All adverse effects of β_2-adrenergic agonists are similar. The most common adverse effects include palpitations, pharyngitis, tremor, tachycardia, headache, nervousness, and hypokalemia at high doses. Inhaled

agents have a lower and less severe incidence of side effects compared with systemic agents. Worsening bronchospasms or paradoxical bronchospasms and allergic reaction have been reported with use, but are rare. The onset, duration of action, and dosing for each agent are given in Table 6-4.

NEED TO KNOW

β-Agonists (e.g., albuterol) are useful to treat acute and chronic bronchospasms; α-agonists (e.g., racemic epinephrine) are useful in treating acute mucosal edema such as in croup or postextubation laryngeal edema.

Long-Acting β_2-Adrenergic Agonists

LABAs are most commonly used for the chronic treatment of COPD. They are also used in combination with an ICS for the treatment of asthma. The benefit of LABAs is that their duration of bronchodilating effect lasts from 12 to 24 hours. This improves adherence and overall control of dyspnea and bronchoconstriction in the treatment of COPD and asthma. There is the potential for LABAs to cause an increased risk of asthma-related deaths when used as monotherapy for the treatment of chronic asthma. In 2010, the Food and Drug Administration (FDA) required drug manufacturers to add a black-box warning to the labeling of all LABAs and LABAs in combination with other agents. The labeling must state that the use of these agents increases the risk of asthma-related death and that LABAs should never be used as monotherapy in the treatment of asthma and should not be added to patients controlled on low-to-moderate dose of ICS. In 2017, studies investigating the risk of using combination LABA and ICS compared with ICS alone in the treatment of asthma showed that the combination did not lead to significantly more serious asthma-related complications than treatment with an ICS alone. These studies resulted in the removal by the FDA of the warning from inhaled medicines that contain LABA and ICS combined but are still required on single-agent LABA medications. This effect has not been shown in patients with COPD. There are currently six LABAs

commercially available in the United States. They are available alone and in combination with ICS and some with long-acting muscarinic antagonists. All drugs in this class are approved for use in the chronic management of COPD, and salmeterol, formoterol, and vilanterol are approved for the chronic treatment of asthma in combination with an ICS. LABAs can also be used 30 minutes before exercise to prevent exercise-induced bronchospasm. Although some of these agents have an onset of action similar to that of SABAs, they should not be used for the treatment of acute bronchospasm. Patients will also be prescribed a SABA to use on an as-needed basis for acute bronchospasm in addition to LABAs. The drugs in this class are available in different inhaler devices and inhaled dosage forms (**Figure 6-4**). Table 6-4 includes each agent, dose, dosage form, and onset and duration of action. All drugs in this class have similar adverse effects, including tachycardia, tremor, nervousness, hypertension, nausea, and headaches. Most of these adverse effects are less likely to occur with LABAs than with SABAs.

FIGURE 6-4 Selected long-acting β_2-adrenergic agonist inhaler formulations. (**A**) Diskus dry powder inhaler used for salmeterol. (**B**) Ellipta inhalation device used with vilanterol in combination with other inhaled agents. (**C**) Neohaler drug powder inhaler for indacaterol. (**D**) Metered-dose inhaler used for albuterol and levalbuterol.

(**B**) © GlaxoSmithKline. Used with permission; (**C**) Courtesy of Novartis Pharmaceuticals Corporation; (**D**) © M. Dykstra/Shutterstock, Inc.

Description

NEED TO KNOW

Many of the adrenergic bronchodilators have a generic name ending in *-erol*, for example, albuterol, levalbuterol, formoterol, arformoterol, salmeterol, vilanterol, indacaterol, and olodaterol.

Sympathomimetic Drug Interactions

It is important for the RCP to be knowledgeable about other medications a patient is receiving and to anticipate or recognize signs of adverse reactions associated with the interaction of multiple drugs. Because the RCP remains with a patient throughout the duration of an aerosolized medication treatment, it is important to recognize signs or symptoms that may be associated with drug interactions (as well as those considered to be side effects of the aerosol being delivered). Certain drugs or categories of drugs are potentiated by sympathomimetics, whereas others are less effective; the combination of some drugs with sympathomimetics increases the likelihood or severity of adverse reactions. **Table 6-5** lists interactions of sympathomimetics (β_2-agonists) with other commonly used drugs.

TABLE 6-5
Sympathomimetic Drug Interactions

Drug(s)	Interaction with Sympathomimetics
β-Blockers (propranolol and nadolol)	Inhibit β-adrenergic stimulation; reduce or eliminate effectiveness of sympathomimetics (this effect is usually only seen with nonselective β-blockers)
CYP3A4 inhibitors (salmeterol only), e.g., atazanavir, clarithromycin, ritonavir, and voriconazole	Salmeterol is a CYP3A4 substrate, and use with CYP3A4 inhibitors may lead to increased cardiovascular effects
Digitalis (Digoxin and Lanoxin®)	May lead to a decrease in digoxin concentrations (seen with oral albuterol only)
Diuretics (loop or thiazide)	May lead to acute hypokalemia with

	potential for arrhythmias when β_2-agonists are used frequently or at high doses
MAO inhibitors (Marplan®, Nardil®, and Parnate®)	Potentiate all sympathomimetic effects; may cause hypertensive crisis. This has not been seen with inhaled agents but there is a potential risk
Tricyclic antidepressants (Elavil®, Pamelor®, Sinequan®, and Tofranil®)	Potentiate all sympathomimetic effects. This has not been seen with inhaled agents but there is a potential risk

MAO, monoamine oxidase.

Case Study 6-1

Acute Severe Asthma

Sally C is a 22-year-old woman with a history of asthma admitted to the ER in acute distress. Currently, she has no signs of infection but she states that her roommate recently adopted a kitten. She also admits that she has not been taking her inhalers as regularly as she had been in the past except for albuterol.

History and Physical Examination

History: This patient has been hospitalized for severe exacerbation of asthma four times over the last 3 years. Intubation was required during one admission.
Family history: Father deceased due to respiratory failure from asthma. Mother has chronic bronchitis, and brother has asthma.
Vital signs: Heart rate, 120 beats/min; blood pressure, 130/70 mm Hg; and respiratory rate, 30 breaths/min. O_2 saturation 93% on room air.
Cardiovascular: Tachycardia.
Respiratory: Patient is in severe respiratory distress. Breath sounds decreased throughout, with inspiratory and expiratory wheezes.

Laboratory Values

Chest radiograph: Hyperinflation without infiltrates.
Blood chemistry:
Electrolytes: HCO_3^- = 19 mEq/L.
Hematology: Hgb = 11.8 g/dL; Hct = 42.2%; WBC count = 9500/mm^3.

Hospital Course

Day 1: Patient was placed on oxygen 6 L/min by nasal cannula. Her FEV_1 was 45% of the predicted value. Blood was drawn for arterial blood gases and blood chemistry. Albuterol and methylprednisolone 125 mg IV (intravenous) were given immediately. An aerosol treatment via small-volume nebulizer (SVN) with 2.5 mg of albuterol in 3 mL of saline was

given with little improvement. After 20 minutes, another treatment was given; the patient improved slightly. Ipratropium nebulizer was added to albuterol. The patient continued to improve over the next 2 hours. Her FEV_1 increased to 75%, and inspiratory and expiratory wheezes decreased significantly.

Day 2: The patient continued to improve. Aerosol treatments were decreased to three times a day. Patient was titrated to room air with a SaO_2 of 95%. PEFR was 370 L/min (78% predicted).

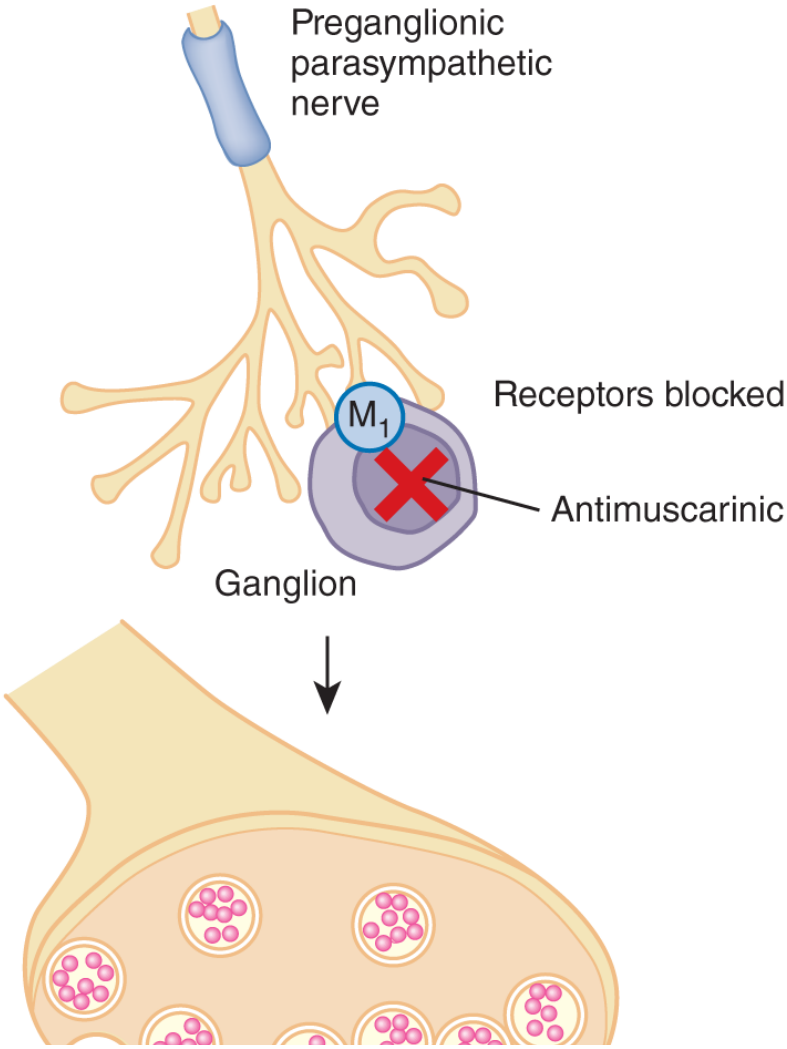
Day 3: She was discharged on prednisone 50 mg PO daily for 5 days, and aerosol treatments were changed to albuterol MDI four times a day as needed, and she was started on mometasone 100 μg/formoterol 5 μg MDI two inhalations twice daily.

Questions

1. Was continuous aerosol administration indicated in this situation? What side effects could be expected with maximal doses of β_2-agonists? What was the alternative course of action?
2. What other medications were given for this patient's asthma exacerbation?
3. What should this patient be educated on before discharge?

Anticholinergic Bronchodilators

Bronchodilators in this category are also referred to as parasympatholytics, **antimuscarinic** or muscarinic antagonists. Anticholinergic bronchodilators *block* or inhibit the effects of ACh at the muscarinic receptors in the parasympathetic system (**Figure 6-5**). In the airways, ACh is released from the nerve ending of the vagus nerve and binds to the muscarinic receptors, causing contraction or constriction of the smooth muscle in the airways secondary to the formation of cGMP in the smooth muscle cell. When ACh reaches a parasympathetic smooth muscle receptor, it stimulates the conversion of GMP to cGMP and smooth muscle constriction occurs.



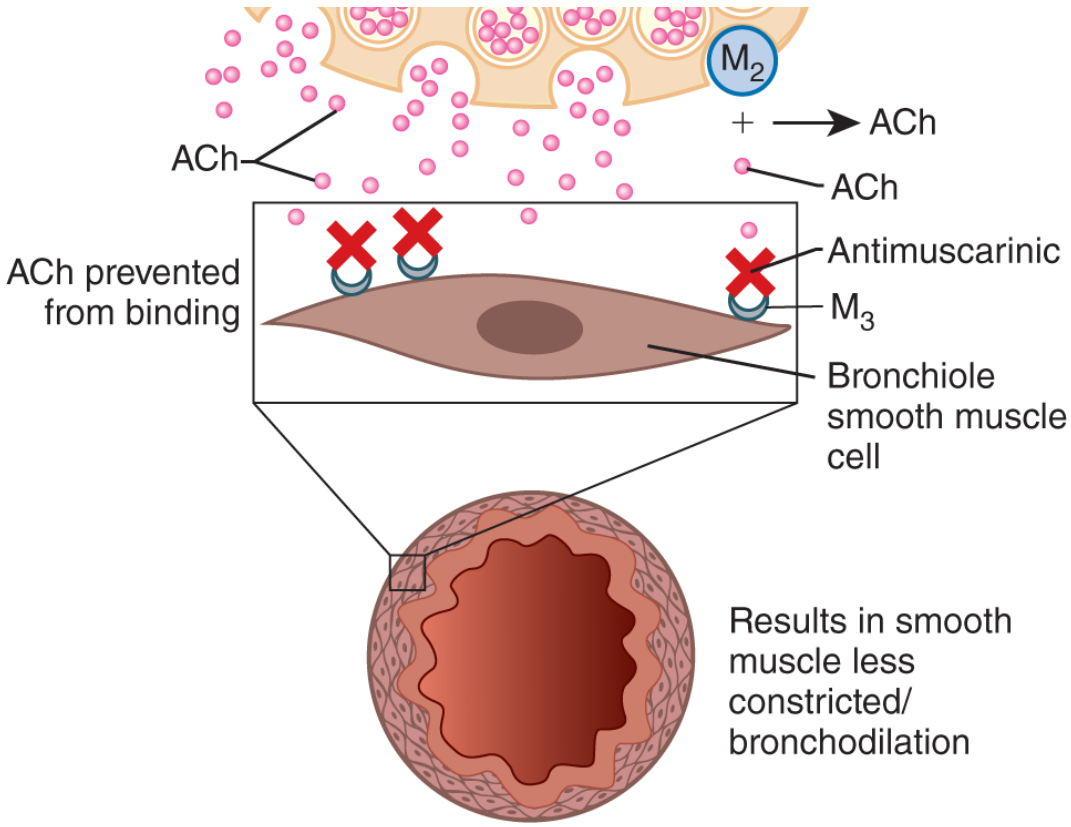


FIGURE 6-5 Mechanism of antimuscarinic bronchodilators.

Description

Stimulation of the parasympathetic nervous system causes:

1. increased secretions
2. slowing of the heart rate
3. bronchoconstriction (by stimulating cGMP)
4. pupillary constriction

There are three muscarinic receptors that are found in the lung tissue and that are affected by the anticholinergic bronchodilators: M_1, M_2, and M_3. M_1-receptors facilitate neurotransmission, and M_2-receptors are located in the presynaptic parasympathetic nerve endings and the neuromuscular junction and offset bronchodilation. The M_3-receptors are found on the neuromuscular junction and trigger bronchoconstriction and tracheal secretions. The M_3-receptors dominate the control of bronchial airway tone. Anticholinergic

bronchodilators inhibit ACh at M_1, M_2, and M_3 but the affinity and duration of activity on the M_3-receptor depend on the agent.

Use of anticholinergic (parasympatholytic) drugs to block the effects of the parasympathetic system will therefore lead to:

1. drying of the pulmonary secretions
2. increase of the heart rate
3. bronchodilation (refer to Figure 6-5)

Inhaled anticholinergics seem to be most effectively used in the control of bronchospasm associated with COPD. These agents may be more effective than β_2-adrenergic agonists in the treatment of COPD. The short-acting agent ipratropium is most frequently used in the treatment of acute bronchospasms associated with asthma and COPD. Bronchodilators, including anticholinergics, reduce air trapping and improve exercise tolerance in the COPD population. The newest inhaled anticholinergics, for example, aclidinium, glycopyrrolate, tiotropium, and umeclidinium, have extended durations of action, from 12 to 24 hours, and are used in the chronic control of bronchospasm in the treatment of COPD and asthma. The newer agents more selectively bind and inhibit activity at the M_3-receptor. Aclidinium, glycopyrrolate, ipratropium, tiotropium, and umeclidinium are quaternary amines, which do not readily cross the blood–brain barrier or other membranes, and this limits their systemic absorption and adverse effects. Cardiovascular effects are negligible with the inhaled agents. Paradoxical bronchospasms rarely occur due to antagonism at M_2-receptor.

Short-Acting Antimuscarinic Agents

The only commercially available inhaled short-acting antimuscarinic agent **SAMA** is ipratropium. Atropine has historically been used as inhaled therapy but is not currently used because of availability of ipratropium and increased adverse effects associated with its use. Bradycardia is the most common indication for atropine. It may also be used IV or IM to inhibit or decrease tracheal secretions to

facilitate intubation or in the symptomatic treatment of cholinergic toxicity or organophosphate poisoning to treat symptoms of bradycardia, excess salivation, and bronchial secretions. Dose-related tachycardia, paradoxical bradycardia (with doses <0.5 mg), palpitations, fever, confusion, agitation, urinary retention, nausea, vomiting, dysphagia, heartburn, thickening of secretions, and mucus plugging can be caused by atropine use. It should not be used in patients with narrow angle glaucoma, except for emergency situations. Ipratropium and atropine produce bronchodilation by blocking ACh at muscarinic receptors, therefore blocking the direct constrictor effects of ACh on bronchial smooth muscle. Ipratropium and atropine block all three muscarinic receptors. Ipratropium is available as a nebulizer solution, as an MDI, and in combination with albuterol. It is frequently used in addition to a SABA for the treatment of acute bronchospasms associated with COPD or in asthma when improvement is not made with a SABA alone. Bronchodilatory effects are seen within 15 minutes, which is longer than with SABAs. Because ipratropium is a quaternary amine, its side effects are limited to dry mouth, bitter taste, cough, and, very rarely, urinary retention. Paradoxical bronchospasms may rarely be seen with ipratropium. If it is accidently sprayed into the eyes, it can worsen narrow angle glaucoma or increase intraocular pressure.

Long-Acting Antimuscarinic Agents

There are currently four long-acting antimuscarinic agents (**LAMA**s) available—aclidinium, glycopyrrolate, tiotropium, and umeclidinium—and all are available in various inhalation devices (**Table 6-6**). Their duration of activity ranges from 12 to 24 hours. Glycopyrrolate is also available as an IV/IM preparation used to decrease oral or respiratory secretions and treat vagally induced bradycardia. These drugs bind to M_1-, M_2-, and M_3-receptors, but detach most rapidly from M_2-receptors, on the efferent nerve ending. This means that they do not inhibit the M_2-receptor–mediated inhibition of ACh release. They dissociate slower from the M_3-receptors, causing a

longer duration of bronchodilatory effects. These agents are indicated in the chronic treatment of COPD and have been shown to reduce the number of exacerbations and improve FEV_1. Some have been studied in the treatment of asthma, and tiotropium can be added to asthmatics that are uncontrolled on LAMA and ICS combination. The most common adverse effects include dry mouth and, rarely, urinary retention. Dry mouth usually subsides with continued therapy. Drugs in this class are also available in combination with ICS and LABAs.

TABLE 6-6
Anticholinergic Bronchodilators: Onset, Duration, and Clinical Uses

Drug	Dose	Onset of Action	Duration of Effectiveness	Clinical Indications
Aclidinium Br (Tudorza® Pressair™)	400 μg inhaled twice daily	Within 30 min	12 h	Maintenance of COPD
Atropine	Depends on indication (see drug reference for specific dosing)	Rapid onset (within 15 min)	3–6 h	*Rarely used for respiratory conditions*, newer agents are effective with fewer side effects
Glycopyrrolate (Seebri Neohaler, Lonhala Magnair)	INH: one cap inhaled twice daily NEB: 25 μg inhaled twice daily	Within 30 min	24 h	Maintenance of COPD
Ipratropium Br (Atrovent®)	MDI: two inhalations four times daily NEB: 0.5 mg NEB every 6–8 h (more frequently in exacerbations)	Within 15 min	4–6 h	COPD (chronic and acute); may be useful in acute asthma when β-agonists have not been effective when treating exacerbations
Tiotropium Br (Spiriva®)	HandiHaler: one cap (18 μg) inhaled daily Respimat: two inhalations (2.5 μg) daily	Within 30 min	Up to 24 h	Maintenance of COPD, adjunct to other therapies in chronic asthma
Umeclidinium (Anoro® Ellipta™)	One inhalation (62.5 μg) daily	Within 30 min	Up to 24 h	Maintenance of COPD

COPD, chronic obstructive pulmonary disease; INH, inhaled; MDI, metered-dose inhaler; NEB, nebulized.

NEED TO KNOW

Many of the anticholinergic bronchodilators have a generic name ending in -ium or *-tropium*, for example, aclidinium, ipratropium, tiotropium, and umeclidinium.

Table 6-6 provides a comparison of the actions and clinical indications for anticholinergic bronchodilators.

Anticholinergic Drug Interactions

Concomitant use of inhaled anticholinergics with systemic anticholinergic agents may lead to additive anticholinergic effects, but this is rarely seen. These effects may include dry mouth, confusion, tachycardia, fever, urinary retention, and blurred vision. Examples of systemic anticholinergic agents include antihistamines, tricyclic antidepressants, antipsychotics, and drugs used for the treatment of urinary incontinence.

Combination Preparations: Adrenergic/Anticholinergic and Adrenergic/Corticosteroid

Because useful additive effects have been noted when a β_2-agonist bronchodilator is administered with an anticholinergic, many COPD patients currently receive a combination of these drugs. In clinical trials, FEV_1 improved more and the duration of this improvement was sustained longer when albuterol and ipratropium were given together, in comparison to the results of each being given alone. Albuterol and ipratropium combinations are available in an oral inhalation spray (Respimat) or solution for nebulization. Also, studies have shown that a combination of LAMA and LABA reduced COPD exacerbations, had a larger impact on FEV_1 changes, and improved symptomatic dyspnea more frequently than individual agents given as monotherapy. These data may lead to more frequent use of LAMA and LABA combinations in the chronic management of COPD. There are currently five combination LAMA/LABA inhaled formulations available. Anoro® Ellipta™ combines a new long-acting bronchodilator (vilanterol) and a new anticholinergic (umeclidinium). Symbicort® (formoterol and budesonide), Dulera® (formoterol and mometasone), Advair® (salmeterol and fluticasone), and Breo® Ellipta™ (vilanterol and fluticasone) are combinations of a LABA with a corticosteroid. Breo® Ellipta® is recommended for COPD maintenance. Symbicort, Dulera, and Advair are used primarily for asthma management but will also be used for COPD. Trelegy Ellipta® is a combination of fluticasone, umeclidinium, and vilanterol used for COPD.

The LABA/corticosteroid combinations will be described in Chapter 7 (anti-inflammatory drugs). All these combination preparations (anticholinergic/β-agonist) are summarized in **Table 6-7** for reference to their clinical uses. Combination preparations also improve patient adherence by limiting the number of inhalers that must be used on a daily basis.

TABLE 6-7
Inhaled β_2-Agonist and Muscarinic-Antagonist Combination Preparations

Drug	Components	Dose	Actions	Clinical Indications
Combivent®, DuoNeb®	Ipratropium and albuterol	INH: one inhalation four times daily NEB: one vial four times daily (both may be used more frequently in exacerbations)	Anticholinergic and adrenergic bronchodilators	COPD, may be useful in acute asthma when SABA has not been effective in exacerbations
Anoro® Ellipta™	Umeclidinium and vilanterol	One inhalation daily	Anticholinergic and long-acting β-adrenergic bronchodilators	COPD maintenance
Bevespi Aerosphere	Glycopyrrolate and formoterol	Two inhalations twice daily	Anticholinergic and long-acting β-adrenergic bronchodilators	COPD maintenance
Stiolto Respimat	Tiotropium and olodaterol	Two inhalations once daily	Anticholinergic and long-acting β-adrenergic bronchodilators	COPD maintenance
Trelegy Ellipta	Vilanterol, umeclidinium, and fluticasone	One inhalation daily	Long-acting β-adrenergic and anticholinergic (bronchodilators) and corticosteroid (anti-inflammatory)	COPD maintenance
Utibron Neohaler	Olodaterol and glycopyrrolate	One capsule inhaled twice daily	Long-acting β-adrenergic and anticholinergic (bronchodilators)	COPD maintenance

COPD, chronic obstructive pulmonary disease; INH, inhaled; NEB, nebulized; SABA, short-acting β_2-adrenergic agonists.

General Bronchodilator Special Considerations

Device Selection

There are multiple factors that play a role in the appropriate device for each patient. Unfortunately, the major determinant of a patient's medication device is prescription drug coverage and cost. It is important to ensure that patients have access to the most affordable therapy available. Age and physical coordination are important characteristics that need to be assessed before deciding on the optimal aerosol device. A very young or elderly patient may have difficulty coordinating breaths needed for an MDI. A spacer or valved holding chamber device would be required in these patients.

The inspiratory flow rates required for proper administration of dry powder inhalers may not be generated by the very young, elderly, or patients with uncontrolled obstructive lung disease. An SVN may be preferable in these patient populations.

Diluents

Inhaled medications that do not come premixed require a diluent to be added to the nebulized solution. The diluent of choice for most bronchodilators should be normal saline, unless specifically contraindicated. Studies have found that bronchodilators diluted with normal saline show greater efficacy than those diluted with sterile distilled water for aerosolization or nebulization.

Continuous Bronchodilator Aerosol

Continuous administration of aerosolized bronchodilators has been helpful in selected clinical situations such as status asthmaticus, refractory bronchospasm in COPD, or cystic fibrosis. Studies have shown that continuous albuterol is more effective than intermittent treatment in patients with severe status asthmaticus in the emergency department and intensive care unit. In these situations, the patient may benefit from continuous aerosol by face mask or endotracheal tube. The specific procedure will vary, but the essential equipment required includes a large-volume nebulizer or SVN, IV bag of 0.9% sodium chloride for injection with a small-bore tubing set (volume depends on patient dosage and type of nebulizer), and appropriate IV infusion pump and tubing. The normal dosage ranges from 2.5 to 20 mg/h of albuterol. To provide continuous therapy, the dosage in mg/h, the number of hours the therapy should be provided, and the nebulizer output in mL/h are needed.

NEED TO KNOW

RCPs must know how to calculate the appropriate amount of active drug and the amount of diluent to be used for administering a continuous nebulized bronchodilator.

1. Albuterol 0.5% is ordered at 10 mg/h over 8 hours. The nebulizer output is 25 mL/h.

2. Albuterol 0.5% = 0.5 g/100 mL = 5 mg/mL.
3. 5 mg/mL = 10 mg/X mL, X = 2 mL albuterol 0.5% per hour.
4. 2 mL/h × 8 hours of therapy = 16 mL of albuterol 0.5% needed for the 8-hour treatment.
5. Nebulizer output 25 mL/h × 8 hours = 200 mL solution needs to be nebulized over 8 hours.
6. 200 mL total solution − 16 mL albuterol = 184 mL sterile normal saline diluent needed.

Methylxanthines and PDE Inhibitors

Although there are no bronchodilators in the methylxanthine/PDE inhibitor category that are administered by aerosol, it is important for the RCP to be familiar with these drugs. The RCP must be aware of the actions, side effects, and drug interactions associated with methylxanthines so that optimal patient care can be achieved safely.

Caffeine and theophylline constitute the methylxanthine group, but only theophylline and its derivatives are used therapeutically as bronchodilators. Theophylline is used as add-on therapy in the treatment of COPD and asthma. Caffeine is primarily used as a respiratory stimulant in the treatment of neonatal apnea. Aminophylline is the salt formulation of theophylline and is only available outside of the United States. The use of theophylline in respiratory conditions is limited because of the need for monitoring serum concentrations and potential for serious adverse effects. Methylxanthines are administered by oral or IV routes and have numerous effects in addition to weak bronchodilation. They promote pulmonary vasodilation, coronary vasodilation, cardiac stimulation (both rate and contractility are increased), skeletal muscle stimulation (including enhanced diaphragmatic contractility), central nervous system (CNS) stimulation (medullary), and diuresis. Theophylline has more effects in smooth muscle, and caffeine has more stimulant CNS activity.

The selective PDE inhibitor (roflumilast [Daliresp®]) has been approved by the FDA for use in COPD patients to reduce the risk of acute exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Its beneficial effects in COPD are a result of anti-inflammatory properties. It does not cause bronchodilation and is not considered a bronchodilator.

Mechanism of Methylxanthines and PDE Inhibitors

Theophylline works by multiple proposed mechanisms of action, but definitive mechanisms are still uncertain. It causes bronchodilation by inhibiting multiple PDE enzymes, PDE3, PDE4, and PDE5, which lead to an increase in cAMP and relaxation of bronchial smooth muscle. PDE enzyme inhibition and bronchodilation occur minimally at therapeutic concentrations. The clinical bronchodilating effects of theophylline are very weak. Inhaled β_2-agonists are more effective bronchodilators than theophylline. Theophylline's use for asthma and COPD is now limited to add-on therapy. Theophylline also antagonizes adenosine receptors. Adenosine causes bronchoconstriction in patients with asthma by causing a release of histamines and leukotrienes. Theophylline's anti-inflammatory effects are due to apoptosis of eosinophils and neutrophils and also cause an increase in interleukin-10, an anti-inflammatory interleukin. Theophylline has been found to be clinically effective in controlling asthma and COPD at serum concentrations of 10 mg/L. This concentration is too low to cause significant bronchodilation. Anti-inflammatory activity may be responsible for these clinical benefits in COPD and asthma. Caffeine has replaced theophylline for use in apnea of prematurity but is not used as a bronchodilator. It stimulates the respiratory center in the medulla and enhances diaphragmatic contractility. Its bronchodilating effects occur at doses that would cause significant life-threatening CNS effects.

Roflumilast inhibits PDE4, which leads to an accumulation of intracellular cAMP in inflammatory cells. This mechanism mainly causes anti-inflammatory effects such as suppression of cytokine release and a decrease in neutrophil activity in the lungs. This agent has no bronchodilating properties.

Therapeutic Use of Methylxanthines

Theophylline may be prescribed for the long-term management of bronchospasm in COPD. The Global Initiative for Chronic Obstructive Lung Disease suggests theophylline as additional therapy for COPD patients who are still symptomatic while receiving long-acting anticholinergic and/or LABAs and/or ICS. Methylxanthines have a slow onset but long duration of effectiveness and are reasonably well tolerated by many patients. The ability of methylxanthines to enhance diaphragmatic contractility contributes to their usefulness in COPD patients. The Global Initiative for Asthma recommends the addition of theophylline only in patients with chronic asthma uncontrolled on moderate-to-high dose of ICS and LABA. Theophylline should be avoided in children for the treatment of asthma due to safer available options. Theophylline and caffeine also are used in the treatment of neonatal apnea and bradycardia because of their CNS stimulation, but caffeine is used primarily for this indication. Roflumilast (Daliresp) is approved in COPD patients to reduce the risk of acute exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. It is prescribed at a fixed dose of a 500-mg tablet once daily.

Side Effects of Methylxanthines

Patients receiving methylxanthines must be closely monitored through measurement of serum levels of the drug because the therapeutic range is very narrow and quite close to toxicity. The dose of theophylline will vary on the basis of multiple patient-specific factors and serum concentrations. A theophylline serum level of 10–20 mg/L has been the traditional optimal therapeutic range, but it is now preferred to maintain an even narrower range of 5–15 mg/L. Seventy-five percent of patients whose serum level of theophylline exceeds 20 mg/L experience side effects, whereas levels greater than 35 mg/L are usually toxic and may be fatal. Side effects are manifested primarily in the CNS, cardiovascular system, or gastrointestinal system, and include the following:

1. dizziness, convulsions, or seizures

2. headache, insomnia, restlessness, irritability, and nervousness
3. palpitations, tachycardia, and arrhythmias
4. nausea, vomiting, diarrhea, epigastric pain, dyspepsia, and anorexia

Many pulmonologists are managing asthmatic patients with mast cell or leukotriene inhibitors (e.g., cromolyn sodium, nedocromil, zafirlukast, and montelukast) and reducing or eliminating the dosage of methylxanthines where possible. These antiasthmatic drugs are discussed in detail in Chapter 7. However, methylxanthines continue to have a role in the long-term management of COPD and may be useful as an adjunct in the management of chronic asthmatic patients. Roflumilast has some adverse effects similar to theophylline. The most common and serious side effects include nausea, diarrhea, decreased appetite, dyspepsia, weight loss, suicidal thoughts, anxiety, and insomnia. Roflumilast may be started at a lower dose (250 mg) for the first few weeks of starting therapy to help improve tolerability.

Description of Methylxanthines

Theophylline and its salt, aminophylline, are the primary methylxanthines used therapeutically. These drugs are marketed for oral and IV use in several forms and under many brand names. The most commonly used theophylline formulation is the sustained release or extended release tablets. Aminophylline is no longer available in the United States. Dosing ranges for methylxanthines vary on the basis of type of drug, patient's weight and age, and tolerance. Refer the Physicians' Desk Reference for specific drug information or product inserts for dosage administration guidelines. *Special considerations*: special care must be taken when administering chest physiotherapy or drawing an arterial blood gas on a patient with an IV infusion of aminophylline. Disruption or infiltration of the IV site may lead to localized irritation and tissue necrosis. This is not an issue with IV theophylline.

Methylxanthine Drug Interactions

Because theophylline is metabolized by the liver, many clinical situations will affect serum theophylline levels. The presence of liver disease, congestive heart failure, alcoholism, smoking status, and respiratory infections may alter serum theophylline levels. Drugs that compete with theophylline for metabolic activity by the liver (i.e., antibiotics) are often administered to patients with respiratory infections, resulting in fluctuation of serum theophylline levels, sometimes reaching toxicity. **Table 6-8** lists interactions of methylxanthines with other drugs.

TABLE 6-8
Methylxanthine Drug Interactions

Drug(s)	Interaction with Methylxanthines
Allopurinol (Zyloprim®)	Increases serum theophylline levels
Barbiturates	Reduce serum theophylline levels
Benzodiazepines (Valium®, Librium®, Xanax®, Halcion®, and Dalmane®)	Theophylline may antagonize sedative effect
Carbamazepine (Tegretol®)	May decrease serum theophylline levels
Cimetidine (Tagamet®)	Increases serum theophylline levels
Ciprofloxacin (Cipro®)	Increase serum theophylline levels with increased risk of side effects
Disulfiram (Antabuse®)	Increases serum theophylline levels
Fluvoxamine	Increases serum theophylline levels
Interferon	Increases serum theophylline levels
Isoniazid	May increase serum theophylline levels

Lithium	Reduces effectiveness of lithium because of increased rate of secretion
Macrolide antibiotics (erythromycin and clarithromycin only)	Increase serum theophylline levels
Mexiletine	Increases serum theophylline levels
Phenytoin (Dilantin®)	Decreases serum theophylline levels
Rifampin	Decreases serum theophylline levels
Riociguat	Additive adverse effects when used with theophylline
Ritonavir	Decreases serum theophylline levels
Tobacco smoking	Reduces effectiveness of theophylline
Zileuton	Increases serum theophylline levels

Case Study 6-2

COPD

A 57-year-old woman is being seen in the pulmonary and respiratory clinic for assessment of COPD. She has had recurrent exacerbations of COPD. Her chief complaints are worsening shortness of breath, yellow sputum production, and general malaise.

History and Physical Examination

History: The patient was diagnosed as having COPD 1 year ago. She has hypertension and hyperthyroidism and has a 40 pack-year smoking history. Her FEV_1 6 months ago = 1.9 L.
Vital signs: Heart rate, 90 beats/min; respiratory rate, 20 breaths/min; blood pressure, 150/90 mm Hg; and temperature, 38°C.
Neurologic: Pupils equal and react to light and accommodation.
Cardiovascular: No jugular venous distension.
Respiratory: Expiratory wheezes and decreased breath sounds. Use of accessory muscles. FEV_1 = 1.77 L before bronchodilator and 1.84 L after bronchodilator.

Laboratory Values

Chest radiograph: Mild diffuse emphysema. No heart failure, pneumonia, or pleural effusion.

Electrolytes: Na^+ = 139 mEq/L; K^+ = 4.6 mEq/L; Cl^- = 95 mEq/L; HCO_3^-= 30 mEq/L.

Hematology: Hgb = 15.8 g/dL; WBC count = 9400/mm^3.

Home Medications

Ipratropium/albuterol (Combivent) Respimat one inhalation four times daily as needed for shortness of breath.
Amlodipine 10 mg PO daily for hypertension.

Respiratory Care

1. Albuterol 2.5 mg/ipratropium 0.5 mg aerosol solution/3 mL nebulized now.
2. Bronchial hygiene and airway clearance.

Days 1–3: Prednisone 40 mg PO daily was prescribed. A sputum sample was obtained. Gram stain revealed gram-positive cocci in chains. A sputum culture and sensitivity test were ordered. Antibiotic therapy with clarithromycin was started.
Day 7 postvisit: The patient's symptoms have improved and she is feeling better.

Questions

1. What medication changes would be necessary to her COPD medications to control her daily symptoms of shortness of breath?
2. What concerns would you have with starting theophylline therapy in this patient?
3. What other patient education would be helpful to prevent or reduce future exacerbations?

Magnesium

IV and nebulized magnesium have been used as an adjunctive bronchodilator in patients with severe, life-threatening asthma exacerbations. It should be considered in patients with life-threatening asthma exacerbations who fail to respond to initial therapy. Studies have shown that 2 g of magnesium sulfate IV over 20 minutes may prevent hospitalizations and improve lung function in patients presenting to the emergency department with severe asthma exacerbations or FEV_1 less than 25%. Nebulized isotonic magnesium has been used in children under 5 years old with asthma exacerbations as an adjunct to albuterol and ipratropium.

Mechanism of Bronchodilation Using Magnesium

Magnesium sulfate appears to cause smooth muscle relaxation by reducing cellular Ca_2^+ concentrations in airway smooth muscle cells. It has also been thought that magnesium may reduce neutrophils involved in the inflammatory process and decrease ACh, histamine, and mast cell release. The most common adverse effects reported were flushing, fatigue, nausea, headache, and hypotension.

Review Questions

1. Define bronchoconstriction.
2. Describe three mechanisms (causes) of bronchoconstriction.
3. Describe appropriate respiratory care for the reversal of bronchoconstriction caused by bronchospasm.
4. Describe the reaction within a bronchial smooth muscle cell when a β_2-receptor is stimulated.
5. What is cyclic 3′,5′-AMP (cAMP)? What is its role in the relief of bronchospasm?
6. What is PDE? How does it affect cAMP?
7. What is the effect of cholinergic stimulation of a bronchial smooth muscle cell?
8. List three categories of bronchodilators, defined by their mechanism of action.
9. Draw a diagram of the chemical mediators and reactions that occur when a sympathomimetic (β-adrenergic) bronchodilator is given.
10. Define anticholinergics and describe how parasympatholytic bronchodilators achieve relief of bronchospasm (what is the mechanism of action?).
11. List three categories of sympathomimetics and drugs in each class.
12. Describe the mechanism of action, drug class, most common adverse effects, and differences in clinical use of epinephrine, albuterol, terbutaline, and salmeterol.
13. List two categories of anticholinergic bronchodilators and drugs in each class.
14. Describe the mechanism of action, drug class, most common adverse effects, and differences in clinical use of atropine, ipratropium, and tiotropium.
15. Why would a patient be receiving both an anticholinergic and a β-agonist for control of bronchospasm?

16. Why are methylxanthines used in the management of COPD? List at least three therapeutic effects of methylxanthines.
17. Describe how methylxanthines achieve relief of bronchospasm (what is the mechanism of action?).
18. List the most common drugs or categories of drugs that interact with sympathomimetic bronchodilators. Describe the effects of these drug interactions.
19. List the most common drugs or categories of drugs that interact with anticholinergic bronchodilators. Describe the effects of these drug interactions.
20. List at least five drugs or categories of drugs that interact with methylxanthines. Describe the effects of these drug interactions.

Posttest

For each of the following questions, try to select the one best answer from the choices given.

1. Which of the following terms is synonymous with β-adrenergic?
   a. Parasympatholytic
   b. Sympathomimetic
   c. Anticholinergic
   d. Antimuscarinic
2. Which of the following drugs is a sympathomimetic bronchodilator? (Select all that apply.)
   a. Terbutaline
   b. Albuterol
   c. Theophylline
   d. Vilanterol
   e. Ipratropium bromide
3. Which of the following drugs stimulate production of cAMP by stimulating β_2-adrenergic receptors?
   a. Metaproterenol
   b. Formoterol
   c. Albuterol
   d. All of the above stimulate β_2-adrenergic receptors
4. Which of the following is a brand name of tiotropium?
   a. Serevent®
   b. Atrovent®
   c. Spiriva®
   d. Combivent®
5. Which of the following drug mechanisms promote bronchodilation?
   a. Increase levels of cGMP
   b. Increase levels of cAMP
   c. Decrease levels of cAMP
   d. Increase levels of PDE

6. Which of the following drugs are methylxanthines? (Select all that apply.)
   a. Theophylline
   b. Aminophylline
   c. Caffeine
   d. Terbutaline
7. What are three categories of bronchodilators?
   a. Sympatholytics, anticholinergics, and methylxanthines
   b. Parasympathomimetics, cholinergics, and methylxanthines
   c. Parasympatholytics, cholinergics, and methylxanthines
   d. Muscarinics, anticholinergics, and methylxanthines
8. Drying of secretions and mucus plugging may occur as a side effect from the use of which bronchodilator?
   a. Ipratropium
   b. Albuterol
   c. Aminophylline
   d. Magnesium
9. A COPD patient has been taking Advair® (salmeterol and fluticasone) and continues to complain of dyspnea throughout the day. The respiratory therapist should recommend adding which of the following agents to his or her regimen to control shortness of breath throughout the day?
   a. Formoterol
   b. Atropine
   c. Theophylline
   d. Tiotropium
10. Which of the following side effects may occur with the use of β-agonists?
    a. Appetite suppression
    b. Tremor
    c. Hematemesis
    d. Seizures
11. Which of the following bronchodilators can be used in the treatment of acute bronchospasms? (Select all that apply.)
    a. Umeclidinium
    b. Ipratropium

c. Theophylline
d. Albuterol
e. Formoterol
f. Levalbuterol

12. Which of the following is a brand name of levalbuterol?
    a. Xopenex®
    b. Serevent®
    c. Ventolin®
    d. Atrovent®
13. Which of the following agents is the drug of choice in the presence of upper airway mucosal edema?
    a. Terbutaline
    b. Albuterol
    c. Racemic epinephrine
    d. Formoterol
14. Which of the following medications would be the most appropriate first-line agent used to treat bronchospasm associated with an acute asthmatic attack?
    a. Atropine
    b. Magnesium
    c. Albuterol
    d. Ipratropium
15. Which of the following drug classes may cause an increased effect of dry mouth if used concomitantly with ipratropium?
    a. β-Blockers
    b. Tricyclic antidepressants
    c. Adrenergic agents
    d. Digoxin
16. Which of the following drug classes should never be used as monotherapy in the treatment of chronic asthma?
    a. ICSs
    b. LABA
    c. SABA
    d. Combination ICSs and LABAs
17. Theophylline produces bronchodilation by inhibiting PDE enzymes, resulting in an increase in cAMP, and is considered the most

effective bronchodilator. True or False?

18. Which of the following agents, if used with theophylline, may lead to increases in theophylline concentrations and potential toxicity?
    a. Ciprofloxacin
    b. Albuterol
    c. Phenytoin
    d. Tobacco

References/Recommended Readings

Ameredes BT, Calhoun WJ. Levalbuterol versus albuterol. *Curr Allergy Asthma Rep*. 2009;9:401-409.

Andrews T, McGintee E, Mittal MK, et al. High-dose continuous nebulized levalbuterol for pediatric status asthmaticus: a randomized trial. *J Pediatr*. 2009;155:205-210.

Barnes PJ. Pulmonary pharmacology. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics.* 13th ed. New York, NY: McGraw-Hill. http://accesspharmacy.mhmedical.com.libproxy.temple.edu/content.aspx?bookid=2189&sectionid=172481165. Accessed January 04, 2018.

Bellia V, Foresi A, Bianco S, et al. Efficacy and safety of oxitropium bromide, theophylline, and their combination in COPD patients: a double-blind, randomized, multicenter study (BREATH Trial). *Respir Med*. 2002;96:881-889.

Bianco S, Vaghi A, Robuschi M, et al. Prevention of exercise-induced bronchoconstriction by inhaled furosemide. *Lancet*. 1988;2:252-255.

Boscia JA, Pudi KK, Zvarich MT, et al. Effect of once-daily fluticasone furoate/vilanterol on 24-hour pulmonary function in patients with chronic obstructive pulmonary disease: a randomized, three-way, incomplete block crossover study. *Clin Ther*. 2012;34(8):1655-1666.

Calzetta L, Rogliani P, Ora J, et al. LABA/LAMA combination in COPD: a meta-analysis on the duration of treatment. *Eur Respir Rev*. 2017;26:160043. doi:10.1183/16000617.0043-2016

Camargo CA Jr, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. *Cochrane Database Syst Rev*. 2003;(4):CD001115. doi:10.1002/14651858.CD001115

Carl JC, Myers TR, Kirchner HL, et al. Comparison of racemic albuterol and levalbuterol for treatment of acute asthma. *J Pediatr*. 2003;143:731-736.

Chin T, Franchi L, Nusabaum E. Reversal of bronchial obstruction in children with mild stable asthma by aerosolized furosemide. *Pediatric Pulmonol*. 1994;18:93-98.

Decramer M, Celli B, Kesten S. Effect of tiotropium on outcomes in patients with moderate COPD (UPLIFT): a prescribed subgroup analysis of a randomized controlled trial. *Lancet*. 2009;374(9696):1171-1178.

Decramer ML, Hanania NA, Lotvall JO, Yawn BP. The safety of long-acting β_2-agonists in the treatment of stable chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2013;8:53-64.

Emerman CL, Cydulka RK, Effron D, et al. A randomized, controlled comparison of isoetharine and albuterol in the treatment of acute asthma. *Ann Emerg Med*. 1991;20(10):1090.

Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with long-acting bronchodilators: two randomized clinical trials. *Lancet*. 2009;374:695-703.

Gawchik SM, Saccar CL, Noonan M, et al. The safety and efficacy of nebulized levalbuterol compared with racemic albuterol and placebo in the treatment of asthma in pediatric patients. *J Allergy Clin Immunol*. 1999;103:615-621.

Global Initiative for Asthma. Global Initiative for Asthma Web site. 2017. https://www.ginasthma.org

GOLD (Global Initiative for Chronic Obstructive Lung Disease, Inc.). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2017. https://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/

Goodacre S, Cohen J, Bradburn M, et al. Intravenous or nebulized magnesium sulphate versus standard therapy for severe acute asthma (3 mg trial): a double-blind, randomized controlled trial. *Lancet Respir Med*. 2013;1:293-300.

Gross NJ, Petty TL, Friedman M. Dose response to ipratropium as a nebulized solution in patients with COPD. *Am Rev Respir Dis*. 1989;139:1188-1191.

Hanania NA, Feldman G, Zachgo W, et al. The efficacy and safety of the novel long-acting β_2 agonist vilanterol in patients with COPD: a randomized placebo-controlled trial. *Chest*. 2012;142(1):119-127.

Ide T, Nichols DG, Buck JR, et al. Effect of aminophylline on high-energy phosphate metabolism and fatigue in the diaphragm. *Anesthesiology*. 1995;83(3):557.

Jones PW, Singh D, Bateman ED, et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. *Eur Respir J*. 2012;40(4):830-836.

Karpel J, Dworkin F, Hager D. Inhaled furosemide is not effective in acute asthma. *Chest*. 1994;106:1396-1400.

Kew KM, Kirtchuk L, Michell CI. Intravenous magnesium for treating adults with acute asthma in the emergency department. *Cochrane Database Syst Rev*. 2014;(5):CD010909. doi:10.1002/14651858.CD010909.pub2.

Kondili E, Alexopoulou C, Prinianakis G, et al. Effect of albuterol on expiratory resistance in mechanically ventilated patients. *Respir Care*. 2011;56:626-632.

Konig P, Gayer D, Barbero GJ, et al. Short-term and long-term effects of albuterol aerosol therapy in cystic fibrosis: a preliminary report. *Pediatr Pulmonol*. 1995;20:205.

Kornberg AE, Zuckerman S, Welliver JR. Effect of injected long-acting epinephrine in addition to aerosolized albuterol in the treatment of acute asthma in children. *Pediatr Emerg Care*. 1991;7:1.

Lam S, Chen J. Changes in heart rate associated with nebulized racemic albuterol and levalbuterol in intensive care patients. *Am J Health Syst Pharm*. 2003;60:1971-1975.

Levin DC, Little KS, Laughlin KR. Ipratropium bromide solution in COPD augments extent and duration of FEV_1 increases achieved by albuterol up to 85 days. *Chest*. 1993;104:112S.

Lockhart A, Slutsky A. Furosemide and loop diuretics in human asthma. *Chest*. 1994;106:244-249.

Moita J, Barbara C, Cardoso J. Tiotropium improves FEV_1 in patients with COPD irrespective of smoking status. *Pulm Pharmacol Ther*. 2008;21(1):146-151.

Nannini LJ, Pendino JC, Molfino NA. Inhaled furosemide and salbutamol in acute asthma. *Am Rev Respir Dis.* 1992;145:A422.

Nelson HS, Weiss ST, Bleecker ER, et al; SMART Study Group. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006;129:15-26.

Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of COPD with tiotropium, a once-daily inhaled anticholinergic bronchodilator. *Ann Intern Med*. 2005;143(5):317-326.

Oba Y, Lone NA. Comparative efficacy of long-acting muscarinic antagonists in preventing COPD exacerbations: a network meta-analysis and meta-regression. *Ther Adv Respir*

Dis. 2015:9;3-15.
Orlowski L, Zychowicz C, Migdał M, et al. Effect of salbutamol on specific airway resistance in infants with a history of wheezing. *Pediatr Pulmonol*. 1991;10:191.
Pendino C, Nannini LJ, Chapman, KR, et al. Effect of inhaled furosemide in acute asthma. *J Asthma*. 1998;35(1):89-93.
Peters SP, Bleecker ER, Canonica GW, et al. Serious asthma events with budesonide plus formoterol vs. budesonide alone. *N Engl J Med*. 2016:375;850-860.
Proventil HFA [package insert]. Whitehouse Station, NJ: Merck & Co. Inc.; 2012.
Rajakulasingam K, Polosa R, Church MK, et al. Effect of inhaled furosemide on responses of airways to bradykinin and adenosine 5′-monophosphate in asthma. *Thorax*. 1994;49:485-491.
Rossi A, Kristufek P, Levine BE, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. *Chest*. 2002;121:1058-1069.
Rowe BH, Bretzlaff JA, Bourdon C, et al. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. *Cochrane Database Syst Rev*. 2000; (2):CD001490.
Sestini P, Pieroni MG, Refini RM, et al. Time-limited protective effect of inhaled furosemide against aspirin-induced bronchoconstriction in aspirin-sensitive asthmatics. *Eur Respir J*. 1994;7:1825-1829.
Sims M, Panettieri R. Profile of aclidinium bromide in the treatment of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2016;6:457-466.
Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with COPD: systematic review with meta-analysis. *JAMA*. 2008;300(12):1439-1450.
Sorkness CA. Beta-adrenergic agonists. In: Adkinson NF, Bochner BS, Busse WW, et al, eds. *Middleton's Allergy: Principles and Practice*. 7th ed. Philadelphia, PA: Mosby; 2009:1485-1503.
Spitzer WO, Suissa S, Ernst P. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med*. 1992;326:501.
Travers AH, Rowe BH, Barker S, Jones A, Camargo CA Jr. The effectiveness of IV beta-agonists in treating patients with acute asthma in the emergency department: a meta-analysis. *Chest*. 2002;122(4):1200.
U.S. Food & Drug Administration. FDA Drug Safety Communication: drug labels now contain updated recommendations on the appropriate use of long-acting inhaled asthma medications called long-acting beta-agonists (LABAs). Safety Announcement. http://wayback.archive-it.org/7993/20170112031853/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm. Accessed January 10, 2018.
U.S. Food & Drug Administration. FDA Drug Safety Communication: FDA review finds no significant increase in risk of serious asthma outcomes with long-acting beta-agonists (LABAs) used in combination with inhaled corticosteroids (ICS). Safety Announcement. https://www.fda.gov/Drugs/DrugSafety/ucm589587.htm. Accessed January 10, 2018.
Undem BJ, Kollarik M. The role of vagal afferent nerves in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2005;2(4):355-360.
Vahedi HSM, Mahshidfar B, Rabiee H, et al. The adjunctive effect of nebulized furosemide in acute treatment of patients with chronic obstructive pulmonary disease with exacerbation: a randomized controlled clinical trial. *Respir Care*. 2013;58:1873-1877.

Vilsvik J, Schaanning J, Stahl E, et al. Comparison between Bricanyl Turbuhaler and Ventolin metered dose inhaler in the treatment of exercise-induced asthma in adults. *Ann Allergy*. 1991;67(3):315.

Vogelmeier C, Kardos P, Harari S, et al. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study. *Respir Med*. 2008;102(11):1511-1520.

Waisman Y, Kein BL, Boenning DA, et al. Prospective randomized double-blind study comparing L-epinephrine and racemic epinephrine aerosols in the treatment of laryngotracheitis (croup). *Pediatrics*. 1992;89(2):302-306.

Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med*. 2016;374(23):222-234.

Xopenex HFA [package insert]. Marlborough, MA: Sunovion Pharmaceuticals Inc.; 2015.

Yohannes AM, Willgoss TG, Vestbo J. Tiotropium for treatment of stable COPD: a meta-analysis of clinically relevant outcomes. *Respir Care*. 2011;56(4):477-487.

Zhou Y, Wang X, Zeng X, et al. Positive benefits of theophylline in a randomized, double-blind, parallel-group placebo-controlled study of low-dose slow-release theophylline in the treatment of COPD for 1 year. *Respirology*. 2006;11:603-610.

© Anna RubaK/ShutterStock, Inc.

OUTLINE

Introduction
Bronchoconstriction and Mucosal Edema
  Alpha-Adrenergic Sympathomimetic Drugs Used in Mucosal Edema
Asthma
  Asthma Management in Adults and Youths ≥12 Years of Age
  Asthma Management in Children
  Peak Flow Monitoring
  Managing an Acute Asthma Episode (Status Asthmaticus)
Corticosteroid Anti-inflammatory Drugs
  Advantages and Disadvantages of Aerosolized Corticosteroids
  Indications for ICSs
  Side Effects/Adverse Reactions of Aerosolized Corticosteroids
Antiasthmatic Drugs
  Mast-Cell Stabilizers
  Leukotriene Modifiers
  Immunomodulators

OBJECTIVES

After completion of this chapter and its learning activities, you will be able to:

1. Describe mucosal edema and how it relates to difficulty breathing or respiratory distress.
2. List the clinical conditions or diseases that may lead to bronchoconstriction caused by mucosal edema and therapies used for the treatment.
3. Recommend a dose and list the important adverse effects that need monitoring and special considerations in the use of racemic epinephrine.
4. Describe the pathophysiology of asthma and the rationale for using corticosteroid therapy for control of asthmatic symptoms.
5. Describe the mechanism of action of corticosteroids used in the treatment of airway inflammation.
6. List the brand and generic names of inhaled corticosteroids used in the treatment of airway inflammation as well as its adverse effects and contraindications.
7. Describe the mechanism of action of leukotriene inhibitors and antagonists.
8. Distinguish between controlled and uncontrolled asthmatic patients and determine who would benefit most from the use of a monoclonal antibody.
9. Suggest the most appropriate drug therapy, including the drug(s) of choice, route of delivery, and recommended dosage(s), given a patient case study.

KEY TERMS

Antiasthmatic monoclonal antibodies
Asthma
Corticosteroid
Croup
Eosinophils
Histamine
ICS
Leukotriene inhibitors or antagonists
Mast cells
Mast-cell stabilizers
Mucosal edema
Racemic epinephrine
Status asthmaticus

Introduction

Drugs that reduce inflammation and swelling in the airway often are aerosolized and may be used for the management of acute inhalational injuries (e.g., poisonous fumes and steam), laryngeal trauma (e.g., intubation/extubation) or infection (e.g., **croup**), severe allergic reactions (e.g., anaphylaxis), and in both acute and chronic asthma and chronic obstructive pulmonary disease (COPD). Drugs in this category can be α-stimulants, which reduce mucosal edema by vasoconstriction, or **corticosteroid**s, which have a nonspecific anti-inflammatory action. Mucosal edema within the airway may be a life-threatening situation that requires immediate treatment. Providing an aerosolized drug directly to the airway may improve ventilation and reduce hypoxemia rapidly, enhancing the effectiveness of systemic drugs.

Both asthma and COPD are diseases where inflammation plays a role in the development or in the pathophysiology of the disease. Inflammation in COPD is minimally reversible compared with asthma. Therefore, drug therapy that treats inflammation is not the mainstay of therapy in patients with COPD. Corticosteroids may be used in some COPD patients, but with less benefit than with asthmatics. Current research regarding asthma and its clinical management suggests that treating the chronic inflammation of the mucosa in the lower airways should be the main treatment target. Common drug classes that target inflammation and used in the management of asthma include corticosteroids and **leukotriene inhibitors or antagonists** (e.g., montelukast, zafirlukast, and zileuton). Cromolyn sodium is an agent that can inhibit the release of inflammatory mediators from **mast cells** and has historically been used to treat asthma but has fallen out of favor due to more effective agents being developed. **Antiasthmatic monoclonal antibodies** that target inflammation have been used in patients with severe asthma who are resistant to high-dose inhaled corticosteroids (**ICSs**) or severe

asthma with an allergic or eosinophilic component nonresponsive to other therapies.

Respiratory care practitioners (RCPs) are often among the first healthcare providers to treat patients who present with difficulty breathing. It is vitally important that RCPs understand the pathology of a patient who has difficulty breathing and are able to suggest and deliver the most appropriate drug to improve the clinical situation. In many cases, a combination of drugs may be appropriate; in other cases, the administration of a bronchodilator for a patient who is suffering from mucosal edema may be inappropriate and may waste precious time. It is equally important that RCPs understand which drugs have immediate effect in the relief of symptoms in contrast to those agents that are preventive or that require more time to take effect.

Bronchoconstriction and Mucosal Edema

Mucosal edema refers to the accumulation of fluid within the mucosal membrane. When this process occurs within the airway, this membrane then invades the airway lumen because all structures in the airway are bound by cartilaginous support (**Figure 7-1**). When someone inhales an antigen and it enters the nose, the response is a sneeze, followed by a “stuffy and runny nose.” The same response in the lungs results in a cough, followed by bronchoconstriction and increased mucus production. The response in the lungs, however, may become life-threatening if the mucosal edema causes enough airway restriction to limit ventilation. This scenario could lead to hypercarbia and hypoxia, which may contribute to cardiac arrhythmias and sudden death.

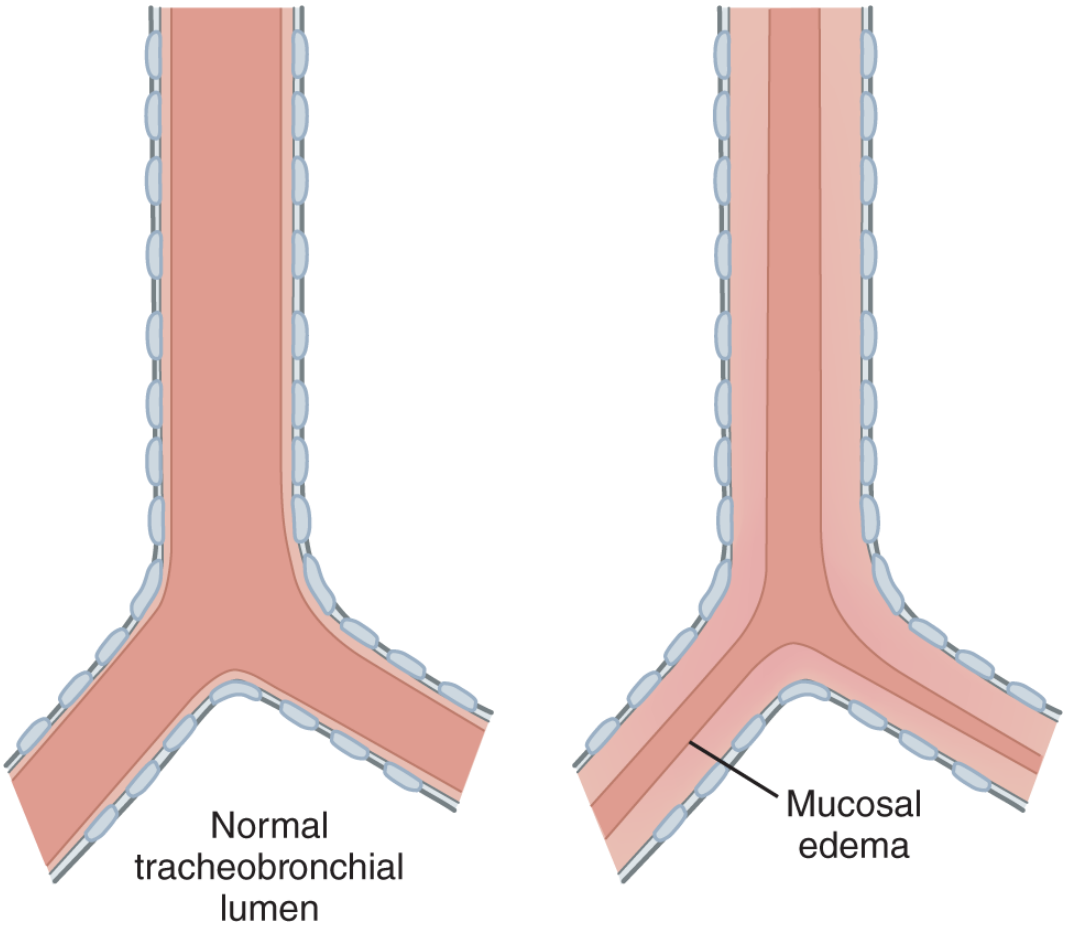


FIGURE 7-1 Bronchoconstriction due to mucosal edema.

There are several pulmonary injuries, infectious processes, and diseases or conditions that may cause mucosal edema (**Table 7-1**). Mucosal edema can occur in the upper airways (e.g., mouth, oropharynx, and larynx) such as in the case of croup, angioedema, intubation/extubation injury, and others can lead to lower airway edema (e.g., asthma, bronchitis, and anaphylaxis). The degree of severity of each disorder is difficult to predict, but clinical signs and symptoms usually determine the appropriate treatment decisions. In severe cases, mechanical ventilation will be needed. When it can be determined that a patient who is experiencing difficulty breathing may have been exposed to one of the causes listed in **Table 7-1**, treatment will depend on if the edema is located in the upper airway, lower airway, and presumed cause. In severe and life-threatening situations of anaphylaxis, the drug should be given systemically (e.g., intravenous [IV] or intramuscular [IM]). If an IV line cannot be established or perfusion is poor, the drug may be instilled directly through an endotracheal tube or a transtracheal catheter. In less severe situations of upper airway edema, such as laryngeal edema from extubation, aerosolized administration of an α-adrenergic drug may be indicated to reduce airway swelling. Aerosolized administration of the drug provides rapid therapeutic response with few systemic side effects. In clinical situations where an allergic reaction is the suspected cause of airway edema, a **histamine**-1 receptor antagonist (e.g., diphenhydramine; Benadryl) and an IV corticosteroid will also be administered. An inhaled bronchodilator is the treatment of choice in patients with airway edema from asthma or COPD.

TABLE 7-1
Causes of Pulmonary Mucosal Edema

Infectious processes
Croup (tracheolaryngobronchitis)
Epiglottitis

- Bronchiolitis

Trauma
- Intubation/extubation
- Laryngeal injury
- Smoke inhalation
- Poisonous fumes inhalation
- Superheated air or steam inhalation

Diseases
- Bronchitis
- Asthma

Conditions
- Angioedema (e.g., allergic, hereditary, or drug-induced)
- Severe allergic reactions
- Anaphylaxis

NEED TO KNOW

Mucosal airway edema is fluid accumulation in the mucous membrane of the airways. Edema can occur in the upper and lower airways, which may lead to mild-to-severe symptoms requiring mechanical ventilation. An α-adrenergic agonist administered IV, IM, or by aerosol or an aerosolized bronchodilator may be administered depending on severity of symptoms and location of airway edema.

Alpha-Adrenergic Sympathomimetic Drugs Used in Mucosal Edema

There are several α-adrenergic drugs available, but only one is commonly used by RCPs for the reversal or reduction of mucosal edema. **Racemic epinephrine**, a modified form of epinephrine, typically is administered by small-volume nebulizer (SVN) or in-line for mechanically ventilated patients as discussed in Chapter 5 and is used for upper airway edema. It is the drug of choice in the treatment of bronchoconstriction associated with mucosal edema (e.g., croup, postextubation laryngeal edema, and inhalation injuries). It is rapidly metabolized and can be given safely as frequently as every hour with close monitoring. Racemic epinephrine is a sympathomimetic amine that stimulates production of cyclic 3′5′-adenosine monophosphate by

acting on α-, β_2-, and β_1-receptors. The mechanism responsible for improvement of airway edema through the inhaled route is by acting as an α-agonist that causes vasoconstriction to reduce airway mucosal edema. It has a rapid onset of action and its activity lasts for 30–60 minutes. The typical dose is 0.25–0.50 mL of 2.25% solution (0.50 mL of 2.25% solution = 11.25 mg racemic epinephrine) in 3 mL of diluent, administered by aerosol every 1–2 hours. Adverse effects include tachycardia, hypertension, and headache but are minimal compared with systemically administered epinephrine. Epinephrine is not given as an aerosol by SVN because of its profound cardiac side effects but is administered intramuscularly or subcutaneously in the case of severe allergic reactions or anaphylaxis. It may be administered subcutaneously or intramuscularly in severe asthma exacerbations as an adjunct to other first-line options. The dose is 0.3–0.5 mg every 20 minutes up to three doses in adults or 0.01 mg/kg in pediatric patients for either indication. When epinephrine is administered subcutaneously or intramuscularly for the treatment of asthma or anaphylaxis, there is a risk for tachycardia, hypertension, palpitations, and arrhythmias.

NEED TO KNOW

Racemic epinephrine administered by inhalation is the drug of choice for treating upper airway inflammation, such as croup, postextubation laryngeal edema, or inhalation injuries (i.e., smoke, steam, or poisonous fumes inhalation).

Asthma

Asthma is one of the most common chronic lung diseases, affecting individuals of all ages and in all degrees. Prevalence and mortality of asthma have been increasing over the past decade; it is now estimated that more than 7.6% of the U.S. adult population and up to 8.5% of children are affected by asthma. Combinations of genetic and environmental factors are the main etiology in the development of asthma. The major characteristics of asthmatics include airway obstruction due to bronchospasm, mucosal edema, and excess mucus production and inflammation. When patients with asthma are exposed to environmental allergens, **mast cells**, **eosinophils**, and macrophages become activated and lead to contraction of the airways and mucus production. The sputum of the asthmatic is often thickened and viscid (sticky), with significant eosinophilia. Chronically, these cells lead to airway remodeling and fibrosis. Asthmatic symptoms include dyspnea, chest tightness, wheezing and persistent cough, which occur during the day and may awake the patient at night. These symptoms may occur after exercise, when exposed to allergens or unexpectedly. The mainstay of therapy for asthma targets and controls inflammation. Management of asthma usually involves the concurrent use of multiple medications for control of both symptoms and etiology of asthma attacks. The goals of asthma therapy are to control symptoms, maintain normal activity, and prevent acute asthma symptoms or exacerbations. Patients should be instructed to monitor their asthma control using a peak flowmeter at home on a regular basis. Asthma is largely manageable with monitoring and proper use ofmedication therapy, but is still responsible for significant morbidity and mortality when a patient experiences an acute attack that is not responsive to emergency treatment. When a patient exhibits severe dyspnea, hypoxemia, and airway obstruction that is not responding to aggressive bronchodilator therapy, the condition is referred to as **status asthmaticus**. It is important for the RCP to fully understand the rationale for using all

drugs employed in asthma management, for both in-patient care and providing effective patient education in an ambulatory setting.

Case Study 7-1

Postextubation Stridor

Tommy N, a 35-year-old white, obese (192 kg [422 lb]) male, presented in the emergency department (ED) with a complaint of shortness of breath (SOB). The patient had been having difficulty breathing for a long time, with extreme loud snoring and daytime somnolence. The patient also had been experiencing inability to stay awake, with periods of apnea during sleep. Over the past 4 days, the patient's dyspnea worsened until he could not walk to the bathroom. He had been sleeping sitting up. Shortly after admission, the patient went into respiratory failure and was intubated. Arterial blood gases on room air at that time were as follows: pH = 7.30, $PaCO_2$ = 63 torr, PaO_2 = 47 torr, and HCO_3^- = 28.5 mEq/L. The patient is believed to have obstructive sleep apnea.

History and Physical Examination

History: Previous abdominal surgery (unknown procedure).
Social history: Smokes 2 packs/day; does not use alcohol. Unemployed.
Vital signs: Blood pressure (BP) = 166/106 mm Hg, temperature =37°C, and heart rate (HR) = 100 beats/min.
Neurologic: Pupils equal and react to light and accommodation.
Cardiovascular: Heart beat distant but regular.
No jugular venous distension.
Respiratory: Basilar fine crackles.
Gastrointestinal: Old healed abdominal scar, unable to palpate liver or spleen.
Extremities: 4+ Pedal edema.

Laboratory Values

Chest radiograph: Cardiomegaly with bilateral, fluffy infiltrates, and pulmonary edema.
Electrolytes: Within normal limits.
Hematology: Red blood cell count = 5.34 M/mm^3, Hgb = 16 g/dL, and white blood cell count = 21,000/mm^3.

Hospital Course

Days 1–3: The patient's ventilator settings are as follows: A/C = 14, V_t = 800 mL, F_iO_2 = 0.5, and SaO_2 = 97%. Wheezes were heard throughout the lungs and suctioning returned a large amount of yellow secretions from the endotracheal tube.
Medications: Lasix®, Captopril®, metered-dose inhaler (MDI) albuterol, cefazolin, acetaminophen, and morphine.
Days 4–6: Pitting edema is improved and patient is more arousable. The patient has lost 17.5 kg since admission. On day 4, the patient was started on a pressure support trial of 5 cm H_2O. Pressure support trials were progressively lengthened until, on day 6, the

pulmonary function parameters indicated the patient could be extubated. Following extubation, the patient developed stridor.

Questions

1. What could be causing this patient's postextubation respiratory difficulty?
2. What respiratory drug could you recommend to the physician that would help relieve the patient's stridor? Explain the rationale for your recommendation.

Asthma Management in Adults and Youths ≥12 Years of Age

Asthma management has been a topic of interest for the National Institutes of Health (NIH) and the National Heart, Lung, and Blood Institute (NHLBI) for the past two decades. The initial Expert Panel Report (EPR-1) was published in 1991, and the current guidelines were published in 2007. The Global Initiative for Asthma (GINA) also collaborates with NHBLI and the World Health Organization (WHO), publishes updated guidelines, and reports on the management and prevention of asthma on an annual basis. These reports provided new asthma classifications (intermittent, mild persistent, moderate persistent, and severe persistent) and a stepwise approach for the management of each classification. Management of the stable asthmatic patient includes the use of β-agonists and inhaled anti-inflammatory drugs (i.e., corticosteroids). **Mast-cell stabilizers** (i.e., cromolyn sodium and nedocromil) or leukotriene inhibitors or antagonists (i.e., montelukast, zafirlukast, and zileuton) may be added to therapy as prophylactic agents. Some patients also require oral xanthines (i.e., theophylline preparations). For severe persistent asthma or patients with an allergic component, the use of a monoclonal antibody (e.g., omalizumab) may be indicated. Bronchodilators (e.g., β-agonists, anticholinergics, and xanthines) have been described in Chapter 6. The anti-inflammatory agents as well as mast-cell stabilizers, leukotriene inhibitors, and monoclonal antibodies used in asthma will be described in detail in this chapter.

Patients with asthma are classified as having intermittent or persistent asthma depending on the frequency of daytime and

nighttime symptoms, frequency of short-acting β-agonist (SABA) use, and limitation of normal activity (**Figure 7-2**). Patients classified as having persistent asthma may be further classified as having mild, moderate, or severe asthma depending on how frequent and severe the symptoms are.

Classifying severity for patients who are not currently taking long-term control medications.

Components of Severity		Classification of Asthma Severity (Youths ≥12 years of age and adults)			
			Persistent		
		Intermittent	Mild	Mild	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2/month	3–4/month	>1/week but not nightly	Often 7/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not >1/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	Normal FEV_1 between exacerbations FEV_1 >80% predicted FEV_1/FVC normal	FEV_1 ≥80% predicted FEV_1/FVC normal	FEV_1 >60% but <80% predicted FEV_1/FVC = reduced 5%	FEV_1 <60% predicted FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1			

- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

Classifying severity in patients after asthma becomes well controlled, by lowest level of treatment required to maintain control.*

Lowest level of treatment required to maintain control	Classification of Asthma Severity			
		Persistent		
	Intermittent	Mild	Moderate	Severe
	Step 1	Step 2	Step 3 or 4	Step 5 or 6

EIB, exercise-induced bronchospasm; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

*For population-based evaluations, clinical research, or characterization of a patient's overall asthma severity after control is achieved. For clinical management, the focus is on monitoring the level of control, not the level of severity, once treatment is established.

FIGURE 7-2 Classification of asthma severity in adults and in youths >12 years of age.

Reproduced from National Asthma Education Program, National Heart, Lung and Blood Institute. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Full Report 2007. Bethesda, MD: National Institutes of Health; 2007. NIH Publication 08-4051.

The usual treatment regimen for control of asthmatic symptoms is adjusted as follows:

- *Step 1 (intermittent asthma):* SABAs for occasional, exertional, or seasonal asthma symptoms.
- *Step 2, if still symptomatic or requiring multiple daily dosages of SABAs (mild persistent asthma):* Add low-dose ICSs to the use of as needed SABAs.
- *Step 3, if still symptomatic while using both SABAs and inhaled steroids (mild-to-moderate persistent asthma):* The preferred treatment is increase to moderate-dose ICS or add a long-acting β-agonist (LABA) to the low-dose ICS. An alternative option is to add a leukotriene inhibitor or theophylline.
- *Step 4, if still symptomatic despite step 3 therapy (moderate persistent asthma):* The preferred option would be to use a medium-dose ICS and a LABA. Alternative options include adding a leukotriene inhibitor, tiotropium in patients with a history of exacerbations, or theophylline to medium-dose ICS.
- *Step 5, if still symptomatic while using medium-dose inhaled steroids and LABAs (severe persistent asthma):* Increase to high-dose ICS and LABA and consider adding a monoclonal antibody targeted to treat asthma in patients who have allergies.
- *Step 6, if still symptomatic using high-dose LABA and ICS (severe persistent asthma):* Add tiotropium or oral corticosteroids and consider adding omalizumab for patients who have allergies.

This stepwise approach is summarized in **Table 7-2**. The guidelines also provide recommendations for low-dose, medium-dose, and high-dose corticosteroids based on age. Equivalent daily dosages of ICSs based on age are listed in **Table 7-3**.

TABLE 7-2
Stepwise Approach for Managing Asthma in Adults and Youths ≥12 Years of Age

Asthma Classification	Preferred Daily Medications	Alternative Medications (Consider Adding These Medications to the Preferred Daily Medications)
Intermittent asthma (step 1)	SABAs PRN	
Mild persistent asthma (step 2)	SABA rescue MDI + low-dose ICSs	Cromolyn, LTRA, or low-dose theophylline
Mild-to-moderate persistent asthma (step 3)	SABA rescue MDI + low-dose ICS + LABA or SABA rescue + medium-dose ICS	Medium-/high-dose ICS or low-dose ICS + either LTRA or theophylline
Moderate persistent asthma (step 4)	SABA rescue MDI + medium-/high-dose ICS + LABA	High-dose ICS or add an LTRA, tiotropium, or theophylline to medium-dose ICS
Severe persistent asthma (step 5)	SABA rescue MDI + high-dose ICS + LABA or if already on high-dose ICS, add tiotropium, LTRA, or theophylline	Monoclonal antibody for patients who have allergies
Severe persistent asthma unresponsive to step 5 (step 6)	SABA rescue MDI + high-dose ICS + LABA + oral corticosteroid	Monoclonal antibody for patients who have allergies or eosinophilic asthma

ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonist; MDI, metered-dose inhaler; PRN, as needed; SABA, short-acting β-agonist.

Data from NHLBI Guidelines for the Diagnosis and Management of Asthma, EPR-3, Section 4 and Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018.

TABLE 7-3

Equivalent Dosage Chart of Low-Dose, Medium-Dose, and High-Dose Corticosteroids Based on Age

Drug	Low Dose (μg)			Medium Dose (μg)			High Dose (μg)		
	Age <5 y	Age 5–11 y	Adults	Age <5 y	Age 5–11 y	Adults	Age <5 y	Age 5–11 y	Adults
Beclomethasone	100	80–160	80–240	N/A	<160–320	<240–480	N/A	>320	>480
Budesonide inhaler	N/A	180–400	180–600	N/A	>400–800	>600–1200	N/A	>800	>1200
Budesonide nebulizer	250–500			>500–1000	1000		>1000		
Fluticasone furoate	N/A	N/A	100	N/A	N/A	N/A	N/A	N/A	200
Fluticasone propionate HFA	176	88–176	88–264	>176–352		>264–440	>352		>440
Fluticasone propionate Diskus	100	100–200	100–300	N/A	>200–400	>300–500	N/A	>400	>500
Mometasone	N/A	110	110–220	N/A	≥220–440	>220–440	N/A	≥440	>440
Triamcinolone	N/A	300–600	300–750	N/A	>600–900	>750–1500	N/A	>900	>1500

HFA, hydroflurocarbon.

Data from NHLBI Guidelines for the Diagnosis and Management of Asthma, EPR-3, Section 4 and Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018.

NEED TO KNOW

Controlling the inflammatory component of asthma is the primary focus in managing asthma and avoiding acute episodes requiring hospitalization. ICSs are essential in asthma management and should be part of the management of all patients with persistent asthma.

Anticholinergics have not been shown to be as effective as β-agonists in the control of bronchospasm associated with asthma. Some research has suggested that cholinergic tone may be more prominent in asthmatics who smoke, and that adrenergic receptors may not be as responsive. This suggests that the use of a combination drug (i.e., albuterol/ipratropium) could be more effective than β-agonists alone in treating asthmatics who smoke. Ipratropium may be added to albuterol for the treatment of acute bronchospasms

and tiotropium may be added to ICS and LABAs in patients not responding to first-line therapies.

Asthma Management in Children

Children 5–11 years of age with asthma are classified as having intermittent or mild, moderate, or severe persistent asthma using a similar classification to adults (Figure 7-2). The NHLBI included in their 2007 EPR-3 (expert panel report) specific dosage recommendations for children for corticosteroid drugs used in asthma management. The complete report may be obtained from the NIH (Bethesda, MD, 20892) or viewed on their website at https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma. The report provides a stepwise approach for managing asthma in children (5–11 years of age) as shown in **Table 7-4** and dosage guidelines for corticosteroids for children (5–11 years of age) as listed in Table 7-3.

TABLE 7-4
Stepwise Approach for Managing Asthma for Children 5–11 Years of Age

Asthma Classification	Preferred Daily Medications	Alternative Medications (Consider Adding These Medications to the Preferred Daily Medications)
Intermittent asthma (step 1)	SABA PRN	
Mild persistent asthma (step 2)	SABA rescue MDI + low-dose ICS	Mast-cell inhibitor (cromolyn), LTRA, or theophylline
Mild-to-moderate persistent asthma (step 3)	SABA rescue MDI + low-dose ICSs + *either* LABA + LTRA (zafirlukast or montelukast), *or*	

	theophyllineor SABA + medium-dose ICS	
Moderate persistent asthma (step 4)	SABA rescue MDI + medium-dose ICS + LABA	Medium-dose ICS + either LTRA (zafirlukast or montelukast) or theophylline
Severe persistent asthma (step 5)	SABA rescue MDI + high-dose ICS + LABA	High-dose ICS + either LTRA (zafirlukast or montelukast) or theophylline
Severe persistent asthma unresponsive to step 5 (step 6)	SABA rescue MDI + high-dose ICS + LABA + oral systemic corticosteroid	Either high-dose ICS + LTRA (zafirlukast or montelukast) or theophylline + oral systemic corticosteroid

ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonist; MDI, metered-dose inhaler; PRN, as needed; SABA, short-acting β-agonist.

Data from NHLBI Guidelines for the Diagnosis and Management of Asthma, EPR-3, Section 4.

The stepwise approach for managing asthma in children (0–4 years of age) is shown in **Table 7-5**, and dosage guidelines for corticosteroids for children (0–4 years of age) are listed in **Table 7-3**. Most of the ICSs have not been approved for children of 0–4 age group but other antiasthmatic agents may be used.

TABLE 7-5
Stepwise Approach for Managing Asthma in Children 0–4 Years of Age

Asthma Classification	Preferred Daily Medications	Alternative Medications (Consider Adding These Medications to the Preferred Daily Medications)
Intermittent asthma (step 1)	SABAs PRN	
Mild persistent asthma (step	SABA rescue MDI + low-dose	Cromolyn or

2)	ICS	montelukast
Mild-to-moderate persistent asthma (step 3)	SABA rescue MDI + medium-dose ICS	
Moderate persistent asthma (step 4)	SABA rescue MDI + medium-dose ICS + LABA or montelukast	
Severe persistent asthma (step 5)	SABA rescue MDI + high-dose ICS + either LABA or montelukast	
Severe persistent asthma unresponsive to step 5 (step 6)	SABA rescue MDI + high-dose ICS + either LABA or montelukast and oral systemic steroids	

ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonist; MDI, metered-dose inhaler; PRN, as needed; SABA, short-acting β-agonist.

Data from NHLBI Guidelines for the Diagnosis and Management of Asthma, EPR-3, Section 4.

Peak Flow Monitoring

Use of a peak flowmeter by asthmatics has become a very useful and recommended tool to help monitor control of symptoms, adjust medications, or indicate when to contact their physician. Peak flowmeters are recommended to be used in patients with moderate or severe persistent asthma, poor awareness of asthma and symptoms, worsening asthma, or those with unpredictable response to environmental exposures. **Figure 7-3** shows examples of commercially available peak flowmeters. There is no specific age at which peak flow measurements should begin; some children under 12 are able to perform reproducible peak flows, but the peak flow readings are extremely effort-dependent. Patients should be provided with a written action plan that will vary depending on symptoms and peak flow readings. The Expert Panel Report-3: Guidelines for the Diagnosis and Management of Asthma (2007) provides patient

information about using peak flows and has published samples of easy-to-use action plans for adults and children based on these values.

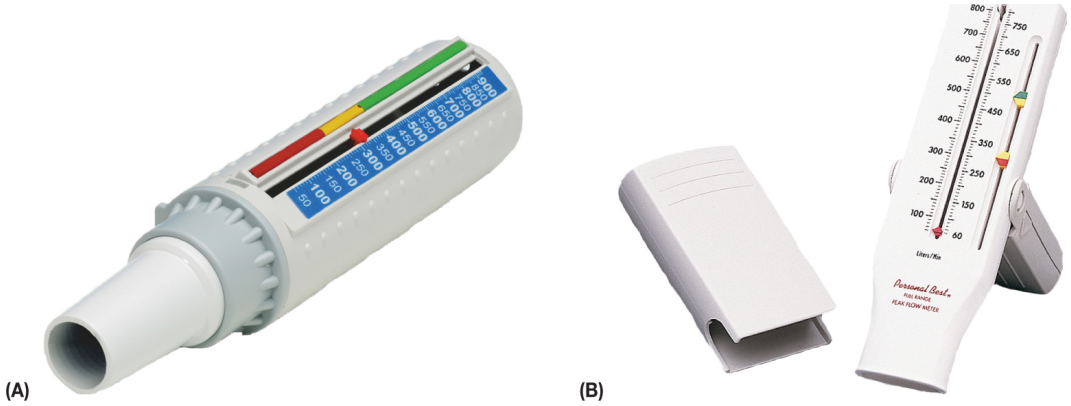


FIGURE 7-3 Commercially available peak flowmeters.

(A) Reproduced with permission from CareFusion; **(B)** Courtesy of Philips Respironics.

Description

Establishing Peak Flow Zones

When patients with asthma are given peak flowmeters to use as a monitoring tool, the first step is to establish a personal best peak flow. This is accomplished by having the patient measure peak flowrate when there are no symptoms of bronchospasm, no wheezing, and no other acute symptoms (upper respiratory infection, fever, etc.) are present. This should be done twice a day for 2 weeks. The highest number achieved during this time is considered the “personal best.” Once the personal best has been established, patients should measure their peak flow rates daily and record the results. The patient’s clinician should provide an action plan to the patient based on peak flow numbers. The values are set up like traffic lights. If the patient’s numbers are 80% or more of their personal best, they are considered to be in the green zone and their asthma is in good control; the yellow zone is when values are between 50 and 79% of the personal best and signal caution. If the peak flow values are less than 50% of the personal best, it signals a medical alert. The physician managing asthma should provide an action plan that states

what medication therapy to take, what to monitor, and when to contact the physician or go to the hospital based on peak flow values.

The zones and actions provided in **Table 7-6** are an example of the use of peak flows to monitor and manage asthma. The example peak flow rates have been provided to illustrate the zones. The patient's physician should determine specific actions for each patient in each zone, and this will vary depending on each patient's level of asthma control. The action plan provided is only an example and may not be appropriate for all patients.

TABLE 7-6
Example Peak Flow Action Plan

Peak Flow	Zone	Example of an Action Plan
Personal best *Example: 300 L/min*	N/A	Record personal best.
Over 80% of personal best *Example: ≥240 L/min* "I feel well."	Green	*Prevent asthma symptoms:* Take long-term control medications: Fluticasone HFA one inhalation twice daily, may use rescue albuterol MDI as needed and take two puffs before exercise.
50–79% of personal best *Example: 150–239 L/min* "I do not feel well."	Yellow	Use albuterol MDI every 20 min up to 1 h and increase fluticasone to four puffs twice daily. If peak flow does not return to green zone in 1 h, use albuterol four puffs every 20 min. If worsening in 48 h add oral prednisone 40 mg daily for 5 d if prescribed; and *call MD* within 12 h of taking prednisone.
Less than 50% of personalbest *Example: <150 L/min* "I feel awful."	Red	Use rescue MDI 4–6 puffs every 10 min for 30 min or until peak flow returns to yellow zone; add oral prednisone 40 mg daily if prescribed and immediately call MD. Go to the hospital or call an ambulance if still in the red zone after 15 min and you cannot reach your MD.

HFA, hydroflurocarbon; MDI, metered-dose inhaler.

National Asthma Education Program, National Heart, Lung and Blood Institute. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National

Institutes of Health; 2007.

Managing an Acute Asthma Episode (Status Asthmaticus)

In an acute asthmatic attack, when the patient is experiencing severe dyspnea and profound airway obstruction, the addition of an anticholinergic bronchodilator (e.g., ipratropium) to a SABA may be helpful. Management of an acute attack is quite different from management of the stable asthmatic. In an acute severe asthma attack, medications are typically administered in the following sequence and manner:

- *First line:* Inhaled SABAs (high dose or as frequently as every 20–30 minutes or continuously until therapeutic response is noted) and oxygen are added in hypoxic patients. Systemic corticosteroids should be considered in any patient not responding to SABAs or in patients requiring steroids for exacerbations in the past.
- *Second line:* Consider adding an inhaled short-acting anticholinergic (i.e., ipratropium) to aerosolized β-agonists in hospitalized patients or when not responding to initial therapy. In severe exacerbations, one can consider adding IV magnesium and high-dose systemic corticosteroids.

  If a patient is becoming fatigued and blood gases are deteriorating (i.e., respiratory acidosis with hypoxemia), the patient will probably require sedation, intubation, and mechanical ventilation.

  As previously discussed in Chapter 5, the use of salmeterol (Serevent®), arformoterol (Brovana®), formoterol (Foradil®), and other LABAs are specifically contraindicated during an acute asthmatic attack. Although these agents are potent and are long-acting (up to 12 hours), they may require 10–20 minutes for effective bronchodilation. Patients who are using LABAs for control of their chronic bronchospasm should always have a fast-

acting β-agonist available to use (i.e., albuterol or levalbuterol) when acute symptoms and dyspnea occur.

Corticosteroid Anti-inflammatory Drugs

Glucocorticosteroids (referred to for simplicity as corticosteroids or steroids in this chapter) are used in the management of many diseases states where the main pathophysiology is inflammation. Glucocorticoid receptors are located throughout most cells in the human body. When steroids bind to these receptors, they lead to RNA production and the release of anti-inflammatory mediators and suppression of proinflammatory cytokines. Blocking of proinflammatory cytokines on cells by steroids leads to a decrease in vascular permeability and inflammation. Steroids inhibit the formation of cytokines that are secreted in asthma by T-lymphocytes, macrophages, and mast cells. This also leads to decreased number of eosinophils and mast cells. Overall, corticosteroids decrease mediators of inflammation in the airways. This chapter discusses their use in the treatment of acute and chronic asthma, which will be discussed again in Chapter 15 (Pharmacology of the Endocrine System). Inhaled and systemic corticosteroids are also commonly used in the treatment of COPD. Inhaled steroids are used in severe COPD to prevent exacerbations or acute worsening of the disease. Similar to asthma, systemic steroids are used only in COPD patients for the treatment of an exacerbation. These drugs have many other medical uses because of their nonspecific anti-inflammatory action, but they also have serious systemic side effects. Use of corticosteroids by aerosol has been adopted wherever practical in the management of asthma because of the reduction of systemic effects compared with systemic administration. However, in contrast to other drugs that have rapid onset when administered by aerosol, corticosteroids given systemically (IV) are more effective than those given by aerosol in the acute or emergency setting. Thus, administering a steroid by aerosol to a croup or status asthmaticus patient is not as effective as IV administration.

There are five Food and Drug Administration (FDA)–approved corticosteroids available by inhalation and four corticosteroid–LABA

combinations currently in use in the United States. There is one agent that is a combination of an ICS, LABA, and long-acting anticholinergic indicated for chronic COPD. The advantages and disadvantages of this route, indications for use, contraindications, side effects, and adverse reactions are comparable among these drugs.

Advantages and Disadvantages of Aerosolized Corticosteroids

Advantages of aerosolized corticosteroids in comparison with oral administration are related primarily to the reduction of serious systemic side effects. Inhaled therapy has been shown to decrease eosinophils and mast cells, which is beneficial in patients with asthma and some with COPD. An interesting and important beneficial effect of corticosteroids is their ability to potentiate or increase the effectiveness of β-adrenergic drugs. One of the actions of corticosteroids is to increase the affinity of the receptors on the cell surfaces to β-agonists (i.e., sympathomimetics). With optimal doses of aerosol steroids, the development of Cushing's syndrome (i.e., the moon-faced appearance associated with fluid retention) and adrenal suppression is very rare, and there is a very low risk of steroid dependency. These advantages, when considered in light of the excellent localized (i.e., pulmonary) anti-inflammatory action, have led to ICSs recommended as first-line therapy in the treatment of persistent asthma.

Disadvantages to this route of administration include the following:

1. Aerosolized steroids are more expensive than oral dosage.
2. Aerosolized steroids are not helpful in treating status asthmaticus.
3. Risk of oral thrush or candidiasis is higher with aerosol steroids than with the oral dosage form.
4. Airway side effects (i.e., hoarseness, coughing, and dry throat) are experienced only when aerosolized corticosteroids are

given; this side effect is not associated with the oral dosage form.

5. Patient effort and understanding are required for effective aerosolized corticosteroid therapy. Patients must be able to take a satisfactory MDI treatment and must reliably follow their prescribed regimen. Improper use of aerosol corticosteroids (i.e., as a bronchodilator) is a hazard.

Indications for Inhaled Corticosteroids

ICS therapy should be considered for any asthma patient who demonstrates little responsiveness to sympathomimetic drugs (β-agonists) or who must use SABAs on a daily basis. ICSs are used in patients with COPD who continue to be at risk for developing acute exacerbations despite using chronic long-acting antimuscarinic (LAMA) and LABA therapies. When ICSs are used in the chronic management of asthma and COPD, it is important to educate patients that these agents need to be used every day as prescribed to improve and prevent worsening of their disease. ICSs should not be used to treat acute SOB. Doses of ICS for chronic asthma start with low dose and will increase based on control of symptoms. Only moderate- and high-dose ICSs have been studied and are approved in the management of chronic COPD. When steroids are used in the management of status asthmaticus or COPD exacerbations, the therapy regimen is very different:

1. IV or IM corticosteroids as first-line drugs
2. taper with a short course of oral steroids
3. manage with chronic aerosol drugs

NEED TO KNOW

ICSs are not useful in severe acute asthma or status asthmaticus. Steroids must be given IV or IM in acute life-threatening asthma episodes.

Side Effects/Adverse Reactions of Aerosolized Corticosteroids

Systemic side effects of corticosteroids (i.e., Cushing's syndrome, immunosuppression, and diabetes) are not seen in the dosages used by aerosol administration (i.e., usually less than 1000 µg/day). Throat irritation, hoarseness, dysphonia, coughing, and dry mouth are the most frequent side effects of aerosolized corticosteroids. These effects can be prevented almost completely by having the patient thoroughly rinse the mouth and gargle after each MDI or dry powder inhaler (DPI) treatment. If an MDI is being used, the use of a spacer device may limit the disposition of the steroid in the throat and limit these side effects. If concurrent use of a bronchodilator by MDI is prescribed, the bronchodilator should be administered before the corticosteroid.

Occasionally, a patient will develop oral candidiasis (fungal superinfection) following aerosolized corticosteroid therapy. Oral candidiasis presents as a white plaque that coats the patient tongue and potentially throat that results from overgrowth of *Candida* species. This is avoidable by instructing the patient to thoroughly rinse the mouth and gargle after a treatment, preferably with water or an alcohol-based mouthwash. Discontinuation or interruption of aerosol therapy is usually not required if oral candidiasis develops. If rapid clearance of the fungal infection is desired, the patient may be prescribed fungal lozenges or systemic antifungal treatment.

Systemic adverse effects of ICS are rare but can be seen in patients using high doses of ICS, except growth suppression in children may occur at low to moderate doses. Long-term side effects of concern include reduced growth velocity in pediatric patients, development of cataracts, glaucoma, osteoporosis, adrenal axis suppression, bruising, delayed wound healing, thinning of the skin, and immunosuppression.

Aerosolized corticosteroids should be used cautiously in patients with bronchiectasis, or those who are susceptible to pneumonia or purulent bronchitis. Studies have shown that inhaled steroids seem to predispose some patients to pulmonary infections.

NEED TO KNOW

Patients should be instructed to thoroughly rinse the mouth after inhalation of a corticosteroid.

Use of ICS

All the following aerosol corticosteroids are administered by SVN, MDI, or DPI. Please refer Chapter 5 for special considerations and techniques for optimal drug deposition by inhalation. Dosage strengths are provided in micrograms (µg) or milligrams. Dosage guidelines are indicated in **Table 7-3** depending on requirements for low-dose, moderate-dose, and high-dose corticosteroids. Dosages recommended in the EPR-3 guidelines may exceed package labeling (particularly in the high-dose ranges). The most important determinant of appropriate dosing is the judgment of the physician and the patient's response to therapy. The clinical effect of ICS starts at 1–2 weeks after initiation of treatment. It is therefore important to stress adherence of therapy to all patients. ICSs are considered as first-line therapy in the treatment of persistent asthma and can be used as monotherapy. COPD patients will be prescribed an ICS in combination with either a LAMA or LABA, or both with a goal of reducing the risk of a flare-up or exacerbation of the disease. ICS should not be used as monotherapy in patients with COPD, but ICS alone can be used for COPD patients but are not FDA-approved for this indication. If ICSs are prescribed in COPD patients, a separate LAMA or LABA inhaler should also be prescribed. ICSs are also available in combination with LABAs and LABA/LAMA combination to improve adherence in patients with asthma and COPD. All available ICSs, for example, beclomethasone, budesonide, ciclesonide, fluticasone, and mometasone, are approved for asthma treatment (**Table 7-7**). Budesonide nebulizer solution is the only agent approved for use in children as young as 1 year old. They may all be used off-label in the treatment of COPD, but agents available in combination with LABA or LAMA are most commonly used in this population.

TABLE 7-7
Available Inhaled Corticosteroids

Generic (Brand)	Starting Dose	Clinical Indications
Beclomethasone MDI (QVAR)	40–80 µg inhaled twice daily	Chronic asthma
Budesonide (Pulmicort Respules, and Pulmicort Flexhaler)	Respules: 0.25 mg nebulized once or twice daily Flexhaler: 360 µg inhaled twice daily	Chronic asthma
Ciclesonide MDI (Alvesco)	80 µg inhaled twice daily	Chronic asthma
Fluticasone propionate (Flovent HFA, Flovent Diskus, and ArmonAir)	HFA: 88 µg inhaled twice daily Diskus: 100–250 µg inhaled twice daily ArmonAir: 55 µg inhaled twice daily	Chronic asthma
Fluticasone furoate (Arnuity Ellipta)	100 µg inhaled daily	Chronic asthma
Mometasone (Asmanex)	Twisthaler: 220 µg inhaled daily HFA: 100–200 µg inhaled twice daily	Chronic asthma

HFA, hydroflurocarbon; MDI, metered-dose inhaler.

Combination Preparations: Corticosteroid and LABA and LAMA

Because most patients with moderate or severe persistent asthma and patients with COPD require both LABAs and ICSs, it has become common for patients to take one medication that includes both drugs that may improve adherence. COPD should not be prescribed an ICS as monotherapy because symptom control is improved as well as the incidence of a flare-up is reduced when taking both a corticosteroid and a LABA or LAMA. There are currently four combinations of LAMA and ICS and one triple agent that includes LAMA, LABA, and

ICS on the market in the United States (Table 7-8). The adverse effects expected with these combination will be consistent with any patient taking ICS, LAMA, or LABA agent.

TABLE 7-8
Corticosteroid/LABAs or LAMA Combination Preparations

Generic (Brand)	Available Dosage Forms (μg)	Starting Dose	Drug Classes	Clinical Indications
Salmeterol and fluticasone propionate (Advair, AirDuo RespiClick)	HFA: 21/45 21/115 21/230 Diskus:50/100 50/250 50/500 AirDuo RespiClick:14/55 14/113 14/232	HFA: two inhalations twice daily Diskus/RespiClick: one inhalation twice daily	LABA (bronchodilator) and ICS (anti-inflammatory)	Asthma and COPD maintenance
Vilanterol and fluticasone furoate (Breo Ellipta)	25/100 25/200	One inhalation daily	LABA + ICS	Adults with asthma and COPD maintenance
Vilanterol, umeclidinium, fluticasone furoate (TrelegyEllipta)	25/62.5/100	One inhalation daily	LABA+ LAMA+ICS	COPD maintenance
Formoterol and mometasone (Dulera)	5/100 5/200	Two inhalations twice daily	LABA + ICS	Asthma and COPD maintenance
Formoterol and budesonide (Symbicort)	4.5/80 4.5/160	Two inhalations twice daily	LABA + ICS	Asthma and COPD maintenance

COPD, chronic obstructive pulmonary disease; HFA, hydroflurocarbon; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LAMA, long-acting antimuscarinics.

Case 7-2: Acute and Chronic Asthma

History of Present Illness

Cindy M. is a 26-year-old female. She was diagnosed with asthma in her childhood. It has been well controlled until recently. A few months ago, she was seen in the urgent care clinic because of increasing SOB and wheezing. At that time, the physician provided her with an albuterol inhaler for home use. She is not on any other asthma treatment. She was using the albuterol inhaler several times a week, and sometimes multiple times in one day. Last week, Cindy saw her primary care physician for a follow-up appointment. She told her physician that she woke up four times last week because she was coughing. Each time, she took two puffs of albuterol and was able to go back to sleep after getting relief from the inhaler. She has been recording her peak flow at home. Her personal best peak flow was 350 L/min. In the last week, her peak flow has remained between 220 and 260 L/min. Early this morning, she was awakened again by wheezing and coughing. She has taken several puffs on her inhaler without relief. She presents now to the ER with

severe difficulty breathing and wheezing. She is anxious and sitting on the edge of the bed.

History and Physical Examination

The following information is collected with an initial evaluation in the emergency department.

History: As stated above, otherwise unremarkable.

Family history: Father with exercise-induced asthma.

Vital signs: HR = 118 beats/min, respiratory rate = 28 breaths/min, BP =132/76 mm Hg, SpO_2 =90% on room air, and temperature = 37.1°C.

Respiratory:Inspiratory and expiratory wheezing bilaterally, use of accessory muscles, and peak expiratory flow 110 L/min.

Laboratory Values

Chest radiograph: Normal, no infiltrates.

Arterial blood gases: pH = 7.42, $PaCO_2$= 36 torr, PaO_2= 78 torr, and HCO_3^-= 23.5 mEq/L.

Electrolytes: Within normal limits.

Hematology: White blood cell count = 7800/mm^3, Hgb = 13.8 g/dL, and hematocrit (HCT) = 42%.

Respiratory Care

The patient is given three SVN treatments with albuterol in the ER. There is little response. Her peak flow is now only 130 L/min. The patient remains in respiratory distress, with wheezing noted bilaterally. She is placed on oxygen by nasal cannula at 2 L/min. Within the next 30 minutes, the patient is admitted to the medical floor for further treatment.

The first-year resident has been asked to write the admitting orders. He asks you for your recommendations. Use the following questions to assist you in providing him with suggestions.

Questions

1. What type of bronchodilator therapy should the patient receive? What frequency would you recommend? Would continuous bronchodilator therapy be appropriate? If so, what dosage?
2. Are there other inhaled or systemic medications you would recommend for this patient? Should the patient receive an IV and aerosol therapy?
3. The patient is being treated and managed while an in-patient in the hospital. You see the need for better management at home. What suggestions do you have as part of discharge planning for Cindy? Medications? Asthma education?
4. At home, Cindy's personal best peak flow was 350 L/min. In the last week, her peak flow has remained between 220 and 260 L/min. What peak flow "zone" would you have characterized her during this time and what would have been an appropriate medication action plan?

5. After this acute asthma episode, Cindy's peak flow returns to the green zone. She is considered to have moderate persistent asthma. What chronic medication therapies should Cindy be initiated on for use at home? What important educational information would need to be provided about these new medications?

Antiasthmatic Drugs

When histamine is released following an antigen–antibody reaction, the classic allergic response occurs. This response includes increased capillary permeability, increased mucus production, mucosal inflammation, edema, and bronchospasm. Histamine is stored within mast cells; when the antigen–antibody reaction occurs, these cells degranulate (rupture) and histamine is released (**Figure 7-4**). Mast-cell stabilizers are inhaled to deposit the medication in the pulmonary tree and prevent the mast cells from degranulating.

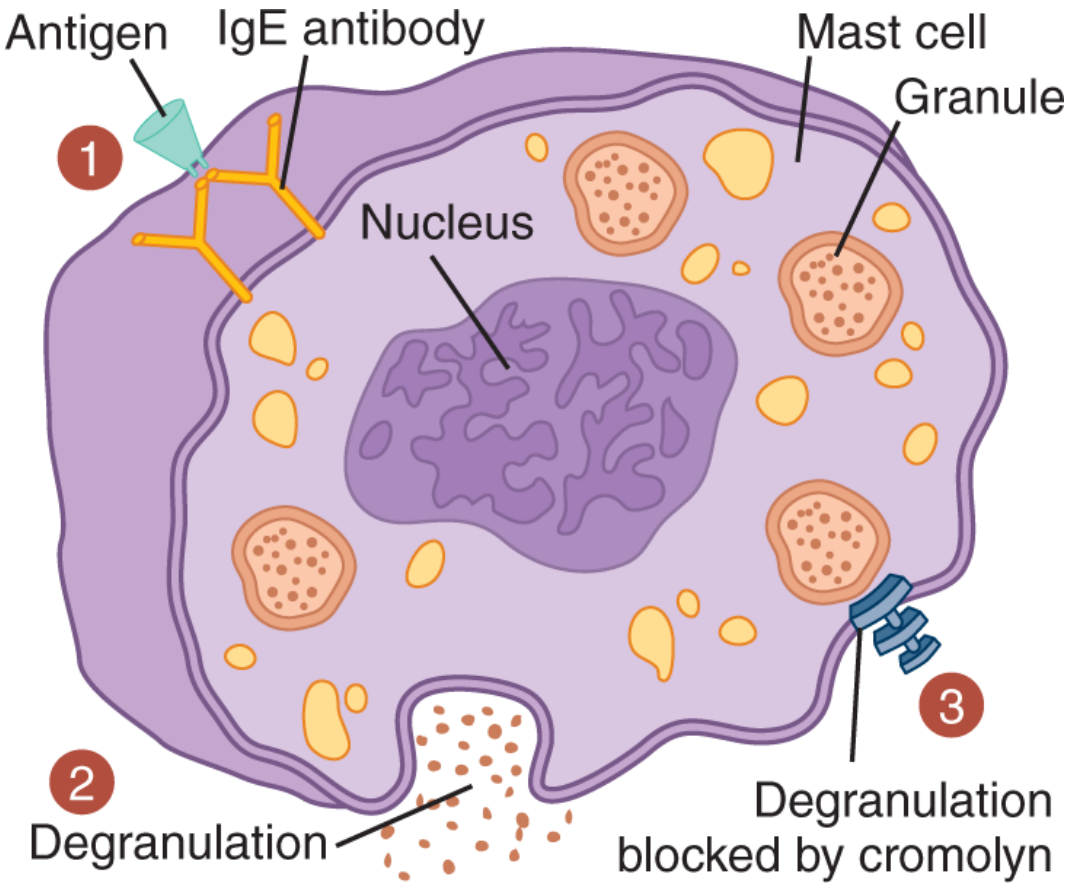


FIGURE 7-4 Mast-cell response to allergen and cromolyn mechanism.

Description

The inflammatory response also involves a complex chemical cascade that causes smooth muscle constriction (i.e.,

bronchospasm), vasodilation (i.e., leading to mucosal edema), increased vascular permeability (i.e., contributing to mucosal edema), increased mucous secretion, and attracts eosinophils (i.e., chemotaxis). These events are associated with leukotrienes when they are released by an inflammatory response and bind to a leukotriene receptor. Antileukotriene agents either prevent leukotrienes from binding to a receptor or they inhibit the synthesis of leukotrienes. The newest antiasthma drug class are monoclonal antibodies. One of these agents block immunoglobulins from binding to mast cells and basophils, thus inhibiting the progression of an inflammatory response. The other agents are interleukin-5 antagonists, which reduce the activation and survival of eosinophils—another major cause of inflammation in asthmatics.

Mast-Cell Stabilizers

Antihistamines have limited value as preventive drugs because they antagonize the effects of histamine once it has been released. Cromolyn sodium and nedocromil sodium were developed as true preventive drugs because they do not allow the mast cell to degranulate when the patient is exposed to an antigen; therefore, the allergic reaction itself is prevented (Figure 7-4). Nedocromil is no longer available as an inhaled agent for the management of asthma. Inclusion of cromolyn sodium is suggested as an alternative to first-line agents at step 2 (mild persistent asthma) in the 2007 EPR-3 NHLBI asthma management guidelines (see Table 7-2) but is not discussed or recommended for any type of asthma in the most updated GINA guidelines.

Cromolyn Sodium

Cromolyn's role in asthma therapy is more of historic interest. Successful use of cromolyn sodium in severe inhalation allergies that are not associated with asthma (i.e., hay fever) has been reported. Cromolyn sodium has been marketed in the United States since the

mid-1970s, but its initial form of administration (i.e., powder aerosol) was irritating to many asthmatics, and the drug was prohibitively expensive. Patient compliance also was a problem (i.e., asthmatics tend to independently reduce their drug dosage when not symptomatic). Cromolyn sodium is available now only as a nebulizer solution for the treatment of asthma or exercise-induced asthma and as nasal and ophthalmic preparations for the treatment of allergic rhinitis and conjunctivitis, respectively. Cromolyn sodium is referred to as a mast-cell stabilizer because it prevents the cell from degranulating. When the mast cell is exposed to an allergen, calcium ions enter the cell and cause it to rupture. Cromolyn sodium prevents the influx of calcium ions and therefore prevents the rupture. It is only when mast cells rupture that the allergic reaction occurs (i.e., after the release of mediators that have been stored in the cell). Cromolyn sodium is not recommended for the occasional asthmatic attack or the seasonal asthmatic. It is effective only when administered by aerosol, and its prophylactic effects require 2–4 weeks to reach maximal levels. The onset is rapid, but prophylactic effects do not occur until 2–4 weeks after beginning therapy. The drug is associated with bronchospasm, wheezing, and, sometimes, coughing. A SABA should be administered if wheezing occurs. Dizziness, headache, throat irritation, and nausea have also been reported.

Leukotriene Modifiers

Two leukotriene receptor antagonists and one 5-lipoxygenase inhibitor are the leukotriene modifiers available in the United States to treat asthma. These agents include montelukast (Singulair®), zafirlukast (Accolate®), and zileuton (Zyflo®). Although these drugs are not administered by aerosol, their addition to the asthma-prevention regimen requires the RCP’s knowledge of their properties and role.

Montelukast, Zafirlukast, and Zileuton

Montelukast and zafirlukast are selective and competitive receptor antagonists of leukotrienes D_4 and E_4. Leukotrienes D_4 and E_4 are components of slow-reacting substance of anaphylaxis. These medications block the inflammatory effects of leukotrienes, which include bronchoconstriction and mucosal edema. Zileuton is the only drug that inhibits 5-lipoxygenase, an enzyme responsible for the production of leukotrienes. Montelukast and zafirlukast are recommended as an alternative to ICS in patients with mild persistent asthma and a nonpreferred add-on in patients with moderate-to-severe asthma. Zileuton is not recommended due to the potential to cause elevated liver enzymes. Appropriate use of these medications has been shown to reduce daytime asthma symptoms, nighttime awakenings, and use of inhaled β-agonists while increasing peak morning and evening expiratory flow rates. Despite these favorable effects, they are less effective than ICS. Because these medications are taken orally, they may be preferable in patients who have a difficult time being adherent to an ICS or have difficulty with proper inhaler technique. These are preventive medications that must be taken daily regardless of the presence or absence of asthmatic symptoms. If the patient reduces or discontinues use when symptoms are absent, the protective effect is lost and symptoms will recur. Montelukast, zafirlukast, and zileuton have no bronchodilating or anti-inflammatory properties, and, therefore, have no role in an acute asthmatic episode. Zafirlukast should be taken on an empty stomach for optimal absorption, but montelukast and zileuton can be taken without regard to meals. Adverse effects are rarely reported with these agents. A rare reaction has been associated with this class of drugs that would present with a systemic vasculitis and worsening asthma, pulmonary infiltrates, and eosinophilia. This reaction is potentially associated with reduction of oral corticosteroid or ICSs and concomitant treatment with a leukotriene modifier. Rare reports of abnormal dreams, aggression, hallucinations, irritability depression, insomnia, and suicidal thoughts have been described by manufacturers of montelukast and zafirlukast. Hepatic failure has

been described with zileuton, which has led to liver testing recommendations.

Immunomodulators

There are two classes of immunomodulators approved for the treatment of asthma. Anti-IgE and anti-IL5 (interleukin-5) monoclonal antibodies are recommended as an adjunct or add-on therapy in patients with severe asthma and as an allergic or eosinophilic component to their asthma. Omalizumab (Xolair®) is a recombinant DNA-derived anti-IgE antibody. Mepolizumab (Nucala), benralizumab (Fasenra), and reslizumab (Cinqair) are anti-IL5 antibodies used in the treatment of eosinophilic asthma. All these agents are expensive and are available only in an injectable form that needs to be administered in a physician office or outpatient infusion center. Omalizumab and reslizumab require a monitoring period in a clinical setting after infusion to observe for development of anaphylaxis.

Anti-IgE Antibody

Omalizumab binds to circulating IgE and prevents it from binding to receptors on mast cells and basophils. It limits the release of mast-cell mediators when exposed to allergens. Its use is currently considered in patients with moderate-to-severe allergic asthma not responding to therapy in step 4. Omalizumab is injected subcutaneously and is administered every 2–4 weeks. It is dosed based on weight and IgE levels. These levels need to be obtained before the injection. It can reduce the IgE levels to decrease exacerbations, leading to hospitalizations and allowing for a reduction on corticosteroid dosing. More than 75% of the asthmatics receiving omalizumab were able to control their asthma symptoms and reduce the use of ICSs and rescue inhalers. Pain and bruising at the injection site are the most common reactions to omalizumab, as well as joint pain, rash, and fever. Anaphylaxis is a rare but serious side effect

that may occur shortly after the injection. Careful monitoring for anaphylaxis is required for at least 2 hours after the injection.

Anti-IL5 Antibodies

A proportion of patients with severe asthma have increased eosinophils thought to be caused by IL5-producing lymphocytes. This leads to increased airway inflammation due to release of proinflammatory cytokines. Mepolizumab (Nucala), benralizumab (Fasenra), and reslizumab (Cinqair) have recently been developed for the treatment of eosinophilic asthma. These agents have been shown to prevent asthma exacerbations in this patient population. Mepolizumab and benralizumab can be added on to therapy in patients >12 years or older and reslizumab for ages ≥18 with severe, uncontrolled eosinophilic asthma not responding to step 4 therapies. Mepolizumab and benralizumab are administered subcutaneously every 4 weeks, and reslizumab is given intravenously every 4 weeks. These agents should not be used to treat acute asthma symptoms or asthma exacerbations. Any corticosteroid (i.e., systemic or inhaled) should be tapered slowly after starting these agents. The most common adverse reactions and warnings for each of these agents are given in **Table 7-9**.

TABLE 7-9
Anti-IL5 Agents: Adverse Effects, Warnings, and Precautions

Drug Name (Brand)	Common Adverse Effects	Severe Adverse Effects	Warnings and Precautions
Benralizumab (Fasenra)	Fever, headache, rash, pharyngitis	Hypersensitivity reactions, anaphylaxis	Should be administered by a healthcare professional
Mepolizumab (Nucala)	Headache, injection site reactions, back pain, fatigue	Hypersensitivity reactions, anaphylaxis, herpes zoster	Should be administered by a healthcare professional, can precipitate herpes zoster (shingles), a vaccine is recommended with use
Reslizumab (Cinqair)	Oropharyngeal pain, myalgia	Anaphylaxis, malignancies, creatinine phosphokinase elevation	Should be administered by a healthcare professional

Review Questions

1. Define mucosal edema and list several diseases or conditions that may cause mucosal edema.
2. Describe how an α-adrenergic drug reduces mucosal edema.
3. Compare and contrast clinical situations when you would recommend inhaled racemic epinephrine and when you would use systemic epinephrine. Include the differences in side effects between each.
4. Discuss how corticosteroids affect the pathophysiology of asthma and what cells do they target?
5. What are the advantages of aerosol administration when compared with oral administration of steroids in asthma?
6. What are the common adverse effects found in patients on ICSs? What specific patient education should occur to ensure safe and effective aerosol corticosteroid therapy?
7. List the five available ICSs and the inhalation devices for each.
8. Describe the rationale for the use of combination preparations that provide a LABA and corticosteroid and list the currently available combinations by generic and trade names.
9. An adult patient is newly diagnosed with asthma. He has been prescribed only albuterol to take as needed. His presentation included a history of using albuterol three times per week for symptoms and he wakes up about three to four times per month from SOB. How would you classify his asthma and what first-line therapy would you expect a prescription for?
10. A patient with COPD is prescribed fluticasone hydroflurocarbon (HFA) 44 µg, one inhalation every 12 hours, as monotherapy. Please assess whether you believe this therapy is appropriate for this patient and include rationale.
11. You are called to the ER on a Saturday night to treat an asthmatic in acute distress. The physician has ordered an immediate treatment of 20 mg cromolyn sodium and blood gases,

but no other therapy. How would you react to this order and how would you advise the physician?

12. Describe the mechanisms of action of montelukast, zafirlukast, and zileuton and their role in the therapy of asthma.
13. Justify why montelukast should be the most commonly recommended leukotriene modifier in regard to its administration and side effect profile?
14. Describe the mechanism of action and clinical indication of immunomodulatory agents in asthma.
15. You are a respiratory therapist that conducts spirometry in the pulmonary clinic and your patient is scheduled to receive reslizumab (Cinqair). What adverse effects would you monitor for as an RCP?

Posttest

For each of the following questions, try to select the one best answer from the choices given.

1. Which of the following drugs has an α-adrenergic effect?
   1) Epinephrine
   2) Cromolyn sodium
   3) Beclomethasone
   4) Racemic epinephrine
   5) Flunisolide
   a. 1 and 4 only
   b. 1, 2, and 4 only
   c. 2 only
   d. 3 and 5 only
2. A pediatric patient in the ER has a harsh, barking cough, inspiratory stridor, tachypnea, and tachycardia. Wheezing is not heard, and the parents report some improvement because the child has been sitting up and during the ride in the cold night air to the hospital. Which of the following drugs should the RCP recommend by aerosol?
   a. QVAR®
   b. Micronefrin®
   c. Intal®
   d. Ventolin®
3. What is the appropriate dosage of racemic epinephrine?
   a. 0.30 mL of 1% solution in 3.0 mL of diluent
   b. 0.50 mL of 2.25% solution in 3.0 mL of diluent
   c. 0.25 mL of 1:100 solution in 3.0 mL of diluent
   d. 0.20 mL of 0.5% solution in 2.5 mL of diluent
4. How frequently can racemic epinephrine be safely given?
   a. Every hour
   b. Every 4 hours
   c. Four times per day
   d. Every 6 hours

5. Which of the following drugs stabilizes the mast cell?
   a. Intal®
   b. QVAR®
   c. AeroBid®
   d. Flovent®
6. Which of the following drugs has a general anti-inflammatory effect?
   1) QVAR®(beclomethasone)
   2) Nasalcrom® (cromolyn sodium)
   3) Flovent® (fluticasone)
   4) Pulmicort® (budesonide)
   5) Singulair® (montelukast)
   a. 2 and 5 only
   b. 3 only
   c. 1, 2, and 4 only
   d. 1, 3, and 4 only
7. A patient is brought to the ER after experiencing SOB, a “tight” feeling in his chest, and tachycardia while swimming at a local pool. It appears to be laryngeal edema. The maintenance crew had added chlorine to the pool by tossing a bucket of solution over the surface just before the patient’s symptoms began. Which of the following drugs should the RCP suggest by aerosol?
   a. Arformoterol (Brovana®)
   b. Flunisolide (AeroBid®)
   c. Epinephrine
   d. Racemic epinephrine (Micronefrin®)
8. Which of the following drugs may be used to control the bronchospasm associated with an acute asthmatic attack?
   1) Cromolyn sodium (Intal®)
   2) Albuterol (Proventil®)
   3) Budesonide (Pulmicort®)
   4) Levalbuterol (Xopenex®)
   5) Formoterol (Foradil®)
   a. 1 and 4 only
   b. 3, 4, and 5 only
   c. 2 and 4 only

d. 2, 4, and 5 only

9. The advantages of administering corticosteroids by aerosol include:
   a. rapid absorption at site of action with reduced systemic side effects.
   b. prolonged duration with reduced side effects.
   c. rapid absorption with reduced dosage.
   d. immediate relief of bronchospasm.
10. Which of the following drugs should not be recommended for the treatment of status asthmaticus?
    a. Cromolyn sodium (Intal®)
    b. Beclomethasone (QVAR®)
    c. Mometasone (Asmanex®)
    d. None of these is correct.
11. Which of the following drugs are often used to control the inflammation associated with chronic asthma?
    1) Fluticasone (Flovent®)
    2) Racemic epinephrine
    3) Arformoterol (Brovana®)
    4) Flunisolide (AeroBid®)
    5) Budesonide (Pulmicort®)
    a. 2 and 3 only
    b. 1, 2, and 4 only
    c. 1, 4 and 5 only
    d. 1 and 4 only
12. Which of the following considerations should be stressed when instructing a new patient in the use of aerosolized steroids?
    a. The patient should use the MDI steroids only when symptoms (e.g., wheezing) are severe.
    b. The patient should use steroids by MDI every day regardless of having symptoms.
    c. The patient should discontinue ICS use when symptoms are controlled for 5 consecutive days.
    d. MDI steroids are safe for use during pregnancy because they are deposited in the lungs and do not reach fetal circulation.

13. With regard to β-agonists, aerosolized steroids have which of the following effects?
    a. They block the effects of bronchodilators.
    b. They have no effect on bronchodilating.
    c. They reduce systemic side effects of dilators.
    d. They potentiate (increase) bronchodilating effects.
14. Which of the following phrases best describes the action of cromolyn sodium?
    a. Prevents degranulation of mast cell
    b. Anti-inflammatory
    c. Bronchodilator
    d. Breaks down histamine inside mast cell
15. Salmeterol is a long-acting, highly specific β-agonist effective in the treatment of:
    a. both acute and chronic asthmatic symptoms.
    b. acute status asthmaticus.
    c. chronic asthmatic symptoms.
    d. asthma when anticholinergics have failed.
16. The usual first-line drugs used in the management of chronic asthma symptoms include:
    a. inhaled and oral SABAs and anticholinergics.
    b. inhaled LABAs and oral xanthines.
    c. ICSs.
    d. inhaled and oral β-agonists, xanthines, and oral corticosteroids.
17. When a patient in an acute asthmatic attack is still experiencing severe bronchospasm after receiving inhaled β-agonists and IV steroids, the drugs to be considered next are:
    a. inhaled anticholinergic.
    b. cromolyn sodium and ICS.
    c. oral β-agonist and IV xanthine.
    d. oral xanthines and inhaled anticholinergic.

References/Recommended Readings

Aggarwal P, Sharad S, Handa R, Dwiwedi SN, Irshad M. Comparison of nebulized magnesium sulfate and salbutamol combined with salbutamol alone in the treatment of acute bronchial asthma: a randomized study. *Emerg Med J.* 2006;23(5):358-362.

Ahmad Z, Singh SK. Relative and additional bronchodilator response of salbutamol and ipratropium in smoker and nonsmoker asthmatics. *J Asthma*. 2010;47(3):340-343.

Barnes P. New therapies for asthma: is there any progress? *Trends Pharmacol Sci*. 2010;31(7):335-343.

Barnes PJ. Scientific rationale for combination inhalers with long-acting β_2-agonists and corticosteroids. *Eur Respir J*. 2002;19(1):182-191.

Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. *Nat Rev Immunol*. 2008;8(3):183-192.

Brandão DC, Britto M, Pessoa M, et al. Heliox and forward-leaning posture improve the efficacy of nebulized bronchodilator in acute asthma: a randomized trial. *Respir Care*. 2011;56(7):947-952.

Blitz M, Blitz S, Beasely R, et al. Inhaled magnesium sulfate in the treatment of acute asthma. *Cochrane Database Syst Review.* 2005;(4):CD003898.

Centers for Disease Control and Prevention. *Most recent asthma data: National current asthma prevalence 2016.* February 12, 2018. https://www.cdc.gov/asthma/most_recent_data.htm. Accessed March 2, 2018.

Cherniack RM, Wasserman SI, Ramsdell JW, et al. A double blind group-comparative study of the efficacy and safety of nedocromil sodium in the management of asthma. *Chest*. 1990;97:1299.

Cinqair [package insert]. Frazer, PA: Teva Respiratory; 2016.

Coates AL, Leung K, Vecellio L, Schuh S. Testing of nebulizers for delivering magnesium sulfate to pediatric patients in the emergency department. *Respir Care*. 2011;56(3):314-318.

Craven D, Kercsmar CM, Myers TR, et al. Ipratropium bromide plus nebulized albuterol for the treatment of hospitalized children with acute asthma. *J Pediatr*. 2001;138(2):51-58.

National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute; 2007.

Fasenra [package insert]. Wilmington, DE: AstraZeneca; 2017

Fluticasone propionate for chronic asthma. *Med Lett*. 1996;38(983):83-84.

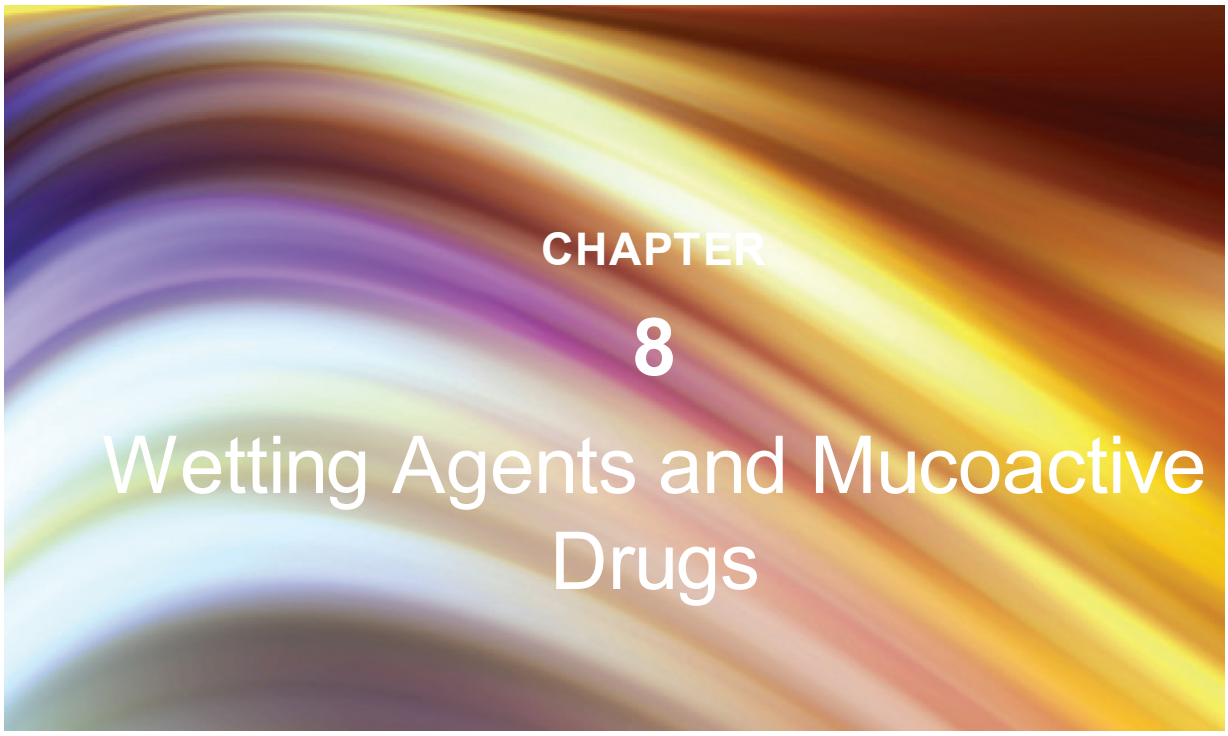
Global Initiative for Asthma (GINA). *Global strategy for asthma management and prevention*. 2018. http://www.ginasthma.org. Accessed March 15, 2018.

Gutglass DJ, Hampers L, Roosevelt G, et al. Undiluted albuterol aerosols in the pediatric emergency department. *Pediatrics*. 2000;105(5):E67.

Haponik EF. Smoke inhalation injury: some priorities for respiratory care professionals. *Respir Care*. 1992;37:609.

Holgate ST, Bradding P, Sampson AP. Leukotriene antagonists and synthesis inhibitors: New directions in asthma therapy [Review, 89 refs]. *Allergy Clin Immunol*. 1996;98(1):1-13.

Kaliner MA. How the current understanding of the pathophysiology of asthma influences our approach to therapy. *J Allergy Clin Immunol*. 1993;92(Pt 2):144.
Lotvall J, Bateman ED, Bleeker ER, et al. 24-hour duration of the novel LABA vilanteroltrifenatate in asthma patients treated with inhaled corticosteroids. *Eur Respir J*. 2012;40(3):570-579.
Melani AS. Nebulized corticosteroids in asthma and COPD. An Italian appraisal. *Respir Care*. 2012;57(7):1161-1174.
Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulfate for acute asthma: systematic review and meta-analysis. *Emerg Med J*. 2007;24(12):823-830.
Murray RK, Panettieri RA Jr. Asthma. In: Fishman AP, ed. *Pulmonary Diseases and Disorders Companion Handbook*. 2nd ed. New York, NY: McGraw-Hill; 1994.
Myers TR, Tomasio L. Asthma: 2015 and beyond. *Respir Care*. 2011;56(9):1389-1410.
Nucala [package insert]. Philadelphia, PA: GlaxoSmithKline; 2017.
Obata T, Matsuda S, Akasawa A, Iikura Y. Preventive effect and duration of action of disodium cromoglycate and procaterol on exercise-induced asthma in asthmatic children. *Ann Allergy*. 1993;70(2):123.
Rebuck AS, Kesten S, Boulet LP, et al. A 3-month evaluation of the efficacy of nedocromil sodium in asthma: a randomized double-blind placebo-controlled trial of nedocromil sodium conducted by a Canadian multicenter study group. *J Allergy Clin Immunol*. 1990;85(3):612.
Sabato K, Picchi P, Asselin J, et al. Use of a clinical asthma score (CAS) as the initial step in an asthma treatment algorithm in a pediatric emergency department. *Respir Care*. 2002;47(9):1072.
Sabato K, Ward P, Hawk W, et al. Randomized controlled trial of a breath-actuated nebulizer in pediatric asthma patients in the emergency department. *Respir Care*. 2011;56(6):761-770.
Schuh S, Johnson D, Stephens D, et al. Hospitalization patterns in severe acute asthma in children. *Pediatr Pulmonol*. 1997;23(3):184-192.
Spector SL. Leukotriene inhibitors and antagonists in asthma [Review, 78 refs]. *Ann Allergy Asthma Immunol*. 1995;75(6)(Pt 1):463-470,473-474.
Spector SL, Smith LJ, Glass M, et al. Effects of 6 weeks of therapy with oral doses of ICI 204,219, a leukotriene D_4 receptor antagonist, in subjects with bronchial asthma. *Am J Respir Crit Care Med*. 1994;150(3):618-623.
Virant FS. Effective once-daily administration of budesonide inhalation suspension by nebulizer with facemasks or mouthpieces for persistent asthma in infants and young children. *Pediatrics.* 2002;110(2):460-461.



© Anna RubaK/ShutterStock, Inc.

OUTLINE

Introduction
Airway Mucus
  Diseases Associated with Mucous Dysfunction
Mucoactive Medications
  Bland Aerosols
  Mucolytic Agents
  Mucokinetic Agents
Expectorants and Bronchorrhea Agents
  Guaifenesin
  Sodium Bicarbonate

Objectives

After completion of this chapter and its learning activities, you will be able to:

1. Compare and contrast the causes of mucus dysfunction in asthma, chronic obstructive pulmonary disease, and cystic fibrosis patients.
2. Define the terms *bland aerosol, mucoactive, mucolytic, mucokinetic*, and *expectorant.*

3. Discuss the therapeutic indications for the use of bland aerosols and mucolytic agents in airway maintenance.
4. Compare and contrast the two primary mucolytic aerosols.
5. Describe the proposed mechanisms of action, contraindications, and hazards of each mucolytic agent.
6. Describe the use of sodium bicarbonate as an expectorant or thinning agent.
7. Suggest the most appropriate mucolytic therapy, including the drug of choice, route of delivery, and recommended dosage, given a patient case study.

KEY TERMS

Bland aerosol
Bronchorrhea
Dornase alfa (Pulmozyme)
Expectorant
Hygroscopic
Mucoactive agents
Mucokinetic
Mucolytic
***N*-acetyl-L-cysteine (NAC)**
Phlegm
Sputum

Introduction

Mucoactive agents are used in respiratory care to humidify the respiratory tract and help loosen, thin, and clear pulmonary secretions. These secretions are normally thin and watery, much like the consistency of saliva, but in many diseases, acute infection, or chronic inflammatory conditions, secretions may be excessive and may become thick and concentrated. One of the important roles of the respiratory care practitioner (RCP) is recognizing when a patient may need an aerosol and knowing which agent is the most effective to recommend to the physician. The therapist must also be knowledgeable about the dosage and concentration of the drug he or she recommends. It is also critical that the RCP understands and recognizes the potential side effects or consequences of using such drugs.

Airway Mucus

The airway responds to inflammation with mucus hyperproduction and retention. Mucus is a gel-like substance that serves as a protective barrier to the airway epithelium. Normal mucus is 97% water and 3% solids, which comprises mucins, proteins, cellular debris, salts, and lipids. The normal mucus molecule is a mucopolysaccharide chain comprising strands of alternating amino sugars and amino acids that are connected by disulfide bonds. Mucus prevents dehydration of the airway, protects the airway from inhaled particles, and aids in the clearance of particles and pollutants. The two types of cells in the small airways are ciliated and secretory cells. Mucus is produced by secretory (goblet) cells on the airway surface. In the large, cartilaginous airways, submucosal glands produce mucin, which is a gel-like polymer. Mucins are glycoproteins mostly containing carbohydrates that have a terminal cysteine that can form disulfide bonds resulting in a gel-like substance. The mucus coats the periciliary fluid layer, which contains mucins and airway surface fluid. The mucus also contains inhaled debris and antimicrobial proteins. Cilia in the lower airways drive the mucus from the airways. Secretions may also be cleared from the airways by cough in states of inflammation and when mucus is thicker or there is damage to the cilia. **Figure 8-1** displays a drawing of a typical ciliated epithelium and healthy airway mucus secretion. In states of inflammation, the secretions are called phlegm. Phlegm contains inflammatory cells, bacteria, and DNA. When **phlegm** is expectorated, it is called **sputum**.

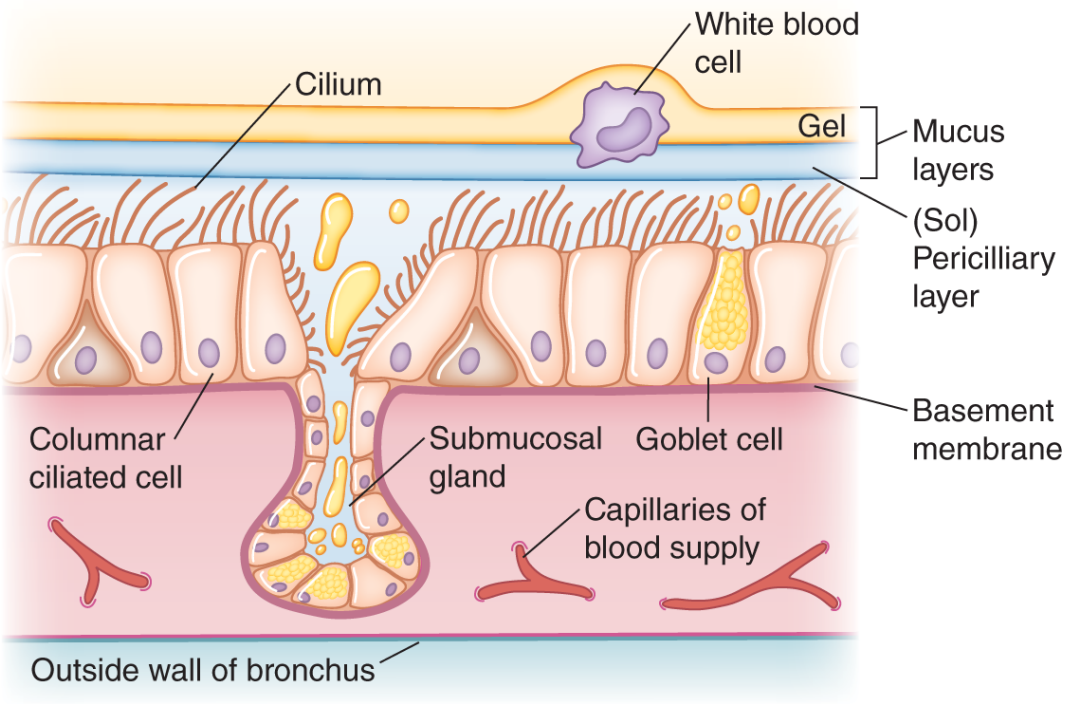


FIGURE 8-1 Ciliated epithelium and mucus secretion in respiratory tract.

Description

Diseases Associated with Mucous Dysfunction

In obstructive pulmonary diseases such as, asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF), there is airway inflammation, increased secretion of mucus, and impaired clearance of mucus. Patients with asthma have increased gel-like mucus production, which may lead to occluded small airways. In patients with COPD, there is increased mucus production and secretion through goblet cell hypertrophy and metaplasia (i.e., abnormal changes in cells) in the bronchi and on the surface epithelium of the bronchi and bronchioles, respectively. These patients have some difficulty expectorating this mucus due to impaired mucociliary action in the small airways. As goblet cell metaplasia increases, the degree of airway obstruction increases as well. It has been shown that cigarette smoke can increase mucin production. The mucus in these patients may be desirable for bacteria and viruses to adhere to and grown in, which is a source of

COPD exacerbations. CF is one of the most common inherited diseases in Caucasians. CF predominately affects the respiratory system by causing impaired mucociliary clearance and mucus hypersecretion, which leads to chronic infections and airflow obstruction. There is decreased airway surface liquid and increased adhesion of the gel layer to the epithelial surface of the airways and an increased amount of DNA in the secretions. All inflammatory airway diseases, including acute viral and bacterial infections, bronchiectasis, bronchiolitis, and mechanically ventilated patients, have been associated with mucus dysfunction, but specific mechanisms and susceptibility for each disease have not been identified for all. Understanding the symptoms and causes of mucus dysfunction in each of these diseases is important to recommend the best therapy for each.

Mucoactive Medications

Mucoactive medications are used to encourage mucus clearance. The classes of medications that are considered mucoactive agents are categorized by their proposed mechanism of action and include **bland aerosols**, **expectorants**, **mucolytics**, and **mucokinetic** medications. Each class of medication, indications, mechanism, warnings, and adverse effects will be discussed in this section. Unfortunately, the evidence supporting the efficacy of these medications are lacking. It should be noted that intervention with mucokinetics and other methods of airway maintenance always should be a secondary treatment. The primary treatment should be assuring adequate hydration and fluid intake through other mechanisms such as oral and intravenous (IV) fluids. Mucokinetic therapy may be avoided, even in patients with chronic excessive secretions, by adequate fluid intake and by the consistent use of coughing and other airway clearance techniques.

Bland Aerosols

Bland aerosols are those that do not have a direct effect on the mucus molecule but are used to improve secretion clearance by providing humidification with saline solutions. Bland aerosols may be given on a continuous basis through a large-volume nebulizer such as a jet nebulizer or ultrasonic nebulizer. They may also be given by small-volume (handheld) nebulizer (SVN), but this use is generally limited to acting as a diluent for other potent drugs, such as bronchodilators or mucolytics. Bland aerosols are appropriate for the patient who requires humidification of the respiratory tract, such as patients who are intubated or a tracheotomy. They may be used for upper airway edema (cool bland aerosol) and they also may be helpful as a thinning agent when administered by heated nebulizer before postural drainage and chest percussion or other airway clearance techniques. There is a lack of data supporting efficacy of

bland aerosols to help with mucus clearance. Another use of bland aerosols is for sputum induction, a procedure used to promote coughing and expectoration of a sputum sample for laboratory analysis. Contraindications for using bland aerosols include bronchoconstriction and airway hyperresponsiveness. Complications of bland aerosol therapy include bronchospasm, bronchoconstriction, infection, over hydration, and airway edema.

The agents considered as bland aerosols include:

- normal saline (NS) (0.9% sodium chloride [NaCl])
- hypotonic saline (less than 0.9% NaCl, most commonly 0.45% NaCl, or half-NS)
- hypertonic saline (greater than 0.9% NaCl, most commonly 3%, 5%, 7%, or 10% NaCl solutions)
- sterile distilled water

Normal Saline

NS refers to a saline solution that has the same osmotic pressure as body fluids; therefore, it is physiologically normal. It is the most common agent used to dilute bronchodilator drugs. Because NS is similar to body fluids, it is unlikely to cause bronchospasm. However, in the treatment of cardiac patients who may be on a strict low-sodium diet, the amount of sodium in NS should be taken into consideration if the patient receives frequent treatments throughout the day. For example:

$$\begin{aligned} 0.9\%\ \text{NaCl} &= 0.9\ \text{g NaCl}/100\ \text{mL water} \\ &= 900\ \text{mg NaCl}/100\ \text{mL solution} \\ &= 9\ \text{mg NaCl/mL solution} \end{aligned}$$

Thus, if a patient receives SVN treatments every 4 hours with a bronchodilator and 3 mL NS, the treatment would contribute 162 mg NaCl/day.

$$(24\ \text{h}/4\ \text{h})\ (9\ \text{mg/mL})\ (3\ \text{mL}) = (6)\ (27\ \text{mg}) = 162\ \text{mg}$$

Although only part of the aerosol actually is absorbed (i.e., much is lost during exhalation), if the patient's diet should be restricted to 1500 mg sodium a day, the treatments could contribute up to 10% of the daily sodium requirements. The therapist should always be aware of any significant patient orders, even those that do not directly affect respiratory care. In a case such as this, sterile distilled water may be suggested as a diluent for the bronchodilator therapy instead of NS.

Hypotonic Saline

Hypotonic saline refers to a solution that has an osmotic pressure less than that of body fluids. The most commonly used hypotonic solution is 0.45% NaCl, or half-NS. Indications for the use of hypotonic saline include use in large-volume nebulizers when the patient cannot tolerate sterile distilled water, or used as a diluent in the case of severe salt restriction (as in the above example).

Hypertonic Saline

Hypertonic saline refers to a solution that has an osmotic pressure greater than that of body fluids. The most commonly used hypertonic solutions are 3%, 5%, 7%, and 10% NaCl. These solutions are used primarily for sputum induction because they irritate the airway and are **hygroscopic** in nature. Hygroscopic means that the aerosol droplets tend to attract humidity as they travel in suspension and therefore become larger in size. The combined effect of the nature of hypertonic saline is that the patient produces more mucus to dilute the higher salt concentration and is stimulated to cough. The administration of a hypertonic saline solution by aerosol is referred to as sputum induction. It is often used when a patient has a dry, nonproductive cough, but the physician needs a sputum sample for microbiological culture and sensitivity. Care should be taken whenever administering hypertonic saline to a patient who has reactive airway disease as the patient may develop bronchospasm. It is recommended that a bronchodilator be available (e.g., metered-dose inhaler [MDI] is the most common method) when performing an

induced sputum procedure. When hypertonic saline is used for sputum induction, the recommended dosage should not exceed 1500 mg/day. This is equivalent to 15 mL of 10% NaCl, or 30 mL of 5% NaCl.

NEED TO KNOW

Sputum induction is a procedure sometimes required to promote coughing and expectoration of respiratory secretions in a patient who has been unable to produce a sputum specimen for laboratory analysis.

CF patients have a deficiency in digestive enzymes that often leads to a failure-to-thrive syndrome in children. CF also causes excess, thickened, and very sticky pulmonary secretions. CF patients are thus highly vulnerable to frequent upper respiratory tract infections, and because of the nature of their secretions, the infections may migrate to the pulmonary system. Managing secretions and improving the effectiveness of bronchopulmonary clearance have become key elements in reducing the morbidity and mortality of CF.

The mucolytic rhDNase (recombinant human deoxyribonuclease) (e.g., **dornase alfa**) is described in detail later in this chapter and is approved for use only in CF patients and is the most effective agent for this disease. However, the use of 7% NaCl hypertonic saline for mucokinesis has also been shown to be highly effective in mobilizing secretions to reduce the frequency and severity of pulmonary infections in these patients but with a risk of causing an acute decrease in FEV_1due to development of bronchospasm. Regular use of a 7% saline aerosol as part of airway clearance therapy has been demonstrated to preserve lung function and decrease acute exacerbations in CF and is recommended as part of a treatment regimen for CF patients.

Sterile Distilled Water

Sterile distilled water is the most commonly used agent in large-volume nebulizers for the humidification of the respiratory tract. It is also used as a diluent for SVN treatments with bronchodilators or other potent drugs. Occasionally, a patient with reactive airway disease (i.e., asthma) may experience bronchospasm from aerosolized sterile water. In such cases, half-NS may be a better agent for general humidification.

Mucolytic Agents

Mucolytics agents disrupt the mucus molecule and damage gels contained in the mucus. Mucolytics cause mucolysis or the breaking apart (lysis) of the mucus molecule itself by degrading mucin polymers, DNA, or fibrin in airway secretions. In contrast to wetting agents or bland aerosols, which tend to add water to secretions and make them less viscous by thinning, mucolytics actually affect the composition of pulmonary secretions. Although mucolytics are more potent in treating patients with exceptionally thick or copious secretions, they should be used with more caution because of side effects, which are not seen with the use of wetting agents.

There are two primary mucolytics, each based on a different method of mucolysis. To understand how a mucolytic works, and therefore be able to select the best agent for a specific patient's needs, it is necessary to have a general understanding of the composition of the mucus molecule itself.

Two commonly used mucolytics break apart the mucus molecule by different mechanisms. One mucolytic process involves ***N*-acetyl-L-cysteine (NAC)** (Mucomyst®) that works by disrupting the disulfide bonds. Another mucolytic process involves disruption of mucus proteins and/or proteinaceous secretions such as those seen in CF or bronchiectasis. This category of mucolytics is referred to as proteolytic, meaning that they break apart proteins that make up the secretions. Pancreatic dornase (Dornavac®) was used from the 1950s through the 1980s as an effective proteolytic aerosol, but its derivation from bovine enzymes caused side effects and allergic

reactions. Bioengineering has enabled the production of the cloned human gene rhDNase, which is FDA-approved for use by CF patients in the form of **dornase alfa (Pulmozyme®)**. Dornase alfa effectively lyses the DNA debris commonly associated with the thickened pulmonary secretions of the CF patient.

Dornase Alfa (Pulmozyme)

Dornase alfa is indicated and approved for use *only* by CF patients. Dornase alfa has been shown to be safe and improves lung function in CF patients 5 years of age and older who are clinically stable and have thick DNA-containing sputum. It works by reducing viscosity and adhesiveness of infected sputum in patients with CF. Dornase alfa is a DNA enzyme that selectively cleaves DNA in sputum and decreases viscosity when administered as an aerosol. This action improves pulmonary function regardless of baseline lung function and may reduce the risk of bacterial infection in patients with CF and an FVC >40% predicted. **Figure 8-2** illustrates the action of dornase alfa.

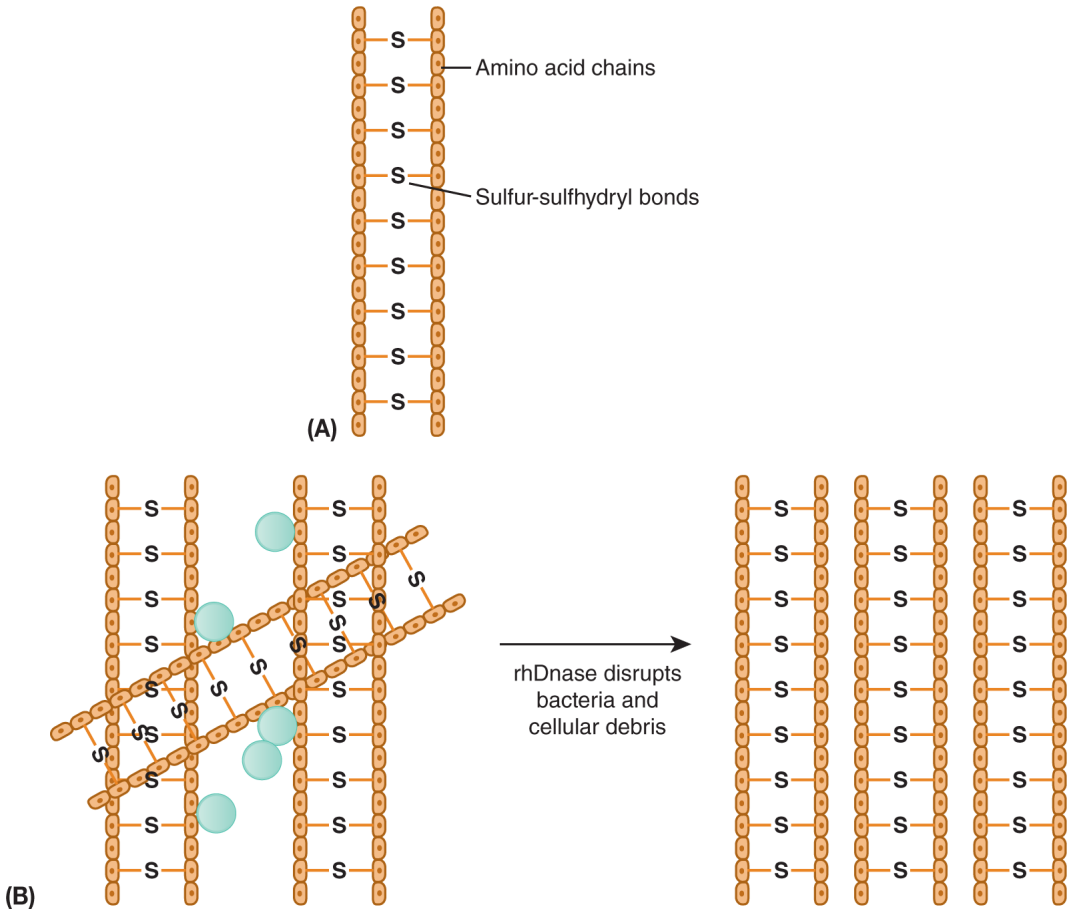


FIGURE 8-2 (**A**) Simplified structure of a mucus molecule. (**B**) Mucolytic action of dornase alfa.

Description

Dornase alfa has not been shown to be effective in diseases other than CF. In patients with non-CF bronchiectasis, dornase alfa caused worsening of lung function and increased exacerbations. There was an increase in death seen in COPD patients with the use of dornase alfa. Therefore, it is not recommended to use dornase alfa for any airway disease other than CF.

NEED TO KNOW

Pulmozyme® (dornase alfa) is FDA-approved only for CF patients.

It is contraindicated in patients with known hypersensitivity to dornase alfa or Chinese hamster ovary cell products. CF patients should continue all other therapies while receiving dornase alfa, but other aerosol medications (i.e., β-agonists or anticholinergics) should *never* be mixed in the same SVN with Pulmozyme. If the patient also requires nebulized bronchodilator therapy, the treatments should be given separately, and the nebulizer should be thoroughly rinsed before use with Pulmozyme. An alternative to using the nebulizer is to administer the bronchodilator by MDI. There are no specific recommendations regarding the sequence of such therapies, but the administration of a bronchodilator before Pulmozyme may enhance deposition.

Table 8-1 lists the recommended nebulizer devices with dornase alfa. Ultrasonic nebulization is not recommended because the drug may be inactivated by heat.

TABLE 8-1
Recommended Nebulizer Devices with Dornase alfa

Jet nebulizer	Compressor
Hudson T Up-draft II	Pulmo-Aide
Marquest Acorn II	Pulmo-Aide
PARI LC Plus	PARI PRONEB
PARI BABY	PARI PRONEB
Durable Sidestream	MOBILAIRE
Durable Sidestream	Porta-Neb
Nebulizer system	
eRapid Nebulizer System	

Modified from Pulmozyme product insert.

Dornase alfa must be stored in their protective foil pouch under refrigeration and protected from light until ready to use. Pulmozyme is supplied in unit-dose ampules of 2.5 mL, containing 1 mg dornase alfa/mL solution (2.5 mg/ampule). Do not use beyond expiration date stamped on the ampules or if the solution is cloudy or discolored.

Standard dosage is one ampule per treatment (i.e., 2.5 mg or 2.5 mL), aerosolized in a specific nebulizer, once or twice daily. This is a maintenance drug, and once therapy is begun, it is usually beneficial for the patient on a daily basis.

Side effects associated with dornase alfa are generally mild and usually resolve within the first several weeks of therapy. The most common side effects reported include pharyngitis, laryngitis, voice alteration, rash, chest pain, rhinitis, and conjunctivitis. Fever, dyspnea, and a decrease in FVC ≥10% may occur in less than 3% of patients.

N-Acetylcysteine

N-Acetylcysteine (NAC) is an antioxidant drug that has been studied orally for multiple uses such as liver, lung, and kidney disease. Its primary use, and where it is most effective, is as an antioxidant in the treatment of liver injury resulting from acetaminophen overdose. NAC has also been used as a mucolytic because it has the ability to hydrolyze and break apart sulfide bonds found in mucin. **Figure 8-3** shows a representation of NAC's proposed mechanism on a mucus molecule. It has been thought to decrease the viscosity of mucus, making it easier to clear. There is very little data to show that NAC is an effective mucolytic agent in humans with lung disease when administered through the aerosol route. Therefore, is not recommended to improve airway clearance.

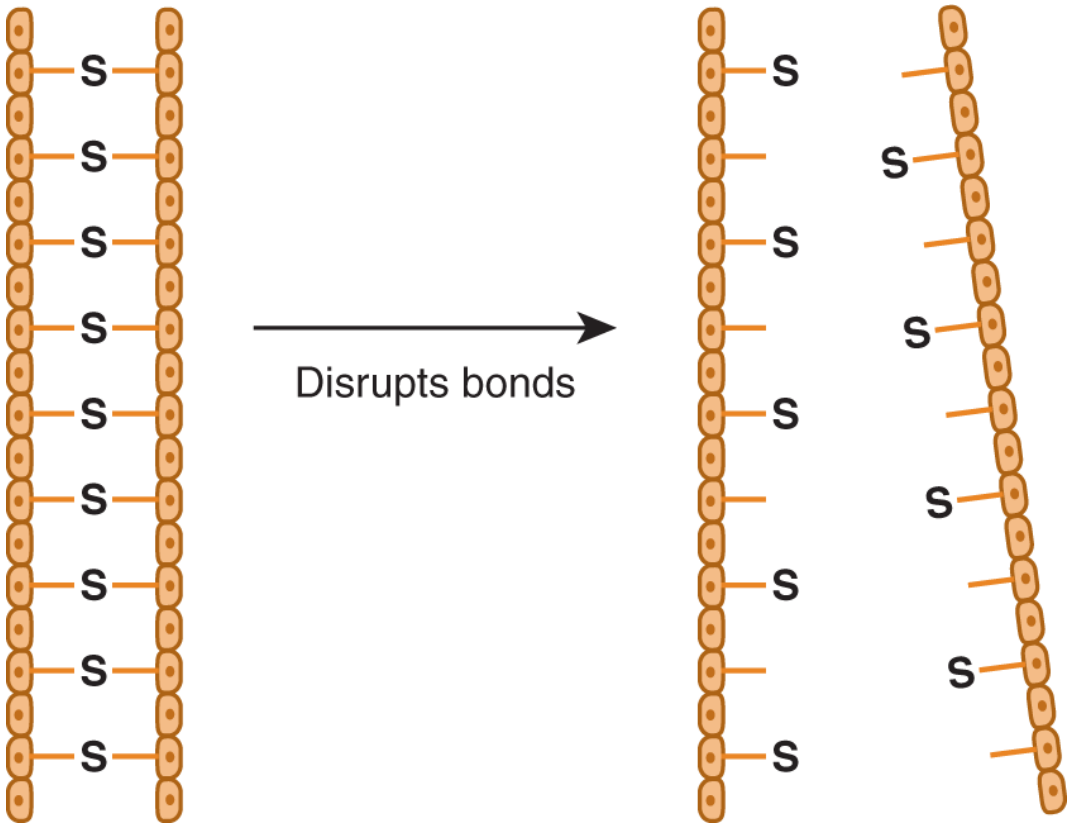


FIGURE 8-3 Mucolytic action of *N*-acetylcysteine (NAC).

Description

NAC is commercially available in unit-dose vials in two concentrations, 10 and 20%. The 10% solution may be administered undiluted, but the 20% solution should be diluted in a 1:1ratio with NS or sterile water for inhalation. Once the vials are opened, they should be stored in the refrigerator for up to 96 hours. The opened solution may turn a light purple color, but it does not affect the safety or efficacy.

NAC may cause an increased amount of liquefied bronchial secretions after administration. When cough is not adequate, suction equipment should be readily available for such patients. The therapist should remain with the patient for 10–15 minutes after aerosolized or instilled administration of acetylcysteine, and nursing or other support staff should be alerted to monitor for signs of sudden airway obstruction due to mucus plugging.

Acetylcysteine has also been reported to stimulate bronchospasm, even in patients without primary pulmonary disease but asthmatics are at the highest risk of this effect. If NAC is used, it is recommended that an aerosolized bronchodilator be administered before the administration of inhaled acetylcysteine. It is important to note that because of the tendency of NAC to stimulate bronchospasm, the therapist should always question an order to aerosolize it without a bronchodilator. The use of a β-agonist (i.e., albuterol) with NAC is standard practice; in this case, the bronchodilator is not given to relieve bronchospasm but rather to prevent it. NAC has also been reported to cause nausea, vomiting, stomatitis, fever, rhinorrhea, and drowsiness. Some respiratory therapy professionals have reported dermal reactions after repeated exposure to aerosolized NAC.

The drug is incompatible with inhaled amphotericin B, tetracycline, erythromycin, and ampicillin. These agents should not be mixed in the same solution. They may cause precipitation, a change in the clarity of the solution or a change in potency of either agent. Some materials that are found in nebulization equipment (e.g., rubber, iron, copper, and silver) may react and discolor when they come in contact with NAC solution.

NEED TO KNOW

A bronchodilator should always be used in conjunction with aerosolized acetylcysteine.

NAC may have a corrosive effect on metal parts and may irritate the mucosal membranes of the oropharynx. Patients should be instructed to rinse their mouths vigorously following the treatment.

Although NAC has a distinctive and somewhat offensive odor (i.e., associated with its sulfhydryl groups), it is actually tasteless. If a patient does not smell the drug before administration, it is unlikely that this odor should create cause for concern or the use of an alternative agent.

Nonrespiratory Use of NAC

NAC has been found to be an effective antidote for acetaminophen (e.g., Tylenol®) overdose when administered IV, orally, or by nasogastric tube. The metabolites associated with acetaminophen normally are broken down (detoxified) in the liver by glutathione, but when acetaminophen is taken in large quantities, glutathione stores become depleted and acetaminophen gets converted to toxic metabolites that cause liver failure. NAC acts as a glutathione substitute and can be effectively administered (orally) to protect the liver from toxicity associated with acetaminophen overdose.

Another use of NAC by oral administration is to prevent kidney damage that may occur secondary to clearance of IV contrast dye material. Patients undergoing cardiac catheterization for angiography or other imaging procedures in which contrast material is used may be given a pre-procedure oral dosage of acetylcysteine. This therapy may be less effective as once thought but is still used despite low efficacy because toxicity is low.

When NAC is requested by the physician for these uses, the order may be routed to the RCP because that department may have the primary in-house supply of the drug. Although the RCP does not administer the drug, he or she should be aware of its use and be able to respond to the physician's request. A typical order for a patient who has ingested an acetaminophen overdose is 140 mg/kg loading dose (which may be 20–50 mL of 20% acetylcysteine), then 70 mg/kg every 4 hours for 17 doses. It is often mixed with a cola beverage and drunk by the patient. It may be also instilled directly into a nasogastric tube. The dosage of NAC for this use is determined by the physician based on the amount of acetaminophen ingested, the patient's age and weight, and the time since ingestion occurred. There is also an IV form of NAC (Acetadote®) available for acetaminophen overdose. The IV formulation is administered over 21 hours.

The physician should refer to the *Physicians' Desk Reference* or other medical reference for dosage information for noninhalation uses of acetylcysteine.

Mucokinetic Agents

A **mucokinetic** agent is a medication or solution that increases the movement of mucous by ciliary activity or by increasing cough by improving expiratory airflow. β_2-Agonists may increase ciliary beat frequency and surfactant may improve cough clearance.

β_2-Adrenergic Agents

The clinical effects of β_2-agonists on mucociliary clearance are controversial. Stimulation of β_2-receptors increases cyclic adenosine monophosphates, which are regulators of ciliary beat in the airway. These agents also increase secretion production. It has been shown that these agents have little mucociliary clearance effect in patients with asthma and bronchitis. Short-acting and long-acting β_2-agonists have been studied in human and animals with healthy and depressed clearance. The studies show a modest but not long-lasting benefit to increase mucociliary clearance.

Surfactant

In healthy lungs, a bronchial surfactant layer located between periciliary fluid and mucus layer works by reducing sputum bonding to the airway epithelial cells. Surfactant can increase mucociliary clearance and decrease airway inflammation. Without surfactant, clearing mucus by coughing will be less effective. The use of aerosolized surfactant has been studied in patients with chronic bronchitis. It caused an improvement in lung function and improvement in sputum clearance by cilia. Ambroxol is an agent that aids in mucociliary clearance and the production of surfactant. It is not approved in the United States but has been used in other countries. There are conflicting data that show this agent may improve lung function and decrease exacerbations in patients with COPD.

Case Study 8-1

CF

Toby W, a 17-year-old, white, 150-lb male, was admitted to the adolescent unit with a chief complaint of exacerbation of his previously diagnosed CF and weight loss of 3 months' duration.

History and Physical Examination

History: The patient was diagnosed as having CF at 3 months of age. He is currently on enzyme replacement therapy, postural drainage and coughing with positive expiratory pressure therapy, and aerosol treatment four times a day at home. He uses oxygen as needed at 2 L/min via nasal cannula. He had all usual childhood vaccinations.

Family history: Toby is the third of three children; the other children are living and are well with no signs of CF. Both parents are living and well, as are both maternal and one paternal grandparent. Toby is in a mainstream school but is 2 years behind his age group in school. Patient denies smoking, alcohol, or recreational drug use. Patient recently has started dating.

Vital signs: Heart rate, 84 beats/min, steady and bounding; blood pressure, 130/80 mm Hg; respiratory rate, 18 breaths/min; temperature, 99.9°F (oral); and SpO_2, 89%.

Neurologic: Pupils equal and react to light and accommodation. Oriented ×3.

Psychiatric: Toby is becoming depressed and fatalistic. Typical statements include, "What's the use? CFers die early," "I get stared at all the time because of my coughing," and "Why can't I be like normal kids?"

Cardiovascular: Heart sounds bounding and slightly distant. Electrocardiography shows changes consistent with left ventricular hypertrophy (LVH).

Respiratory: Decreased lower lobe sounds bilaterally; crackles and rhonchi noted in bases during active inspiration and expiration. Cough loose, "sticky," and nonproductive. Expiratory wheezing noted on exertion.

Gastrointestinal: Patient has lost 20 lb in last 3 weeks. No complaints of pain or discomfort. Appetite decreased; states, "I don't want to use enzymes anymore; I want to eat what regular people do."

Skin: Dry, nonresilient.

Genitourinary: Within normal limits.

Laboratory Values

Chest radiograph: Comparison with films of 3 months ago reveals increased opacities in lower lobes bilaterally and presence of bronchograms. Increased left ventricular size. *Note:* Films are consistent with advanced CF and increased mucus production and retention. LVH suggests increased pulmonary vascular resistance.

Arterial blood gases: pH = 7.36, PCO_2 = 50 torr, PO_2 = 58 torr, HCO_3^- = 28 mEq/L, on room air

Electrolytes: Na^+ = 150 mEq/L, K^+ = 4.0 mEq/L, Cl^- = 115 mEq/L, and HCO_3 = 30 mEq/L.

Hematology: White blood cell count = 30,000/mm^3, hemoglobin = 17.5 g/dL, and hematocrit = 53%.

Diagnosis

1. Exacerbation of CF
2. Lower respiratory tract infection
3. Malnutrition/dehydration
4. Depression

Hospital Orders

Respiratory Care

1. Continuous high-humidity aerosol with 24% oxygen.
2. Aerosolized dornase alfa via SVN; alternate with SVN treatment of 4 mL 10% Mucomyst and 2.5 mg albuterol every 4 hours while awake.
3. Tobramycin 300 mg IV once daily.
4. Pneumatic vest every 4 hours while awake, following aerosol treatments.
5. Precede pneumatic vest with one puff albuterol MDI.

Diet

1. High-protein, high-calorie, low-carbohydrate supplements to keep caloric intake over 4000 kCal/day.

Questions

1. Explain why albuterol is being administered with Mucomyst?
2. Is Mucomyst/albuterol the safest and most effective mucolytic therapy for this patient? What alternative mucolytic would be more effective than acetylcysteine?
3. What particular hazards or side effects must be anticipated as a result of the use of dornase alfa and hypertonic saline if used in this patient?
4. Which type of nebulizer devices should only be used to administer dornase alfa and what dose/frequency would you recommend for this patient?

Expectorants and Bronchorrhea Agents

Bronchorrhea refers to the condition associated with excess thin and watery pulmonary secretions. It is similar to the rhinorrhea process in the nose, which is usually seen in the common cold and is often referred to as having a runny nose. Bronchorrhea can be induced by the use of drugs such as expectorants, one of which (hypertonic saline) has been already discussed.

Expectorants increase the amount of fluid in the respiratory tract and thus stimulate discharge of mucus with a cough. Expectorants are available in a wide variety of over-the-counter cough and cold remedies and are not routinely administered by RCPs. The use of hypertonic saline for sputum induction is the primary clinical application of bronchorrheic agents in respiratory care.

The use of saturated solution of potassium iodide (SSKI) as an expectorant in the treatment of asthma and chronic bronchitis has been reported since 1939. Typically, SSKI is not administered by the aerosol route, but rather by oral ingestion (mixed with water) or orally (as sodium iodide) in tablet form, and is thought to stimulate secretion of airway fluid. These therapies have not been shown to be effective for this indication.

Guaifenesin

Guaifenesin is considered to be an expectorant and stimulates increased mucus production and maintains the airway fluid layer. It is thought to decrease the viscosity and adhesiveness of secretions (enhances hydration of secretions) to enhance cough effectiveness. It has also been shown to inhibit cough receptor sensitivity, which results in an antitussive effect in patients with upper respiratory tract infections. Guaifenesin is available as syrup, extended-release tablet, or granules. Guaifenesin is the active ingredient in cold and cough remedies such as Mucinex® and Robitussin®. Guaifenesin has not been shown to be clinically effective in clinical trials of patients with

chronic bronchitis, but symptoms of cough, chest congestion, and mucus thickness were improved in patients with upper respiratory tract infections. Common side effects include headache, dizziness, and nausea/vomiting at high doses. The formation of kidney stones has also been reported when used at excessive doses.

Inhaled mannitol is currently being investigated for use in controlling mucus and improving pulmonary function in CF and bronchiectasis patients. Although classically utilized as a diuretic (mentioned in Chapter 13, Cardiovascular and Renal Pharmacology), mannitol has been shown to change the physical properties of mucus associated with CF and non-CF bronchiectasis. Aerosolized mannitol improved the surface properties of secretions by drawing water into the airways and this resulted in improved FEV_1 and FEF 25–75% and enhanced quality of life in study subjects. Inhaled mannitol is not approved for use in the United States at this time.

Sodium Bicarbonate

Sodium bicarbonate works by altering the pH and disrupting the stability of the mucopolysaccharide strands. Although sodium bicarbonate has not been demonstrated to dissolve sputum, it may be useful in tracheal irrigation for patients with artificial airways. The use of heat-moisture exchangers in mechanical ventilation may result in thickened secretions in some patients, and the use of sodium bicarbonate as a thinning agent is usually well-tolerated and inexpensive.

Sodium bicarbonate is a somewhat benign mucokinetic agent, but there are some contraindications to its use. If a patient is on a severe sodium-restricted diet, sodium bicarbonate may be contraindicated. Similarly, sodium bicarbonate should not be used if the patient has a severe preexisting metabolic alkalosis.

There are few side effects or hazards when using a 2.0 or 4.2% solution of sodium bicarbonate as a mucolytic or mucokinetic agent. Dosages of 3–5 mL of 4.2% sodium bicarbonate may be administered as frequently as necessary to promote mucokinesis.

Suction equipment should always be available when administering a mucolytic agent because sudden mucolysis may cause airway obstruction.

If a bronchodilator is used in conjunction with sodium bicarbonate, it should be mixed only at the bedside immediately before administration. When bicarbonate is mixed with a sympathomimetic drug (e.g., albuterol, or levalbuterol), the stability of the solution will be altered and discoloration may occur, typically causing the solution to turn pink. There is evidence that the alkaline solution reduces the potency of catecholamine-type bronchodilators; the effect is less pronounced when used with noncatecholamine β-adrenergic bronchodilators such as albuterol or levalbuterol.

Review Questions

1. Explain the difference between (a) bland aerosol, (b) mucolytic, and (c) expectorant and list the available agents of each.
2. Describe the composition of a normal mucus molecule.
3. Describe the mechanism of action dornase alfa and the clinical indication for its use.
4. Describe how NAC accomplishes mucolysis and list the common adverse effects and how they can be prevented.
5. Describe the (a) brand names; (b) standard dosage and concentration of each solution; (c) contraindications; (d) side effects; and (e) special considerations (if any) of dornase alfa and *N*-acetylcysteine.
6. Define sputum induction and list a wetting agent that would be appropriate for this use.

Posttest

For each of the following questions, try to select the one best answer from the choices given.

1. Which of the following is not a bland aerosol?
   a. Half-NS
   b. Sterile distilled water
   c. 0.9%NaCl
   d. Sodium bicarbonate
2. Which of the following agents is/are hypertonic?
   a. 0.9%NaCl
   b. 5%NaCl
   c. 10%NaCl
   d. b and c
3. Which of the following is considered an expectorant?
   a. Normal saline
   b. Hypertonic saline
   c. Mucomyst®
   d. Guaifenesin
4. Sodium bicarbonate may be administered by aerosol in which of the following concentrations?
   a. 5 and 10%
   b. 2 and 4.2%
   c. 10 and 20%
   d. 5% only
5. Mucomyst® is the brand name of:
   a. sulfur hydroxide.
   b. *N*-acetylcysteine (NAC).
   c. dornase alfa.
   d. sodium bicarbonate.
6. NAC may be administered orally for which of the following conditions?
   1) Aspirin overdose
   2) Acetaminophen overdose

3) Before cardiac angiography to prevent renal failure
4) Barbiturate overdose

a. 1 and 2 only
b. 2 and 3 only
c. 3 and 4 only
d. 1, 2, 3, and 4

7. Side effects of aerosolized NAC may include:
   a. bronchospasm, acute airway obstruction, and oropharyngeal irritation.
   b. bronchodilation, oropharyngeal irritation, and fluid overload.
   c. liver damage, bronchospasm, and renal failure.
   d. kidney stones, airway obstruction, and hypernatremia.
8. Which of the following are contraindications for the use of NAC as an aerosol?
   a. Tylenol® overdose
   b. Administration to a semicomatose patient without suction equipment and monitoring
   c. Administration to a patient with bronchiectasis
   d. Administration in concentrations over 10%
9. In which of the following patients should the RCP consider diluting the bronchodilator with sterile distilled water rather than NS for an SVN treatment given every 3 hours?
   a. Postacute myocardial infarction
   b. Diabetic coma
   c. Severe salt restriction
   d. Acetaminophen overdose
10. What is the mechanism of action of NAC in promoting mucolysis?
    a. Lysis of proteins in mucus
    b. Increasing alkalinity of mucus
    c. Hygroscopic properties
    d. Disrupting disulfide bonds in mucus molecule
11. What is the mechanism of action of dornase alfa as a mucolytic agent?
    a. Lysis of DNA in cellular debris of purulent secretions
    b. Disruption of disulfide bonds
    c. Altering the pH of mucopolysaccharide chains

d. Altering the DNA composition of alveolar type II cells

12. Which of the following statements is true regarding the use of bronchodilators with dornase alfa in aerosol therapy?
    a. Only anticholinergic bronchodilators may be mixed with dornase alfa for nebulization.
    b. Only sympathomimetic bronchodilators may be mixed with dornase alfa for nebulization.
    c. Both anticholinergic and sympathomimetic bronchodilators may be mixed with dornase alfa for nebulization.
    d. Neither anticholinergic nor sympathomimetic bronchodilators should be mixed with dornase alfa for nebulization.
13. Dornase alfa has been approved for daily use by:
    a. CF patients only.
    b. patients with CF or tuberculosis.
    c. patients with CF, tuberculosis, or purulent bronchiectasis.
    d. patients with CF or purulent bronchiectasis.
14. Which of the following statements is true regarding the nebulization of dornase alfa?
    a. Most small-volume jet nebulizers currently available are recommended for use with dornase alfa.
    b. There are specific jet nebulizers recommended for use with dornase alfa.
    c. There are specific jet and ultrasonic nebulizers that are recommended for use with dornase alfa.
    d. Ultrasonic nebulizers are ideal for nebulizing dornase alfa.
15. Side effects of aerosolized dornase alfa include:
    a. bronchospasm, rash, and fever.
    b. pharyngitis, laryngitis, and voice alteration.
    c. headache, nausea, and tachycardia.
    d. bronchospasm, laryngitis, and headache.

References/Recommended Readings

Acetadote [package insert]. Nashville, TN: Cumberland Pharmaceuticals Inc; 2016.

Acetylcysteine solution, USP Sterile [package insert]. Shirley, NY: American Regent, Inc; 2014.

Aitkin ML, Burke W, McDonald G, et al. Recombinant human DNase inhalation in normal subjects and patients with cystic fibrosis. *JAMA*. 1992;267:9147.

Albrecht HH, Dicpingaitis PV, Guenin EP. Role of guaifenesin in the management of chronic bronchitis and upper respiratory tract infections. *Multidiscip Respir Med*. 2017;12:1-11.

Anzueto A, Jubran A, Ohar JA, et al. Effects of aerosolized surfactant in patients with stable chronic bronchitis. *JAMA*. 1997;278:1426-1431.

Bilton D, Tino G, Barker AF, et al. Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomized, controlled trial. *Thorax*. 2014;69:1073-1079.

Caramori G, Di Gregorio C, Carlstedt I, et al. Mucin expression in peripheral airways of patients with chronic obstructive pulmonary disease. *Histopathology*. 2004;45:477-484.

Daviskas E, Anderson SD, Jacques A, et al. Inhaled mannitol improves the hydration and surface properties of sputum in patients with cystic fibrosis. *Chest*. 2010;137(4):861-868.

Decramer M, Rutten-van Molken M, Dekhuijzen PN, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomized placebo-controlled trial. *Lancet*. 2005;365:1552-1560.

Donaldson SH, Bennett WD, Zeman KL, et al. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. *N Engl J Med.* 2006;354:229.

Elkins MR, Robinson M, Rose BR, et al. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med*. 2006;354:229-240.

Fahy JV. Goblet cell and mucin gene abnormalities in asthma. *Chest*. 2002;122:320S-326S.

Fahy JV, Dickey BF. Mucus function and dysfunction. *N Engl J Med*. 2010;363:2233-2247.

Henke MO, Saha AS, Rubin BK. The role of airway secretions in COPD: clinical applications. *COPD*. 2005;3:377.

Hubbard X, McElvaney NG, Birrer P, et al. A preliminary study of aerosolized recombinant human deoxyribonuclease I in the treatment of cystic fibrosis. *N Engl J Med*. 1992;326:812.

Kanter MZ. Comparison of oral and I.V. acetylcysteine in the treatment of acetaminophen poisoning. *Am J Health Syst Pharm*. 2006;63(19):1821-1827.

Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. *JAMA*. 2003;289(5):553-558.

King M, Rubin BK. Mucus-controlling agents: past and present. *Respir Care Clin N Am*. 1999;5:575.

Laube BL, Auci RM, Shields DE, et al. Effect of rhDNase on airflow obstruction and mucociliary clearance in cystic fibrosis. *Am J Respir Crit Care Med*. 1996;153(2):752-760.

Lynch RM, Robertson R. Anaphylactoid reactions to intravenous N-acetylcsysteine: a prospective case-controlled study. *Accid Emerg Nurs*. 2003;12(1):10-15.

Maestrelli P, Saetta M, Mapp CE, et al. Remodeling in response to infection and injury. Airway inflammation and hypersecretion of mucus in smoking subjects with chronic obstructive

pulmonary disease. *Am J Respir Crit Care Med*. 2001;164:S76-S80.
Malerba M, Ponticello A, Radaeli A, et al. Effect of twelve-months therapy with oral ambroxol in preventing exacerbations in patients with COPD. Double-blind, randomized, multicenter, placebo-controlled study (the AMETHIST Trial). *Pulm Pharmacol Ther*. 2004;17:27-34.
McCoy K, Hamilton S, Johnson C. Effects of 12-week administration of dornasealfa in patients with advanced cystic fibrosis lung disease. Pulmozyme Study Group. *Chest*. 1996;110:889-895.
O'Donnell AE, Barker AF, Iliwite JS, et al. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. rhDNase Study Group. *Chest*. 1998;113:1329-1334.
Ordonez CL, Khashayar R, Wong HH, et al. Mild and moderate asthma is associated with airway goblet cell hyperplasia and abnormalities in mucin gene expression. *Am J Respir Crit Care Med.* 2001;163:517-523.
Prescott E, Lange P, Vestbo J. Chronic mucus hypersecretion in COPD and death from pulmonary infection. *Eur Respir J*. 1995;8:1333-1338.
Pulmozyme [package insert]. San Francisco, CA: Genentech, Inc; 2018.
Ramsey BW, Dorkin HL. Consensus conference: practical applications of Pulmozyme. *Pediatr Pulmonol*. 1994;17:404.
Restrepro RD. Inhaled adrenergics and anticholinergics in obstructive lung disease: Do they enhance mucociliary clearance? *Respir Care*. 2007;52:1159-1173.
Rubin BK. Aerosol medications for treatment of mucus clearance disorders. *Respir Care*. 2015;60:825-832.
Saetta M, Turato G, Baraldo S, et al. Goblet cell hyperplasia and epithelial inflammation in peripheral airways of smokers with both symptoms of chronic bronchitis and chronic airflow limitation. *Am J Respir Crit Care Med*. 2000;161:1016-1021.
Sathe NA, Krishnaswami S, Andrews J, et al. Pharmacologic agents that promote airway clearance in hospitalized patients: a systematic review. *Respir Care*. 2015;60(7):1061-1070.
Strickland SL, Rubin BK, Haas C, et al. AARC Clinical Practice Guideline: effectiveness of pharmacologic airway clearance therapies in hospitalized patients. *Respir Care*. 2015;60:1071-1077.
Wilkins RL, Stoller JK, Kacmarek RM, eds. *Egan's Fundamentals of Respiratory Care.* 9th ed. St. Louis, MO: Mosby Elsevier Co; 2009.
Tepel M, van der Giet M, Schwarzfeld C, et al. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med*. 2000;343(3):180-184.
Williams OW, Shrafkhaneh A, Kim V, et al. Airway mucus: from production to secretion. *Am J Respir Cell Mol Biol*. 2006;34:527-536.
Wilmott RW, Amin RS, Colin AA, et al. Aerosolized recombinant human DNase in hospitalized cystic fibrosis patients with acute pulmonary exacerbations. *Am J Respir Crit Care Med*. 1996;153:1914.
Ziment I. *Respiratory Pharmacology and Therapeutics.* Philadelphia, PA: WB Saunders Co; 1978.

© Anna RubaK/ShutterStock, Inc.

OUTLINE

Introduction
Surface Tension
Surfactant
  Neonatal RDS
Surfactant Replacement Drugs
  Indications for Exogenous Surfactants
  Surfactant Replacement Drugs

Objectives

After completion of this chapter and its learning activities, you will be able to:

1. Define surface tension and describe the clinical importance of surface tension as it relates to the work of breathing.
2. Describe the physiologic purpose of pulmonary surfactant.
3. Describe clinical indications for the use of surfactant replacement drugs.
4. Compare and contrast the three surfactant replacement drugs currently in use in the United States with relation to:
   a. brand names
   b. indications
   c. contraindications
   d. side effects/adverse reactions

   e. dosage and route of administration
5. Suggest the appropriate surface-active agent, including dosage and method of delivery, given a patient case study.

KEY TERMS

Prophylactic treatment
Rescue treatment
Respiratory Distress Syndrome (RDS)
Surface tension
Surfactant

Introduction

This chapter will review the drug class, surfactants. Endogenous surfactant is a phospholipid compound whose purpose is to reduce alveoli collapse during end-expiration by decreasing surface tension within airways and the alveoli. Surface tension is the physical property that creates tension at a fluid–air interface, similar to that of soap bubble. Surface tension is a necessary component of passive exhalation (i.e., the tendency of the lungs to return to a resting state). In the newborn, the first few breaths of life are the most difficult because the physiologic detergent surfactant has not yet been distributed evenly throughout the lungs. In premature newborns, surfactant production may be inadequate, leading to poor distribution of ventilation and extreme work of breathing. Surfactant replacement therapy is now an integral part of resuscitation and management of premature newborns and has significantly reduced the morbidity and mortality of prematurity.

Although a practitioner may see only a few patients in a year who may benefit from these therapies, it is imperative to retain a working knowledge of the drugs, proper administration, and their applications.

Surface Tension

Surface tension is the result of the attraction (cohesion) of like molecules at the surface of a liquid. This occurs when a liquid is in contact with gas. The liquid molecules on the surface are attracted inward; thus, surface tension makes the liquid contract to minimize its surface area. There are several intermolecular forces that draw the liquid particles together and the particles are pulled toward the rest of the liquid (**Figure 9-1**). It is this property that makes a drop of water form a bead or take on a semicircular shape instead of a formless puddle. In the alveoli, there is a thin layer of water on the surface that is in contact with air within the alveoli. The interaction of the water in contact with the air causes surface tension, which in turn, causes the layer of water molecules to pull tightly together and acts to collapse the alveoli by increasing the pressure within the alveoli. This phenomenon is described by Laplace's law. Laplace's law describes the relationship between the internal pressure in a sphere (bubble, drop, alveoli, etc.), amount of surface tension, and the radius of the sphere. In the alveoli, Laplace's law is as follows:

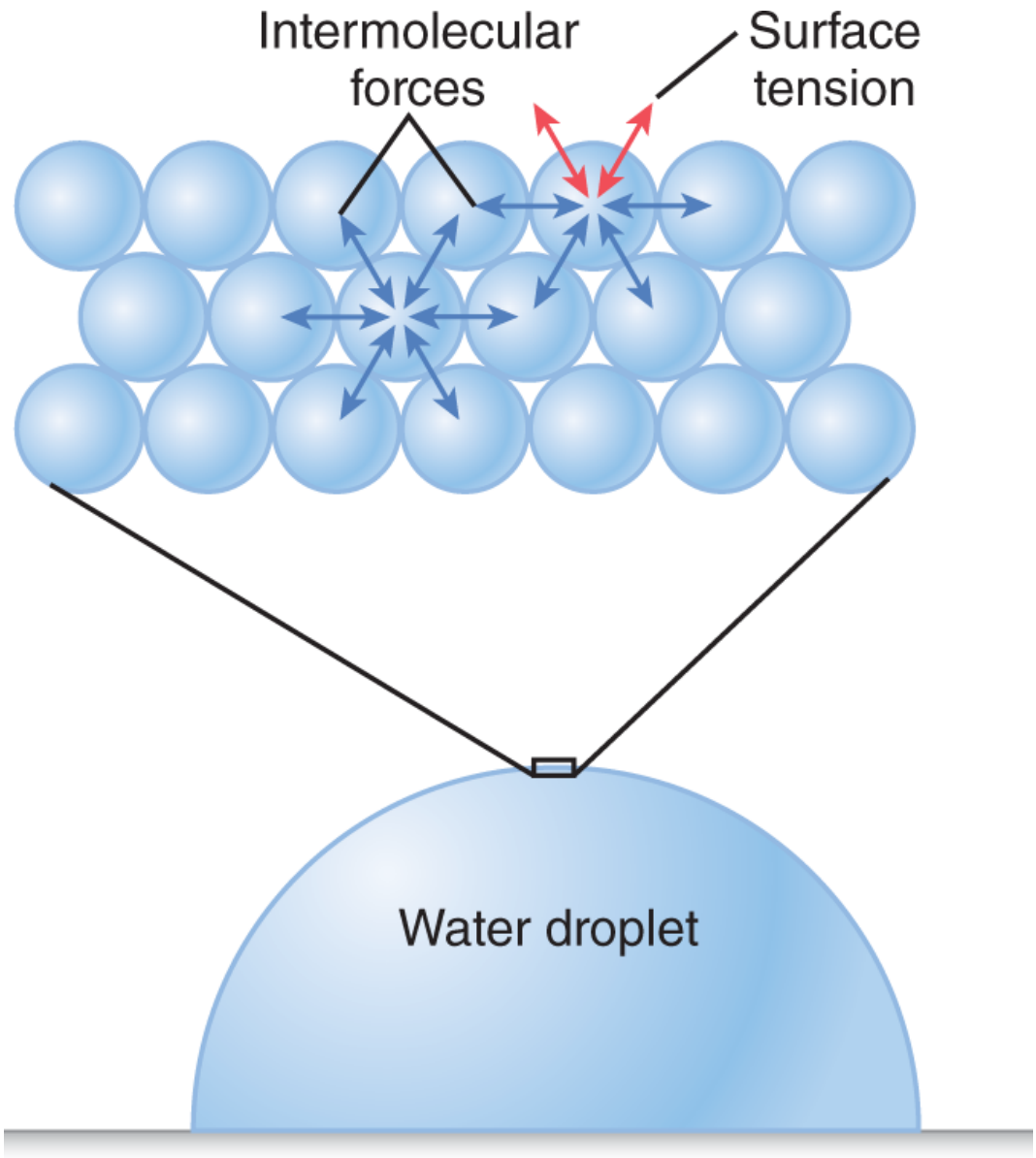


FIGURE 9-1 The concept of surface tension. The intermolecular forces attract water molecules inward toward each other into the form of a sphere.

Description

As the surface tension of the alveoli increases, it causes an increase in collapsing pressure of the alveoli and forces the air out of the alveoli (**Figure 9-2**).

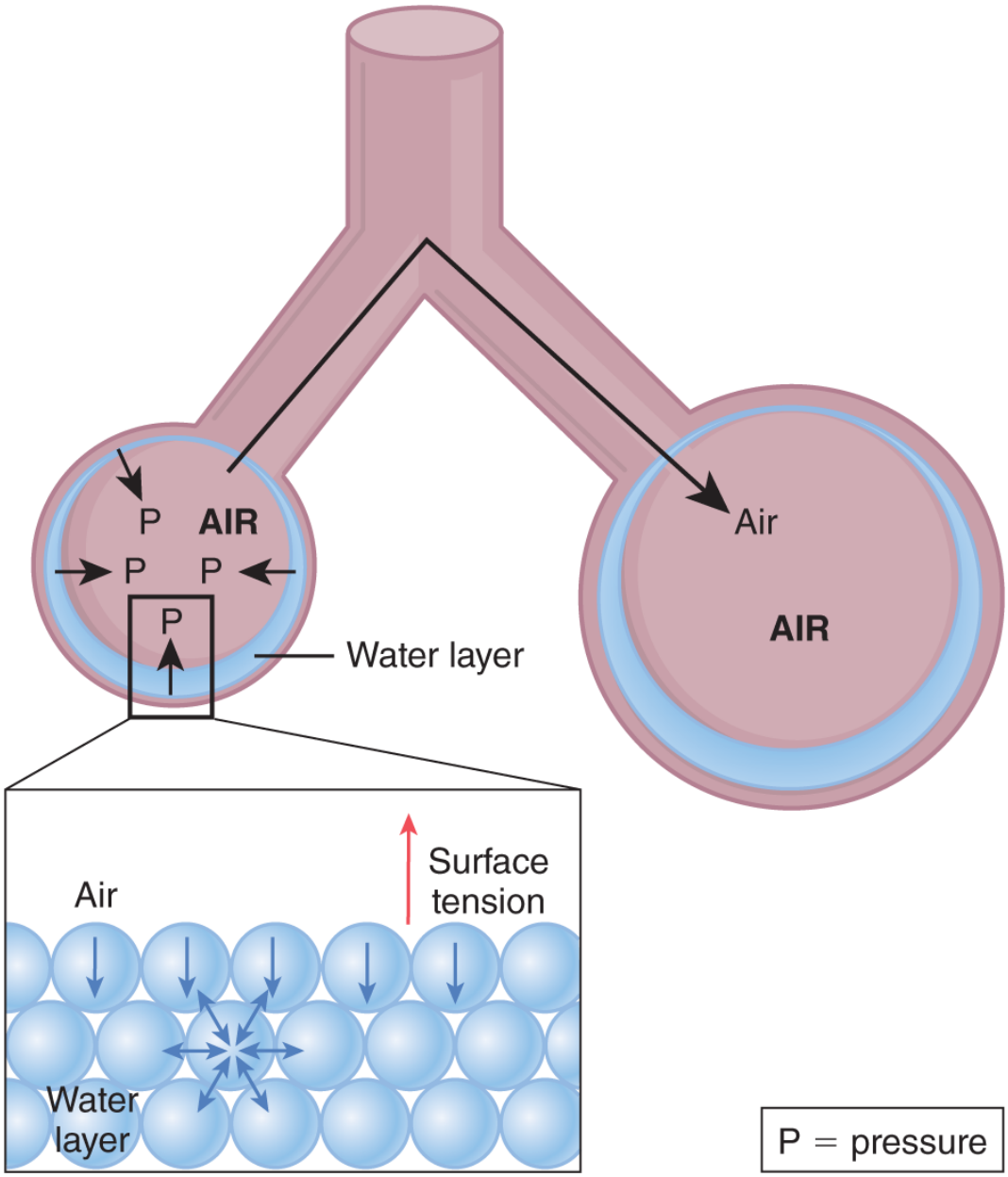


FIGURE 9-2 The thin water layer interacts with the air within the alveoli. The water does not want to interact with the gas (air), which causes water molecules move closer together, away from the air. This interaction causes increase in surface tension within the alveoli, which results in an increasing collapsing pressure within the alveoli.

Description

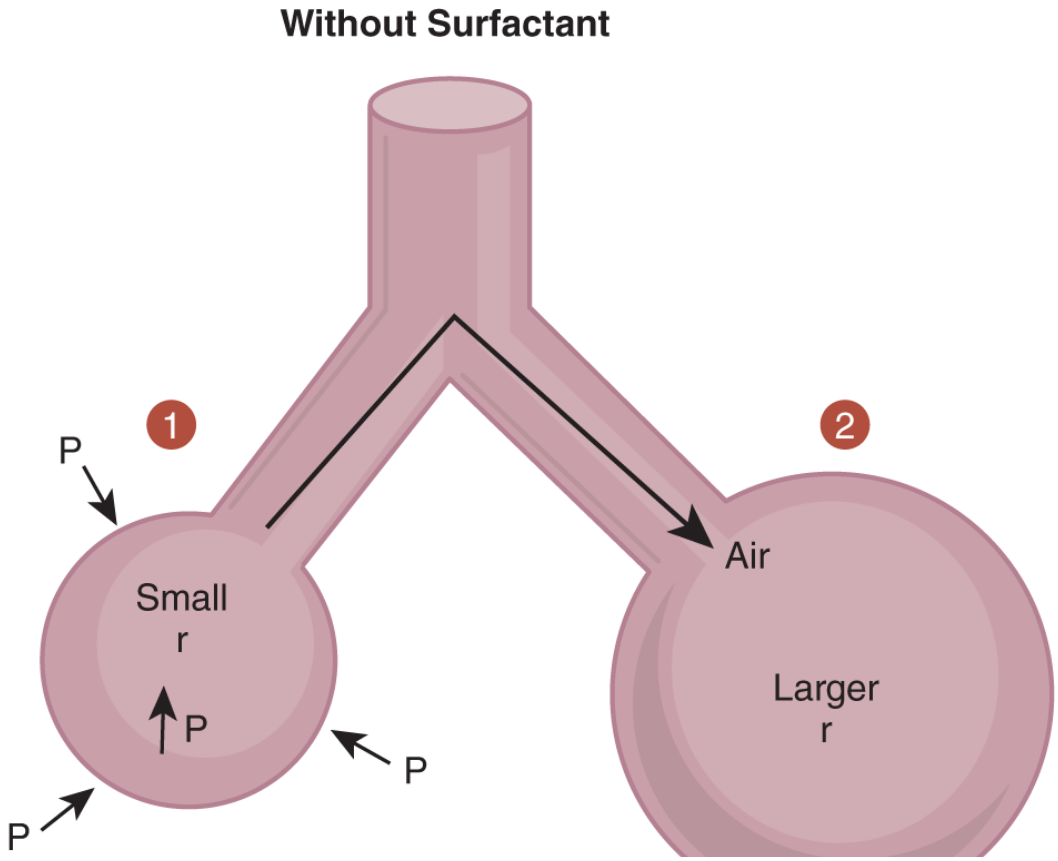
When surface-active agents, such as detergents, are added to such a liquid, the drop actually dissolves into a puddle because the

cohesion between the molecules on its surface has been broken. These agents lower the surface tension of the liquid.

A detergent is a substance that reduces surface tension; this is the basis on which laundry detergents work. When cleaning products are used, they reduce surface tension to allow the water to penetrate the material in the clothing and enable the dirt or stain to be removed from the clothing. In the lungs, detergents or surfactants are used to reduce surface tension to bring down the work of breathing and improve distribution of ventilation.

Surfactant

Pulmonary **surfactant** is the naturally occurring (endogenous) detergent that reduces and regulates alveolar surface tension of the liquid that lines the alveoli. The surfactant forms a liquid film along the water–air alveolar surface. It decreases the cohesiveness of the water molecules, which reduces surface tension, decreases collapsing pressure, and allows the alveoli to expand (**Figure 9-3**). It ultimately decreases the effort to take a breath and increases lung compliance. Surfactant is a mixture of phospholipids and surfactant proteins (SPs) (e.g., types SP-A, SP-B, SP-C, and SP-D). The most abundant phospholipid in surfactant is a phospholipid called dipalmitoylphosphatidylcholine. Surfactant is produced and stored in alveolar type II cells. Without surfactant, the surface tension of pulmonary secretions has a strong cohesive force that contributes to alveolar collapse and opposes inflation.



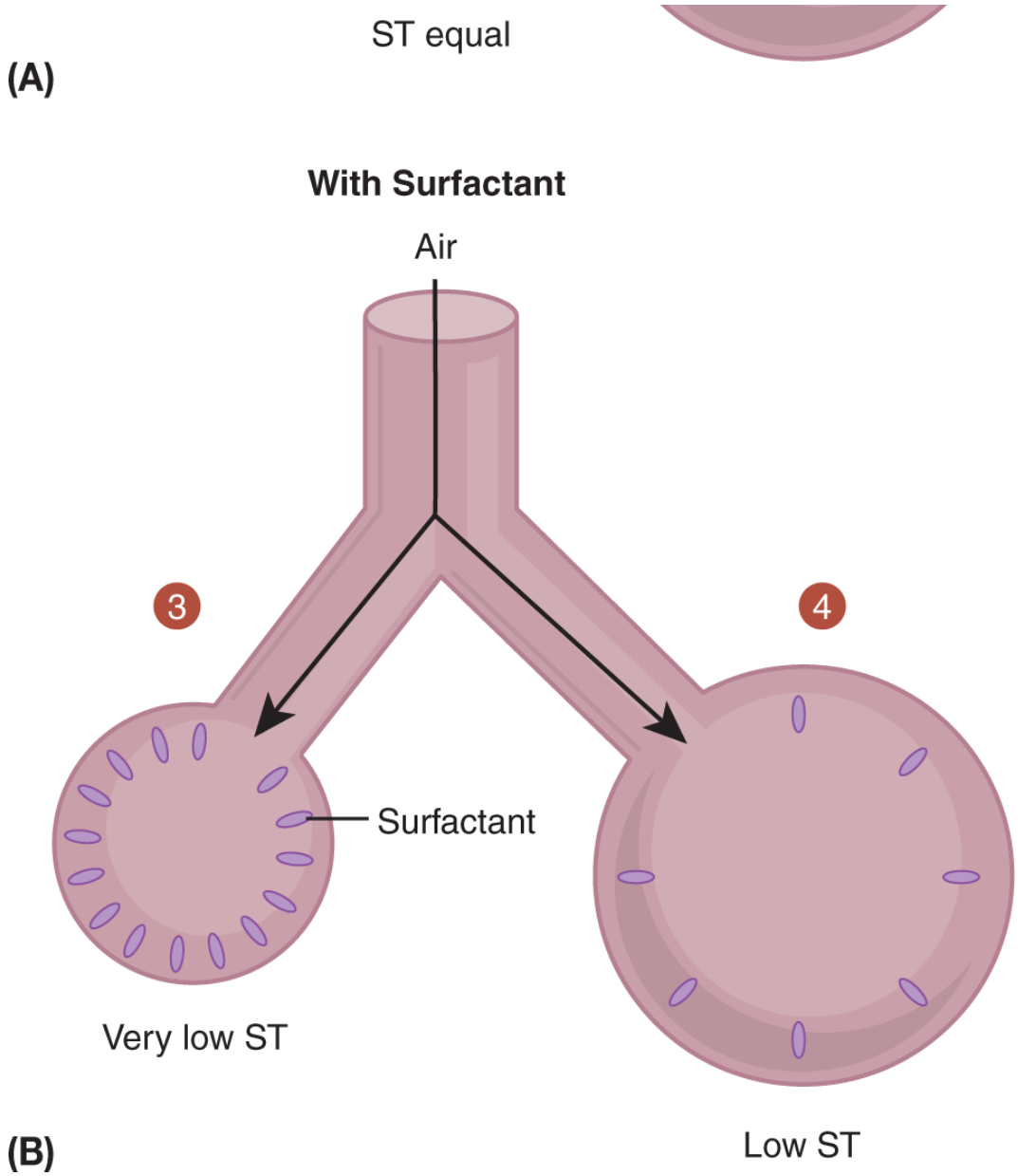


FIGURE 9-3 (**A**) 1 is more likely to collapse and harder to inflate than 2 owing to an increased collapsing pressure. (**B**) 3 has less surface tension based on a smaller area and both 3 and 4 have low pressure because of surfactant lowering surface tension. In this case, air will allow 3 to reinflate quicker until 3 and 4 are equal in size.

ST= surface tension, P=pressure, r= radius.

Description

Surfactant is constantly produced and replenished when the alveolar type II cells are stimulated. Atelectasis sometimes occurs

resulting from the lack of stimulation of these cells by deep breathing. In this case, alveolar collapse occurs when the surface tension is not balanced by surfactant. Atelectasis may also persist in the premature newborn when insufficient surfactant is present at birth.

Within moments of birth, the newborn's work of breathing is minimal (as it should be) because the surfactant is present and distributed throughout the lungs. Under normal physiologic conditions, an inspiratory effort of −5 to −10 cm H_2O pressure will generate enough force to provide a sufficient tidal volume. An infant's first breath may require −40 to −100 cm H_2O pressure, but the presence of surfactant makes subsequent breaths easier. In the premature newborn, surfactant may be absent or present only in small quantities. Surfactant deficiency is the primary cause of **respiratory distress syndrome (RDS)** in premature infants. Another cause of RDS in infants is surfactant dysfunction. This is usually because of surfactant inactivation. Infants born with a surfactant deficiency quickly develop alveoli collapse and difficulty breathing as a result of the effort required to overcome surface tension on each breath (Figure 9-3).

There has been great scientific interest in developing a surfactant replacement that could be used for treatment of disorders characterized by a lack of surfactant (e.g., RDS). Although research continues in the use of surfactant replacement drugs for acutely ill adults (acute lung injury oracute RDS), the three currently available surfactants are approved only for use in premature infants or those who develop RDS. Dosages and guidelines provided in the following sections are limited to use of exogenous surfactant for RDS prevention or rescue. However, there has been considerable success in using this therapy in term infants with meconium aspiration, neonatal pneumonia, and in some children with pulmonary hemorrhage. Some institutions are currently using exogenous surfactants in these populations as an off-label therapy, but dosing guidelines are not available. Rigorous research continues for an appropriate exogenous surfactant composition and delivery method for use in older children and adults.

Neonatal RDS

Neonatal RDS is a condition of pulmonary dysfunction that occurs immediately or shortly after birth. The severity can increase over the first few days of life and can either resolve in 2–4 days or may led to death or respiratory failure if left untreated. This syndrome presents with symptoms of cyanosis, grunting, and tachypnea. It can progress to respiratory failure, causing difficulty or excessive work of breathing, poor ventilation, oxygenation, and deteriorating blood gases. RDS is caused by a combination of immature lungs and a deficit of pulmonary surfactant. It occurs most commonly in preterm babies. The incidence of RDS in an infant born between 24 and 31 weeks' gestation is 92–57%. The lower the gestational age, the higher the incidence of developing RDS. Many strategies or therapies for the treatment or prevention of RDS have been studied over the last few decades. Neonatology has greatly improved the survival rate of these infants. Steroids, antibiotics, and tocolytics (anticontraction medications) are used successfully to prevent RDS before birth. Delaying umbilical cord clamping (30–60 seconds), warming, early continuous positive airway pressure (CPAP), and reserving mechanical ventilation have also led to improved outcomes in preterm infants; but despite advances, surviving patients are still developing complications of bronchopulmonary dysplasia (BPD)because of positive pressure ventilation. Surfactant therapy has transformed respiratory care in preterm infants. Neonatal morbidity and mortality have decreased significantly since the launch of these agents in the 1990s. Early attempts to provide surfactant replacement drugs concentrated on an aerosol drug that could be deposited in the lungs by mechanical (assisted) ventilation or by patient effort. This method of administration was not found to be effective. Different nebulizer devices with higher doses of surfactant are still being studied. Current surfactant replacement therapy involves instillation of the surfactant replacement drug through the endotracheal tube (ETT), followed by manual or mechanical ventilation and position changes of the newborn to provide distribution of the drug. After administration, the infant is either continued on mechanical ventilation or immediately extubated to

CPAP when spontaneous breathing has resumed. Administration of surfactant without endotracheal intubation has been studied in an effort to reduce lung injury causes by positive pressure ventilation by placing a specifically designed catheter into the trachea of the infant for surfactant administration while the baby is kept on CPAP. This method has not yet shown improved survival or reduced BPD in infants at this time.

Surfactant Replacement Drugs

There are currently three forms of surfactant replacement drugs approved by the Food and Drug Administration (FDA). Beractant (Survanta®), calfactant (Infasurf®), and poractant alfa (Curosurf®) are natural bovine or pig lung extracts (natural surfactants) to which stabilizing components have been added to closely resemble the surface tension lowering properties of natural surfactant. All these agents are approved to be administered into an endotracheal tube. Lucinactant (Surfaxin®) is a peptide-containing synthetic (nonanimal derived) surfactant that was once FDA-approved but is now unavailable and being studied with an aerosol administration device. Surfaxin was shown to be as effective as in the rescue treatment and prevention of RDS compared with animal-derived surfactants. The advantage of the natural surfactants is a quicker onset of action. The potential advantage of a synthetic product is a decreased risk of infants acquiring an infectious disease and immunologic sensitivity, but as of now, there are no synthetic products commercially available in the United States.

Exogenous surfactant is a mixture of phospholipids and proteins. The phospholipid components decrease the surface tension and the proteins help decrease surface tension as well as enhance distribution of the compound at the water–air interface in the alveoli. Surfactant therapy has been shown to be most effective and reduce mortality rates in infants born less than 30 weeks' gestation or with a birth weight of less than 1250 g. The administration of surfactant has also reduced the incidence of pneumothorax, pulmonary interstitial emphysema, and BPD in this population. The three approved drugs are similar in dosage and administration guidelines, as well as contraindications, side effects, and adverse reactions.

Indications for Exogenous Surfactants

Exogenous surfactants are effective at reducing mortality and pulmonary-related morbidity. The indications of lung surfactants are the following:

1. **Prophylactic treatment**, or preventive treatment, of premature infants at a high risk of developing RDS, administered within 30 minutes of birth.
2. **Rescue treatment** of premature infants with established RDS ideally, administered within first few hours (2–3 hours) of life.

The specific indications for each exogenous lung surfactant can be found in **Table 9-1**.

TABLE 9-1
Sources of Available Surfactants and Indications

Surfactant	Brand Name	Source	Prophylactic	Rescue Treatment
Beractant	Survanta	Natural (bovine)	Premature infants < 1250 g birth weight or with evidence of surfactant deficiency	Infants with RDS confirmed with X-ray and requiring mechanical ventilation
Calfactant	Infasurf	Natural (bovine)	Premature infants <29 wk of gestational age	Infants ≤72 h of age with confirmed RDS requiring mechanical ventilation
Poractant alfa	Curosurf	Natural (porcine)		Rescue treatment in premature infants with RDS
Lucinactant	Surfaxin	Synthetic, protein analog	Withdrawn from market	
			Currently, being studied for aerosolized administration	

RDS: respiratory distress syndrome.

Prophylactic treatment with a surfactant replacement drug should be administered before the onset of respiratory failure associated with RDS. The rescue treatment refers to infants who develop RDS (often these are infants who did not meet the criteria for prophylactic use of surfactant replacement drugs, e.g., full-term gestation or a birth weight over 1250 g) and require mechanical ventilation.

NEED TO KNOW

Prophylactic or prevention treatment for surfactant replacement is for prevention of RDS in very low-birth-weight infants (<1250 g)/<29 weeks' gestation or those with evidence of surfactant deficiency who are at risk for developing RDS. Rescue treatment is for infants who have developed RDS.

Surfactant inactivation and dysfunction may be seen in conditions other than RDS. Meconium aspiration syndrome, persistent pulmonary hypertension of the newborn, pneumonia, and pulmonary hemorrhage are disorders where surfactant replacement is of interest. Surfactant administration to newborns with meconium aspiration syndrome improves oxygenation and reduces the need for extracorporeal membrane oxygenation but does not affect mortality. Similar results were seen when surfactant replacement was administered to neonates with pneumonia, but the data is limited to small studies and case reports. Surfactant therapy may be considered for treatment of these conditions that may also cause surfactant deficiency/inactivation, but the data is limited.

Surfactant Replacement Drugs

This section will discuss the three FDA-approved (Table 9-1) exogenous surfactants available for use, as well as describe the appropriate intratracheal administration techniques. As stated above, natural surfactant is made of 80% phospholipids, 8% neutral phospholipids, and SPs, SP-A, SP-B, SP-C, and SP-D. SP-A is a large molecular weight, hydrophilic protein. It regulates secretion of surfactant from alveolar type II cells and the reuptake of surfactant for reuse. SP-B and SP-C are low molecular weight, hydrophobic proteins that help enhance adsorption and spreading of the surfactant throughout the air–liquid alveoli interface. SP-D is also a large hydrophilic protein similar to SP-A, which may regulate the production of inflammatory mediators in the alveoli but with no role in surfactant function. All three available agents are administered directly into the lungs. The clearance of the surfactant is rapid, and the surfactant replacement drugs are reutilized and recycled by the lungs' natural

mechanisms. Oxygenation should improve within minutes of administration of these agents. Extubation should occur as soon as possible, but quick extubation may be associated with a higher risk of apnea of prematurity. Surfactants should only be administered by clinicians experienced in intubation and ventilator management of premature infants.

Beractant (Survanta [Intratracheal Suspension])

Beractant is a naturally derived pulmonary surfactant intended for intratracheal use only. It is a bovine lung extract containing 25 mg/mL phospholipids (disaturated phosphatidylcholine), neutral lipids, triglycerides, free fatty acids, and <1 mg/mLSPs, SP-B and SP-C to which colfoscerilpalmitate, palmitic acid, and tripalmitin are added to standardize solution and approximate natural surfactant. Beractant reduces alveolar surface tension to improve distribution of ventilation and reduce work of breathing. It does not contain SP-A. Specific FDA-approved indications for beractant can be found in Table 9-1. It can be used for prevention or as rescue treatment in RDS. It should be used preferably within 15 minutes of birth when being used for prevention and should be used preferably within 8 hours of age when being used as rescue therapy. The dosing procedure is very specific and requires exact determination of accurate birth weight. Two individuals should be present to administer the dose and monitor the infant. Dosage is 4 mL/kg (100 mg phospholipid/kg) birth weight, divided into four equal quarter-doses and instilled directly via ETT in the specified sequence and positions (see **Figure 9-4**). Survanta is supplied in single-dose 8 mL vials that contain 25 mg phospholipid/mL (200 mg of phospholipid per vial). This means that the dosage is 4 mL/kg (4 mL will contain 100 mg of phospholipid). The four doses can be administered in the first 48 hours of life. The usual color of Survanta is off-white to light brown. Survanta is a suspension; if settling has occurred, the vial may be gently swirled but should not be shaken. It is refrigerated and should be warmed by standing at room temperature for 20 minutes or by hand-warming for 8 minutes before administration. Artificial warming methods should not be used.

Unused drug may be refrigerated, but not more than once. In certain situations, infants may require another dose; if an additional dose is needed, do not give more frequently than every 6 hours. The most common adverse reactions associated with beractant are bradycardia and oxygen desaturation. Diffuse rales (crackles) and acute partial airway obstruction occur with initiation of dosing procedure. Suctioning is not recommended for at least 60 minutes following administration unless bradycardia and arterial or transcutaneous oxygen desaturation persist. Other adverse effects noted include reflux, hypotension, and posttreatment sepsis.

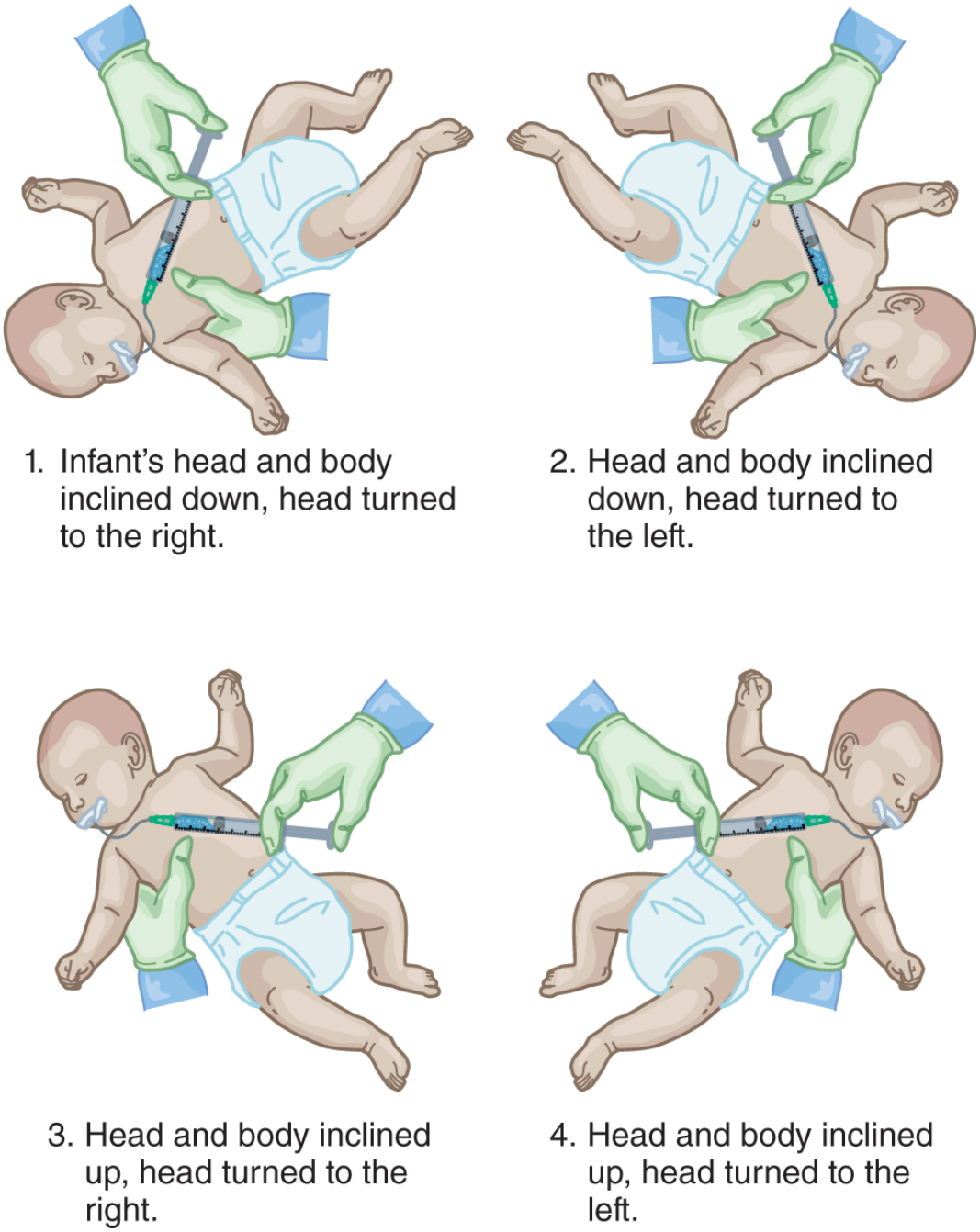


FIGURE 9-4 Surfactant instillation procedure.

Description

Administration Procedure

The first step in administration of surfactant is to confirm placement of the ETT. The surfactant is administered, divided into four aliquots of the total calculated dose. Determine the total dose of surfactant on

the basis of infant's birth weight. Draw the entire contents of the vial into a plastic syringe through a large gauge needle (at least 20 gauge) and attach the premeasured 5-French end-hole catheter to the syringe. Fill the catheter with surfactant and discard excess so that only calculated dose remains in the syringe. Position the infant as described in Figure 9-4 and inject the first quarter-dose into the syringe connected to the 5-French catheter that is inserted into the ETT by passing the neonatal suction valve over 2–3 seconds. Remove the catheter and manually ventilate the infant for 30 seconds or until stable at a rate of 60 breaths/min. Reposition the infant three other times, administering another quarter-dose with each reposition using the same procedure, until the whole dose is administered. Continuous monitoring of heart rate (HR) and oxygen saturation is required. Adjust the ventilator setting on the basis of changes in compliance after surfactant administration.

NEED TO KNOW

Oxygen desaturation and bradycardia are common during initial dosing with surfactant replacement drugs. Dosing should be interrupted. When the infant is stabilized, the dosage may be continued.

Calfactant (Infasurf)

Calfactant is a natural lung surfactant derived from bovine lung extract containing phospholipids, neutral lipids, fatty acids, and proteins. It contains 35 mg total phospholipids, including phosphatidylcholine and disaturated phosphatidylcholine and 0.7 mg proteins, including SP-B. The labeled indications for calfactant can be found in Table 9-1. The initial dose should be given within 30 minutes of birth for premature infants (<29 weeks' gestation) who are at high risk for developing RDS. It is also indicated in infants ≤72 hours of age with RDS (as manifested by clinical and radiographic findings) and requiring endotracheal intubation. Calfactant is a suspension that does not require reconstitution or dilution. Gentle swirling of the vial may be necessary if the drug has settled to the bottom. The approved dose

is 3 mL/kg (105 mg/kg) birth weight, divided into two equal half-doses of 1.5 mL/kg and instilled directly via side-port adapter to ETT; position infant right- or left-side dependent for each half-dose. If given via catheter into ETT, divide into four quarter-doses (0.75 mL/kg) and use positions described in Figure 9-4. Manually or mechanically ventilate with 100% O_2 at a rate of 60 per minute for at least 30 seconds following each instillation. Repeat or additional doses may be given if symptoms persist at an interval of 12 hours apart up to three doses.

Infasurf is an off-white suspension that usually requires gentle swirling, but it should not be shaken. Visible flecks or foaming at the surface is normal; drug does not have to be warmed before administration. Unused and unopened vials may be refrigerated, but should be used within 24 hours. Any used vials should be discarded and should not be saved. Infasurf is supplied in single-dose 6 mL vials that contain 210 mg of phospholipid per vial.

Bradycardia, apnea, cyanosis, and oxygen desaturation may occur during dosing procedure; if these occur, interrupt the drug administration and resuscitate. Transient reflux of calfactant into the ETT and obstruction of the ETT may also occur after administration. When the infant is stabilized, the dosage may be continued.

Administration Procedure

The dose of Infasurf is 3 mL/kg birth weight. The dose is drawn into a syringe using a 20-gauge or larger needle to avoid excess foaming. There are two recommended methods of administration, through a side-port adapter into the ETT or directly into the ETT. Close monitoring is required after administration to assure oxygen and ventilator pressures are adjusted on the basis of improvement in lung compliance and blood oxygenation.

Administration Through Side-Port Adapter

The infant should be positioned with either the right- or the left-side dependent when each aliquot is administered into the side-port adapter. Each dose aliquot should be administered over 20–30

breaths timed to correspond with the inspiratory cycles only. The infant should be repositioned to the other side before the second aliquot is administered.

For Direct Endotracheal Administration

Calfactant should be administered through a 5-French feeding catheter inserted into the ETT. The dose should be administered in four equal aliquots with the catheter removed between each of the instillations, and mechanical ventilation continued for 30 seconds to 2 minutes between each aliquot. The infant should be positioned similar to Figure 9-4 with each aliquot. Repeat doses with this method can be administered as early as every 6 hours after previous dose up to four doses if the infant is still intubated as requires 30% or more inspired oxygen to maintain a $Pa_{O_2} \leq 80$ torr.

NEED TO KNOW

Lung compliance usually improves rapidly following surfactant replacement therapy. Peak airway pressures should be closely monitored after surfactant has been administered.

Poractant Alfa (Curosurf)

Poractant is derived from porcine lung extract containing 99% polar phospholipids, phosphatidylcholine, and dipalmitoylphosphatidylcholine; and 1% hydrophobic proteins (SP-B and SP-C). Like other surfactants, it reduces alveolar surface tension to improve distribution of ventilation and reduce work of breathing. Unlike other available surfactant agents, Poractant is only indicated for rescue treatment of RDS. It has been shown to reduce mortality and pneumothoraces associated with RDS. Initial dose should be given for treatment of premature infants with symptoms of RDS (as manifest by radiographic findings and the need for intubation or mechanical ventilation). The initial dose is 2.5 mL/kg (200 mg/kg) birth weight, divided into two equal half-doses and instilled directly via a catheter to the ETT or in a single dose directly instilled into the ETT.

Up to two repeat doses of 1.25 mL/kg birth weight each may be administered at approximately 12-hour intervals in infants who remain intubated and in whom RDS is considered responsible for their persisting or deteriorating respiratory status. The maximum recommended total dosage (sum of the initial and up to two repeat doses) is 5 mL/kg. Poractant alfa in an initial dose of 200 mg/kg has been found to be more effective than 100 mg/kg of poractant or beractant for rescue therapy of RDS. Administration reactions may include bradycardia, hypotension, ETT blockage, and oxygen desaturation. If these occur, interrupt the drug administration and resuscitate. Pulmonary hemorrhage has been reported in postmarketing studies in patients that have received poractant for RDS. When the infant is stabilized, the dosage may be continued. Other less common adverse reactions include pallor and apnea. Ventilation support should be monitored carefully and adjusted on the basis of changes in lung compliance and oxygen requirement after administration. Maximum recommended total dosage is 5 mL/kg; if repeat dosages are required, they should be given in 1.25 mL/kg dosages at 12-hour intervals.

Administration Procedure

The vial of proactant should be removed from the refrigerator and warmed to room temperature before administration. The vial can be gently turned upside down, but not shaken, to obtain a consistent suspension. Unopened, warmed vials can be returned to the refrigerator for future use.

Recommended dosing procedure uses a 5-French catheter inserted distally into ETT or directly into the second lumen of a dual-lumen ETT.

For the Instillation Through the 5-French End-Hole Catheter

Withdraw the contents of a vial into a syringe (at least 20-gauge) and discard excess drug so that only the dose to be given remains in the syringe. Administer in two 1.25 mL/kg aliquots. The infant should be positioned in a neutral position with either the right- or left-side

dependent, the ventilator setting should be changed to a respiratory rate (RR) of 40–60 breaths/min, an inspiratory time of 0.5 second, and enough oxygen to maintain 92% saturation. Disconnect the ETT from the ventilator and insert the 5-French catheter into the ETT and instill the first aliquot. After instillation, remove the catheter and manually ventilate with 100% oxygen for 1 minute following each half-dose administration at 40–60 breaths/min. Reposition the infant to the other side (right or left) and administer the second aliquot using the same procedure. Ventilator management can continue after the second aliquot is administered.

For Direct Endotracheal Instillation

Slowly withdraw the entire contents of the vial into a 3- to 5-mL plastic syringe (at least 20 gauge). Remove the needs and discard excess poractant so that only the dosage to be given remains in the syringe. Keep the infant in a neutral position and administer the suspension through the end of the second lumen of the ETT as a single dose, given over 1 minute. Mechanical ventilation should not be interrupted.

NEED TO KNOW

Infants should not be suctioned for at least 60 minutes following surfactant replacement therapy unless signs of significant airway obstruction occur.

Case Study 9-1

Infant RDS

An 18-year-old pregnant female who is 25 weeks' gestation is admitted to the labor and delivery ward in a 250-bed hospital with a level III neonatal intensive care unit with a premature rupture of membranes and active contractions. There is no blood or meconium present in the amniotic fluid. The resuscitation team is called to provide support to the preterm infant upon delivery. At delivery, the baby has a HR of 80 beats/min and agonal respiratory effort. The airway is cleared and the neonate is warmed, stimulated, and supported with manual ventilation breaths via T-piece resuscitation device delivering a peak inspiratory pressure (PIP) of 25 cm H_2O and a positive end-expiratory pressure (PEEP) of 5 cm H_2O on 60% FiO_2 in order to achieve appropriate chest rise and maintain

oxygen saturation at 85%. This support is sufficient in raising the HR to >100 beats/min. Because of extreme prematurity and lack of effective spontaneous respirations, the neonate is intubated with a 2.5-mm ETT with the use of a size-0 Miller laryngoscope blade. The ETT is secured and the neonate is placed mechanical ventilation. The settings are as follows:

PIP = 28 cm H_2O. Predicted V_t for 750 g neonate at 4–6 mL/kg = 3–4.5 mL V_t

Patient achieving 2.5–3 mL V_t on present PIP of 28 cm H_2O.

RR =40

PEEP =5 cm H_2O

I-Time =0.3 seconds

Flow =7 L/min

FiO_2= 100%

Physical Examination

Weight: 750 g.

Apgar: Birth = 3, 5 min = 6, 10 min = 7. APGAR deductions at 10 minutes for lack of respiratory effort, poor muscle tone, and cyanosis.

Vital signs: HR, 178 beats/min; RR, 15 breaths/min and agonal; temperature, 36.8°C; and SpO_2 85% on 60% FiO_2.

Neurologic: Minimal muscle tone and slow reaction to external stimulus.

Respiratory: Agonal ineffective respirations, retractions with respiratory effort, nasal flaring, and decreased breath sounds bilaterally with inspiratory crackles.

Cardiac: Regular rhythm without gallops or murmurs.

Head, eyes, ears, nose, and throat (HEENT): Normal.

Laboratory Values

Chest radiograph: Taken 4 hours following delivery. No position rotation noted and film exposure is normal. Nasogastric tube present and placement is correct and ETT placement at T1. Lungs inflated to eighth rib on exposure. Costophrenic angles are visible. Haziness in lung fields with the presence of air bronchograms and slight ground glass appearance.

Arterial blood gas (ABG): pH = 7.21; $PaCO_2$ = 57torr; PaO_2 = 50torr; HCO_3^-= 24 mEq/L; FiO_2 = 60%; SaO_2 = 83%; SpO_2= 85%.

Diagnosis

1. Prematurity
2. Respiratory distress syndrome

Respiratory Care Physician's Orders

1. Maintain SpO_2 between 85% and 93%
2. Maintain secured airway via ETT for mechanical ventilation support
3. Support ventilation and oxygen via mechanical ventilation

4. Administer surfactant via ETT
5. Monitor ABGs: target $PaCO_2$ of 45 torr; target PaO_2 of 60 torr; and target pH >7.25

Questions

1. Should an animal-derived, natural surfactant or synthetic surfactant be administered, and why?
2. Poractant alfa is available in 80 mg/mL vials. How many milliliters should be administered in total to this patient?
3. The surfactant agent on formulary is Poractant alfa. Describe the procedure to administer this surfactant in this patient via a 5-French catheter.
4. How long is it recommended before suctioning is allowed following the delivery of surfactant, and why is this so?
5. What mechanical ventilator changes do you anticipate will need to be made following the administration of artificial surfactant? How soon after administration of surfactant do you anticipate these changes will need to be made?
6. What side effects and complications might you observe during and following the administration of artificial surfactant?

Review Questions

1. Define surface tension.
2. Describe how surface tension affects the work of breathing, particularly in the newborn.
3. Define surfactant (in general terms) and describe pulmonary surfactant.
4. Describe the indications for the use of surfactant replacement drugs, including both prevention and *rescue* protocols.
5. Compare and contrast the three surfactant replacement drugs currently in use in the United States with regard to brand name, approved indications, dosing, administration procedures, and adverse effects.

Posttest

For each of the following questions, try to select the one best answer from the choices given.

1. Surface tension:
   a. is a cohesive force that creates tension at the surface of a liquid.
   b. is an adhesive force that prevents alveolar collapse.
   c. always opposes alveolar deflation.
   d. is the force within a fluid that holds molecules together.
2. Pulmonary surfactant:
   a. is made of phospholipids and proteins.
   b. reduces surface tension.
   c. is produced by alveolar type II cells.
   d. All of these are correct.
3. Surfactant replacement drugs are given:
   a. by aerosol only.
   b. by intratracheal instillation only.
   c. by aerosol or instillation.
   d. by aerosol or intravenous line.
4. What is the minimum length of time during which ETT suctioning should be avoided following administration of surfactant replacement drugs?
   a. 30 minutes
   b. 60 minutes
   c. 90 minutes
   d. 120 minutes
5. The rescue treatment for surfactant replacement drugs is used for infants:
   a. whose birth weight is <1250 g.
   b. whose birth weight is <1350 g.
   c. who are born at <36 weeks' gestation.
   d. who develop RDS.

6. Contraindications for the administration of surfactant replacement drugs include:
   a. persistent fetal circulation.
   b. congenital heart disease.
   c. Apgar score of <5 at birth.
   d. None of these is correct.
7. Adverse reactions of administration of surfactant replacement drugs include:
   1) tachycardia.
   2) bradycardia.
   3) oxygen desaturation.
   4) hyperglycemia.
   a. 1 and 3 only
   b. 2 and 3 only
   c. 3 and 4 only
   d. 2, 3, and 4 only
8. Respiratory failure secondary to surfactant deficiency in the newborn primarily is because of:
   a. ventilation–perfusion mismatching.
   b. diffusion barrier.
   c. fatigue due to excessive work of breathing.
   d. persistent fetal circulation.
9. The recommended procedure for administration of exogenous surfactant to a newborn requires:
   a. using a PARI LC nebulizer and scavenger system.
   b. using a small-volume nebulizer with an aerosol mask.
   c. instillation of two to four equal aliquots with specific positioning for each portion.
   d. instillation of first dosage as one bolus before intubation.
10. Which of the following are accepted non–FDA-approved uses of exogenous surfactant in preterm infants?
   a. Acute RDS in adults
   b. Necrotizing enterocolitis
   c. Patent ductusarteriosus
   d. Meconium aspiration syndrome

References/Recommended Readings

Bhat R, Dziedzic K, Bhutani VK, et al. Effect of single dose surfactant on pulmonary function. *Crit Care Med*. 1990;18:590.

Curosurf (Poractantalfa) [package insert]. Carey, NC: Cheisi Inc; 2014.

Dani C, Corsini I, Poggi C. Risk factors for intubation-surfactant-extubation (INSURE) failure and multiple INSURE strategy in preterm infants. *Early Hum Dev*. 2012;88(suppl1):S3-S4.

Findlay RD, Tauesch HW, Walther FJ. Surfactant replacement therapy for meconium aspiration syndrome. *Pediatrics*. 1996;97(1):48-52.

Fujiwara T, Maeta H, Chida S, et al. Artificial surfactant therapy in hyaline membrane disease. *Lancet*. 1980;1(8159):55-59.

Hallman M, Merritt TA, Kari A, et al. Factors affecting surfactant responsiveness. *Ann Med.* 1991;23(6):693-698.

Hoekstra RE, Jackson JC, Myers TF, et al. Improved neonatal survival following multiple doses of bovine surfactant in very premature neonates at risk for respiratory distress syndrome. *Pediatrics.* 1991;88(1):10-18.

Herting E, Moller O, Schiffman JH, et al. Surfactant improves oxygenation in infants and children with pneumonia and acute respiratory distress syndrome. *Acta Pediatr*. 2002;91(11):1174-1178.

Infasurf (calfactant) [package insert]. Amherst, NY:ONY, Inc; 2011.

Jobe AH. Pulmonary surfactant therapy. *N Eng J Med.* 1993;328(12):861-868.

Kanmaz HG, Erdeve O, Canpolat FE, et al. Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial. *Pediatrics.* 2013;131:e502-e509.

Kendig JW, Notter RH, Cox C, et al. A comparison of surfactant as immediate prophylaxis and as rescue therapy in newborns of less than 30 weeks' gestation. *N Engl J Med.* 1991;324(13):865-871.

Kesecioglu J, Beale R, Stewart TE, et al. Exogenous natural surfactant for treatment of acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2009;180(10):989-994.

Kribs A, Roll C, Gopel W, et al. Nonintubated surfactant application vs conventional therapy in extremely preterm infants: a randomized clinical trial. *JAMA Pediatr*. 2015;169:723-730.

Long W, Corbet A, Cotton R, et al. A controlled trial of synthetic surfactant in infants weighing 1,250 grams or more with respiratory distress syndrome. *N Engl J Med.* 1991;325:1696-1703.

Mingarro I, Lukovic D, Vilar M, et al. Synthetic pulmonary surfactant preparations: new developments and future trends. *Med Chem*. 2008;15(4):303-403.

Moller JC, Schaible T, Rool C, et al. Treatment with bovine surfactant in severe acute respiratory distress syndrome in children: a randomized multi-center study. *Intensive Care Med*. 2003;29(3):437-446.

Morley CJ. Surfactant treatment for premature babies: a review of clinical trials. *Arch Dis Child.* 1991;66(4 Spec No):445-450.

Polin RA, Carlo WA; Committee on Fetus and Newborn. Surfactant replacement therapy for preterm and term neonates with respiratory distress. *Pediatrics.* 2014;133;156-163.

Prange HD. Laplace's law and the alveolus: a misconception of anatomy and a misapplication of physics. *Adv Physiol Educ*. 2003;27:34-40.

Schwartz RM, Luby AM, Scanlon JW, et al. Effect of surfactant on morbidity, mortality, and resource use in newborn infants weighing 500 to 1500 g. *N Engl J Med.* 1994;330:1476-1480.

Singh N, Halliday HL, Stevens TP, et al. Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev*. 2015;12:CD010249.

Sinha SK, Lacaze-Masmonteil T, Valls I Soler A, et al; Surfaxin Therapy Against Respiratory Distress Syndrome Collaborative Group. A multicenter, randomized, controlled trial of lucinactant versus poractantalfa among very premature infants at high risk for respiratory distress syndrome. *Pediatrics.* 2005;115:1030-1038.

Survanta (beractant) [package insert]. Chicago, IL: AbbVie Inc; 2012.

Sweet DG, Carnielli V, Greisen G, et al. European consensus guidelines on the management of respiratory distress syndrome–2016 update. *Neonatology.* 2017;111:107-125.

Varisco BM, Palmatier CM, Alten JA. Reversal of intractable hypoxemia with exogenous surfactant (calfactant) facilitating complete neurological recovery in a pediatric drowning victim. *Pediatr Emerg Care*. 2010;26(8):571-573.

Walmrath D, Grimminger F, Pappert D, et al. Bronchoscopic administration of bovine natural surfactant in ARDS and septic shock. *Eur Respir J*. 2002;19(5):805-810.

Walmrath D, Gunther A, Ghofrani HA, et al. Bronchoscopic surfactant administration in patients with severe adult respiratory distress syndrome and sepsis. *Am J Respir Crit Care Med.* 1996;154(1):57-62.

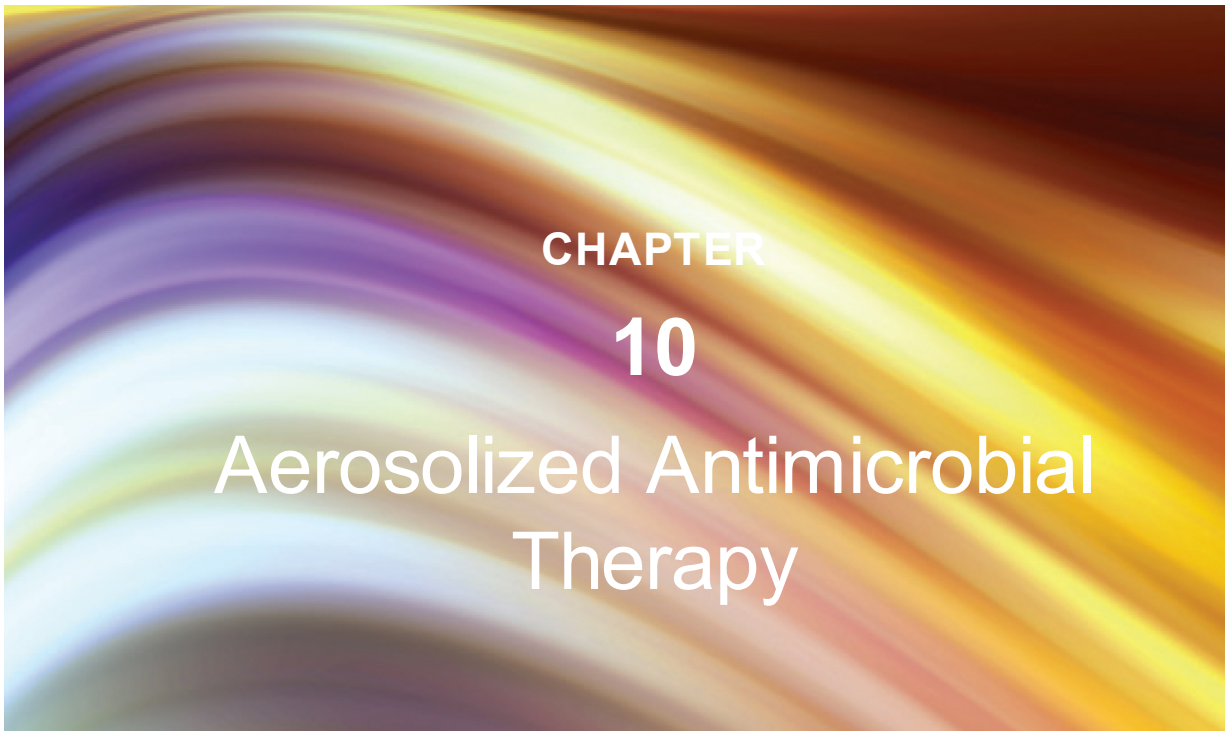
Walsh BK, Daigle B, DiBlasi RM, et al. AARC Clinical Practice Guideline. Surfactant replacement therapy: 2013. *Respir Care*. 2013;58:367-375.

Whitaker KC. *Neonatal and Pediatric Respiratory Care.* Albany, NY: Delmar Publishing, Inc; 1996.

Willson DF, Notter RH. The future of exogenous surfactant therapy. *Respir Care*. 2011;56(9):1369-1388.

Willson DF, Bauman LA, Zaritsky A, et al. Instillation of calf lung surfactant extract (calfactant) is beneficial in pediatric acute hypoxemic respiratory failure. *Crit Care Med*. 1999;27(1):188-195.

Yee WF, Scarpelli EM. Surfactant replacement therapy. *Pediatr Pulmonol*. 1991;11(1):65-80.



© Anna RubaK/ShutterStock, Inc.

OUTLINE

Introduction
Rationale for Aerosolized Antimicrobial Drugs
  Clinical Indications for Aerosolized Antimicrobials
  Factors Associated with Efficacy and Safety of Inhaled Antimicrobials
Categories of Antimicrobial Drugs Administered by Aerosol
  Antibacterial (Antibiotic) Drugs
  Antifungal Drugs
  Antiviral Drugs
  Antiprotozoal Drugs
Limitations of Aerosolized Antimicrobials

Objectives

After completion of this chapter and its learning activities, you will be able to:

1. List the most common indications for the use of aerosolized antimicrobial agents.
2. Discuss the disadvantages or limitations of aerosol administration of antimicrobial drugs.
3. Name the FDA-approved aerosolized antimicrobial agents and the special equipment required for administration of each.

4. Describe contraindications and side effects of each drug that may be administered by aerosol as an antimicrobial agent.
5. Suggest the most appropriate antimicrobial therapy, including the drug of choice, route of delivery, and recommended dosage, given a patient case study.

KEY TERMS

Antibiotic
Antibacterials
Antifungals
Antimicrobials
Antiprotozoals
Antivirals
Bactericidal
Bacteriostatic
Hospital-acquired pneumonia (HAP)
Multidrug-resistant (MDR)
Non–cystic fibrosis bronchiectasis (NCFB)
***Pneumocystis carinii* pneumonia (PCP)**
Ventilator-associated pneumonia (VAP)

Introduction

Although systemic administration of antimicrobial agents is still the best first-line approach in most cases, certain clinical situations may benefit from targeted delivery of therapy to the lungs. The aerosolized mode of drug delivery is able to distribute high concentrations of antimicrobials directly to the site of respiratory infections limiting systemic adverse effects. The use of inhaled antibiotics has changed the disease progression in cystic fibrosis (CF). The inhaled route of anti-infectives may also be beneficial in treating infection or bacterial colonization in patients with **non–cystic fibrosis bronchiectasis (NCFB)**, tracheobronchitis, **hospital-acquired pneumonia (HAP)** and **ventilator-associated pneumonia (VAP)**, and other lower respiratory tract infections caused by **multidrug-resistant (MDR)** bacteria. This chapter describes the general indications and rationale for the aerosol or instilled route of delivery for antimicrobial agents. Specific drugs that have been used successfully by these routes are also presented.

Rationale for Aerosolized Antimicrobial Drugs

Chapter 4 discussed general reasons for aerosol delivery of medications to the pulmonary tract, including deposition of a drug at a specific site of action and reduced systemic side effects of a drug. These reasons also provide the primary rationale for the use of anti-infective (antimicrobial) agents by the aerosol route. The most effective and safe antimicrobials for aerosolized delivery must have a physiologic pH, penetrate infected airway secretions, not become inactivated by the presence of other medications, can be aerosolized before the drug becomes inactivated, and have limited respiratory adverse effects. Aerosolized particles with a mass median aerodynamic diameter of 0.5–3 μm can be deposited efficiently in the lungs.

The following are the rationales for administering antimicrobial drugs by aerosol:

1. As an adjunct to systemic antimicrobial therapy when this has been unsuccessful
2. To eliminate an organism that is colonizing the respiratory tract (e.g., infected sputum in CF or NCFB)
3. To limit systemic concentrations of highly toxic antimicrobials while delivering high concentrations directly to the site of infection
4. As an alternative method of administration of antimicrobials to achieve high lung concentrations of agents that have poor pulmonary penetration when administered systemically

Clinical Indications for Aerosolized Antimicrobials

There are a limited number of aerosolized antimicrobials approved for clinical use. The approved uses of these agents will be discussed in this section. Aztreonam (Cayston®) is indicated to improve

respiratory symptoms in CF with *Pseudomonas aeruginosa* (PA) in the lungs. Pentamidine (NebuPent®) is approved for use via the inhalation route for the prevention of *Pneumocystis jiroveci*, originally termed **Pneumocystis carinii pneumonia (PCP)**, in patients with human immunodeficiency virus (HIV) and a peripheral CD4+ lymphocyte count less than 200/mm^{3}or at least in patients with one incidence of PCP. Ribavirin (Virazole®) is indicated for the treatment of hospitalized infants or children with severe respiratory syncytial virus (RSV). Tobramycin (TOBI, Bethkis, Kitabis Pak, TOBI Podhaler) is available in two-dosage formulations for the aerosolized route. It is available as a nebulizer formulation and as a dry-powder inhaler indicated for the management of CF patients with PA. Zanamivir (Relenza®) is a dry powder inhaler (DPI) approved for the treatment of acute, uncomplicated influenza types A and B infection and for the prophylaxis of influenza. Amphotericin B is an antifungal agent approved for systemic fungal and mold infections. It is used aerosolized off-label for the prevention of mold infections in immunocompromised populations. Colistin DPI is approved for use in CF in Europe but not in the United States. Some of these agents are more commonly used in off-label indications and will be discussed later in this chapter.

Factors Associated with Efficacy and Safety of Inhaled Antimicrobials

Drug administration technique, as well as the characteristics of the drug formulation, plays a major role in determining the effectiveness and safety of inhaled antimicrobials. Very few antimicrobials have been formulated and studied for inhaled use. As a result, the intravenous (IV) preparations of some antibiotics are commonly delivered via nebulization for inhaled administration. Nebulized drug solutions should have an osmolality of 150–1200 mOsm/kg and a sodium content of 77–154 mEq/L, and the pH of nebulized drugs should fall between 4.8 and 8. If formulations have physical characteristics that fall out of these ranges, it may result in cough,

mucosal irritation, and bronchospasm. The preservatives (e.g., phenols and sulfites) found in many of these IV formulations can also lead to cough, throat irritation, and bronchospasm. Optimal drug delivery to the lungs is achieved when the aerosolized particles have a mean mass aerodynamic diameter (MMAD) of 1–5 μm. Low humidification can also improve drug disposition. Jet nebulizers tend to be the preferred delivery device of nebulized antimicrobials. They are cost-efficient, easy to use, and achieve high sputum concentrations of nebulized antimicrobials. The breath-enhanced nebulizer system, PARI-LC PLUS (Pari Respiratory Equipment Inc., Midlothian, VA), is commonly used for many nebulized antimicrobials and is the recommended device for inhaled tobramycin. Vibrating mesh nebulizers can more efficiently nebulize solutions and lead to decreased evaporation or denaturation of drug compared with jet nebulizers. These devices are more expensive but have been increasing in use for nebulization of antimicrobials. Ideal methods for delivery of nebulized antimicrobials in mechanically ventilated patients have not been identified so far.

Proper administration technique of aerosolized antimicrobials in mechanically ventilated patients improves the amount of drug that reaches the lungs. Although there are multiple devices that can be used in patients with mechanical ventilation (MV), vibrating plate nebulizers (VPNs) are preferred ones because they have been shown to improve lung disposition of drugs compared with jet nebulizers. Ideally, these devices would nebulize with an MMAD of 1–5 μm and be able to bypass the humidification system or create particles of an ideal size during humidification. Humidification should be temporarily turned off during administration if the device cannot bypass the system. Nebulization should occur only during inspiration and the device should be placed in the inspiratory loop of the ventilator, 15–45 cm from the endotracheal (ET) tube for ideal administration and drug delivery. VPNs can nebulize only during inspiration and can be placed at the ET tube.

Categories of Antimicrobial Drugs Administered by Aerosol

Although the entire group of **antimicrobial** drugs is large (as described in Chapter 16), relatively few have been used successfully by aerosol. These include drugs in four major categories: **antibacterials** (**antibiotics**), **antifungals**, **antivirals**, and **antiprotozoals**. The following sections describe select aerosolized antimicrobials and include dosages, side effects, contraindications, and special considerations. **Table 10-1** summarizes the antimicrobials that have been successfully used as aerosols and the clinical conditions that each may be used for in clinical practice. The majority of antimicrobials administered by inhalation are used off-label. Only approved agents or commonly used agents will be discussed in further detail in this chapter.

TABLE 10-1
Aerosol Antimicrobial Applications

Drug	Class	Clinical Uses
Amikacin	Aminoglycoside antibiotic	MDR gram-negative pulmonary infections in CF and NCFB and HAP/VAP
Amphotericin B	Polyene antifungal	Prevention of pulmonary aspergillosis in lung transplant patients
Aztreonam	Monobactam antibiotic	Treatment of CF and NCFB patients with PA and MDR gram-negative infections in HAP/VAP
Ceftazidime	Beta-lactam antibiotic	Treatment of CF and NCFB patients with PA and MDR gram-negative infections in HAP/VAP
Ciprofloxacin	Fluoroquinolone antibiotic	Treatment of CF and NCFB patients with PA
Colistimethate	Polymyxin antibiotic	Treatment of CF and NCFB patients with PA and

		HAP/VAP
Fosfomycin	Phosphonic acid derivative antibiotic	HAP/VAP
Gentamicin	Aminoglycoside antibiotic	Treatment of CF and NCFB patients with PA and HAP/VAP
Levofloxacin	Fluoroquinolone antibiotic	Treatment of CF and NCFB patients with PA
Pentamidine	Antiprotozoal	Prevention of *Pneumocystis jiroveci* pneumonia
Polymyxin B	Polymyxin antibiotic	Treatment of PA in cystic fibrosis and HAP/VAP
Ribavirin	Antiviral	Used in the treatment of children with severe RSV and prophylaxis of RSV in bone marrow transplant patients
Tobramycin	Aminoglycoside antibiotic	Treatment of CF and NCFB patients with PA and HAP/VAP
Vancomycin	Glycopeptide antibiotic	MRSA pulmonary infections
Zanamivir	Antiviral	Treatment and prophylaxis of influenza

CF, cystic fibrosis; HAP, hospital-associated pneumonia; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; NCFB, non–cystic fibrosis bronchiectasis; PA, *Pseudomonas aeruginosa*; RSV, respiratory syncytial virus; VAP, ventilator-associated pneumonia.

Antibacterial (Antibiotic) Drugs

Although many antibiotics have been administered successfully by aerosol, aztreonam and tobramycin are the only FDA-approved antibiotics to be administered via the inhaled route with a specific formulation developed for aerosolization. Inhaled formulations of ciprofloxacin and levofloxacin are being studied for the treatment of chronic respiratory infections caused by PA in CF and NCFB, and colistimethate is another agent that is very commonly used as well. The most common use of antibiotics by aerosol is for chronic

pulmonary infections in CF and NCFB and for patients who develop VAP. Aerosolized antibiotics should be used as an adjunct or in addition to systemic antibiotics for the treatment of VAP. These patients often colonize PA or other difficult-to-treat gram-negative organisms in the lower respiratory tract. The following are the rationales for providing aerosolized antibiotics for these patients:

1. It provides direct deposition of drug at the site of infection and reduces systemic effects.
2. There are no effective oral antibiotics for the treatment of PA infections.
3. Some antibiotics (e.g., aminoglycosides) may not achieve sufficient therapeutic levels in the lungs, even when given systemically.

The following descriptions of antimicrobial drugs cover only those drugs that are FDA-approved and have been shown to be safe and effective when given by aerosol. Colistimethate is also discussed owing to potentially important safety issues when used for aerosolization. The recommended dosages for each agent are listed in **Table10-2**. For each drug, the relative spectrum of effectiveness is noted, but specific susceptibility of an organism to the antimicrobial always should be determined by laboratory analysis (i.e., sputum culture and sensitivity).

TABLE 10-2
Brand Names, Available Formulations, and Recommended Doses of Inhaled Antibiotic Agents

Drug	Brand	Formulation and Dosage
Aztreonam	Cayston	75 mg/mL powder for dilution Age ≥ 7 y: 75 mg inhaled three times daily for 28 days on and 28 days off
Colistimethate	Coly-Mycin M or Colomycin	40–160 mg (colistin base activity) nebulized one to three times daily

Tobramycin	TOBI; Bethkis; Kitabis Pak; TOBI Podhaler	TOBI: 300 mg/5mL; Bethkis: 300 mg/4mL; Kitabis Pak: 300 mg/5 mL Age ≥ 6 y: 300 µg nebulized twice daily for alternating periods of 28 days on and 28 days off therapy Non–cystic fibrosis bronchiectasis: 80 mg nebulized twice daily TOBI Podhaler: 28 mg/cap Four (28 mg) capsules inhaled twice daily for 28 days on and 28 days off therapy

Aztreonam (Cayston)

Aztreonam is a monobactam antibiotic, which is structurally different from β-lactam antibiotics. *Mechanism of action*: Aztreonam binds to the penicillin-binding proteins in bacterial cell walls, which disrupts bacterial cell wall synthesis and causes cell death. Aztreonam exhibits **bactericidal** activity against gram-negative organisms, including PA. Bactericidal antibiotics kill 99.9% of bacteria opposed to **bacteriostatic** antibiotics that prevent further growth of bacteria. *Indication*: It is indicated to improve respiratory symptoms in CF patients with PA. It has not been studied in patients less than 7 years of age and in patients with an FEV_1 <25% or FEV_1 >75% predicted or patients colonized with *Burkholderia cepacia*. *Dose*: The dosing of inhaled aztreonam can be found in Table10-2. It comes commercially available in single-use vials that have to be reconstituted before administration. It should be used immediately after reconstitution. Manufacturer's directions on reconstitution and administration should be consulted before use. It is used for a 28-day course followed by 28-days off aztreonam therapy. Aztreonam inhaled therapy should only be administered by inhalation using the Altera® nebulization system. Aztreonam should be stored in the refrigerator or can be stored outside the refrigerator for less than 28 days. *Adverse effects*: Common adverse effects include cough, nasal congestion, bronchospasm, throat pain, fever, chest pain, and abdominal pain. *Special considerations*: Allergic reactions may occur with use and should be discontinued if this occurs. If bronchospasm occurs, a bronchodilator should be used before each treatment.

Colistin/Colistimethate (Colomycin/Coly-Mycin M®)

Colistin is a polymyxin antibiotic (polymyxin E), first discovered in the 1940s. It is most commonly used to treat resistant gram-negative infections, but its use had fallen out of favor because of significant nephrotoxicity and neurotoxicity. Colistin treats most gram-negative bacilli infections, except it is inherently resistant to *Proteus mirabilis*, *Serratia marcescens*, *Morganella morganii*, and *Burkholderia* sp. Recently, there has been an emergence of use because of the lack of treatment options for MDR PA, *Acinetobacter* sp., and *Klebsiella pneumoniae*. Colistin is available in two forms: colistin sulfate and colistimethate sodium. These formulations are not interchangeable. Colistimethate sodium is a prodrug, which is hydrolyzed (i.e., broken down when combined with water) to colistin sulfate and sulfomethylated derivatives. Colistin is the active form of the drug; 1 mg of colistimethate = 0.375 mg of colistin base activity = 12,500 international units (IU). It is important for clinicians to be aware of the differences in dosing and units of dose. Any orders or prescriptions for colistin should note if the dosage is indicated in milligram or IU of colistin base or colistimethate. Any discrepancies could lead to an overdose or underdose of the drug. *Mechanism of action*: Colistin damages the bacterial cell membrane, which causes intracellular contents to leak out and leads to cell death. It is effective against most gram-negative bacteria but clinically reserved to treat MDR gram-negative organisms. It is not active against gram-positive organisms as well as some gram-negative organisms, including *Proteus* sp., *Providencia* sp., *Morganella* sp., *Serratia* sp., and *Burkholderia* sp. *Indication*: Inhaled colistin has been shown to have mixed results with regard to efficacy in the treatment of pulmonary infections and its effect on lung function in CF patients, and therefore evidence is insufficient to recommend for or against chronic use. Inhaled colistin should be considered as an adjunct to patients with MDR gram-negative organisms causing VAP not responding to IV therapy. *Dose*: The appropriate dose of colistin remains unclear but the common clinically used doses can be found in Table10-2. Higher doses may be more effective in critically ill patients with VAP.

Adverse effects: Adverse effects associated with systemic therapy include nephrotoxicity, paresthesias, numbness or tingling of extremities or the tongue, and generalized itching or urticaria. When used inhaled, colistin can cause bronchospasm, chest tightness, throat irritation, and cough. An inhaled β_2-agonist should be administered 15 minutes before administration. Colistin has shown to have more adverse effects compared with inhaled aminoglycosides.

A 150-mg (colistin base) vial should be reconstituted with 2 mL sterile water or normal saline. An additional 5–10 mL of sterile water or saline should be added to provide an adequate solution for nebulization. After reconstitution, the solution should be used for nebulization immediately. *Special considerations*: Storing this solution for more than 24 hours increases the risk for potentially fatal lung toxicity.

NEED TO KNOW

Colistin may be doses in different units on the basis of formulation. All dosage formulations are not interchangeable and dosages should be double-checked to avoid error.

NEED TO KNOW

Reconstituted colistin intended for nebulization should be used in less than 24 hours, and ideally immediately after reconstitution to avoid potentially fatal lung toxicity.

Tobramycin (TOBI,TOBI Podhaler, Bethkis, Kitabis Pak)

Mechanism of action: Tobramycin is an aminoglycoside antibiotic that irreversibly binds to ribosomes to prevent protein synthesis and thus causes cellular death. *Indication*: It prevents and treats chronic pulmonary infections and colonization of PA in CF patients. The safety and efficacy of inhaled tobramycin have not been studied in patients less than 6 years of age and in patients with an FEV_1 <25% or FEV_1 >75–80%. The use of inhaled tobramycin in CF patients leads to improved lung function (FEV_1), reduced need for systemic

administration of antibiotics for *Pseudomonas* sp., and hospitalization for exacerbations. It has also been shown to be effective in treating patients who develop VAP and HAP. Tobramycin has also been studied in the suppression of bacteria or in the treatment of exacerbations of NCFB with mixed results. Tobramycin as well as other aminoglycosides (e.g., amikacin and gentamicin) are bactericidal antibiotics that are effective in the treatment of infection or colonization of gram-negative organisms, including the more resistant and harder to treat *Pseudomonas* sp. It is unknown if tobramycin inhalation is effective to treat the bacteria *Burkholderia cepacia. Dose*: Tobramycin is available in two different formulations: as a nebulization solution and as a drug powder that comes in capsules to be used only with the TOBI Podhaler device. The doses for each formulation can be found in Table10-2. The cycle of treatment alternates with 28 days of using the drug and 28 days of not using the drug. The nebulizer solutions should be inhaled over 15 minutes using only the PARI-LC PLUS reusable nebulizer with a PARI Vios air compressor (Bethkis) or a DeVilbiss Pulmo-Aide (Kitabis Pak, TOBI) to achieve appropriate aerosol output and particle size. Other devices should not be used. Prescribed bronchodilators should be administered before the administration of tobramycin. If other therapies such as mucolytics are prescribed, the appropriate sequence of administration should be bronchodilators, mucolytics and last, tobramycin. Tobramycin should never be mixed with other nebulizer solutions. The nebulizer solutions should be stored in the refrigerator or can be stored outside the refrigerator for less than 28 days. The TOBI Podhaler contains capsules (that should never be swallowed) designed to be administered by oral inhalation via the Podhaler device. If needed, a bronchodilator should be administered 15–90 minutes before TOBI Podhaler administration. *Adverse effects*: The most common side effects associated with inhaled therapy include voice alteration (dysphonia), hoarseness, taste disturbances, tinnitus, and bronchospasm. Bronchospasm can be decreased if a bronchodilator is administered at least 15 minutes before tobramycin administration. There have been reports of nephrotoxicity, hearing loss, and vestibular toxicity with inhaled

therapy, but is rare. The use of tobramycin with other nephrotoxic (e.g., loop diuretics and IV mannitol) or ototoxic medications can increase the risk of these adverse effects. Patients with NCFB have an increased reported risk of adverse effects compared with CF patients. *Special considerations*: When used for treating VAP, administer aerosol over 15–20 minutes with nebulizer placed in the inspiratory limb of the ventilator circuit approximately 15–30 cm from the ET tube. Use with caution in patients with impaired renal function. Tobramycin should also be avoided in pregnant women, because it has shown to cause fetal harm, specifically congenital deafness. Tobramycin should not be used if patients have a reported allergy to any other aminoglycoside antibiotics (e.g., amikacin, gentamicin, kanamycin, neomycin, plazomicin, or streptomycin).

NEED TO KNOW

Colistin and tobramycin are used as aerosols to treat and prevent gram-negative infections in CF.

NEED TO KNOW

Tobramycin nebulizer solution should only be used with the PARI-LC PLUS nebulizer device.

Antifungal Drugs

Pulmonary fungal infections are known to occur in immunocompromised patients such as old organ and bone marrow transplant recipients, leukemia patients, and in patients who receive chemotherapy. Lung and bone marrow transplant recipients commonly develop invasive and pulmonary aspergillosis. Experience with aerosolized antifungals is limited to polyene antifungals, specifically amphotericin B. Amphotericin B comes in three formulations that have been most frequently studied for this purpose with significant clinical improvement and few adverse reactions. Other

classes of antifungals, such as azole antifungals, have been studied but are not in clinical use.

Case Study 10-1

Cystic Fibrosis

A 22-year-old, white, 105-lb female is being seen in the pulmonary clinic after being treated for 10 days at home for a mild pulmonary exacerbation of previously diagnosed CF. She has some mild weight loss and has been unable to attend her college classes because of fatigue.

History and Physical Examination

History: The patient was diagnosed as having CF at birth. She is currently on dornase alpha four times a day at home and has an albuterol metered-dose inhaler to be used PRN for wheezing.
Vital signs: Heart rate, 95 beats/min, steady and bounding; blood pressure, 110/68 mm Hg; respiratory rate, 21 breaths/min; temperature, 98.9°F (oral); and SpO_2, 93%.
Cardiovascular: Heart sounds bounding and slightly distant. Electrocardiogram shows changes consistent with left ventricular hypertrophy.
Respiratory: Decreased lower lobe sounds bilaterally; crackles and rhonchi noted in bases during active inspiration and expiration. Cough has been productive of thick, yellow sputum. Expiratory wheezing noted on exertion.

Laboratory Values

Chest radiograph: Hyperinflation and increased interstitial markings in the right upper lobes. Atelectasis in bilateral lung bases.
Electrolytes: Na^+ = 138 mEq/L; K^+ = 3.9 mEq/L; Cl^-= 114 mEq/L; and HCO_3 = 28 mEq/L.
Hematology: White blood cell count = 14,000/mm^3; hemoglobin = 12.5 g/dL; and hematocrit = 39.5%.
Sputum culture: Sputum more than 100,000 CFU of PA. Sensitive to amikacin, cefepime, piperacillin/tazobactam, gentamicin, and tobramycin. Resistant to aztreonam, ciprofloxacin, and levofloxacin.

Diagnosis

1. Resolving exacerbation of CF

   Her physician wants to modify her home regimen for CF and asks his respiratory therapist to help him with these questions.

Questions

1. Because her sputum is colonized with PA, should an antibiotic be used? If so, what antibiotic at what dosage and frequency is appropriate? Why?
2. What common inhaled antibiotic side effects would you discuss with the patient before discharge?

3. This patient is currently wheezing and has a history of bronchospasm. She has been using a bronchodilator at home. What instructions would you provide to the patient about administration of the inhaled antibiotic, mucolytic, and bronchodilator therapy?

Amphotericin B (Fungizone, Abelcet, and AmBisome®)

Amphotericin B is fungicidal polyene antimicrobial. It is available in three formulations: amphotericin deoxycholate (Fungizone), amphotericin lipid complex (Abelcet), and amphotericin liposomal (Ambisome). The lipid complex and liposomal formulations cause less nephrotoxicity than amphotericin deoxycholate. *Indications*: It has been the most studied aerosolized antifungal agents in the prevention of invasive aspergillosis in patients with hematologic malignancy and lung transplantation. When given systemically, it is used to treat *Aspergillus*, *Blastomyces*, coccidioidomycosis, *Cryptococcus*, candidiasis, *Histoplasma*, and *Mucor. Mechanism of action*: Amphotericin B binds to ergosterol in the fungal cell membrane, which combines with the sequestered ergosterol and alters fungal cellular permeability and causes cell death. It has no effect on bacteria or viruses (**Figure10-1**). *Dose*: The dosing of each formulation is different. There are no standard approved doses for aerosolized amphotericin. The common doses used for prophylaxis of fungal infections in lung transplant recipients vary depending on formulation and whether the patient is on MV or extubated. The dose of aerosolized amphotericin B deoxycholate is 50 mg daily (MV) and 25 mg (no MV) for 4 days, and then once a week. Aerosolized amphotericin B lipid complex is administered as 100 mg (MV) and 50 mg (no MV) daily for 4 days, and then once a week. There is not enough data to include a dose for liposomal amphotericin. The half-life of the lipid complex formulation is longer and has better lung distribution than with aerosolized amphotericin B deoxycholate.

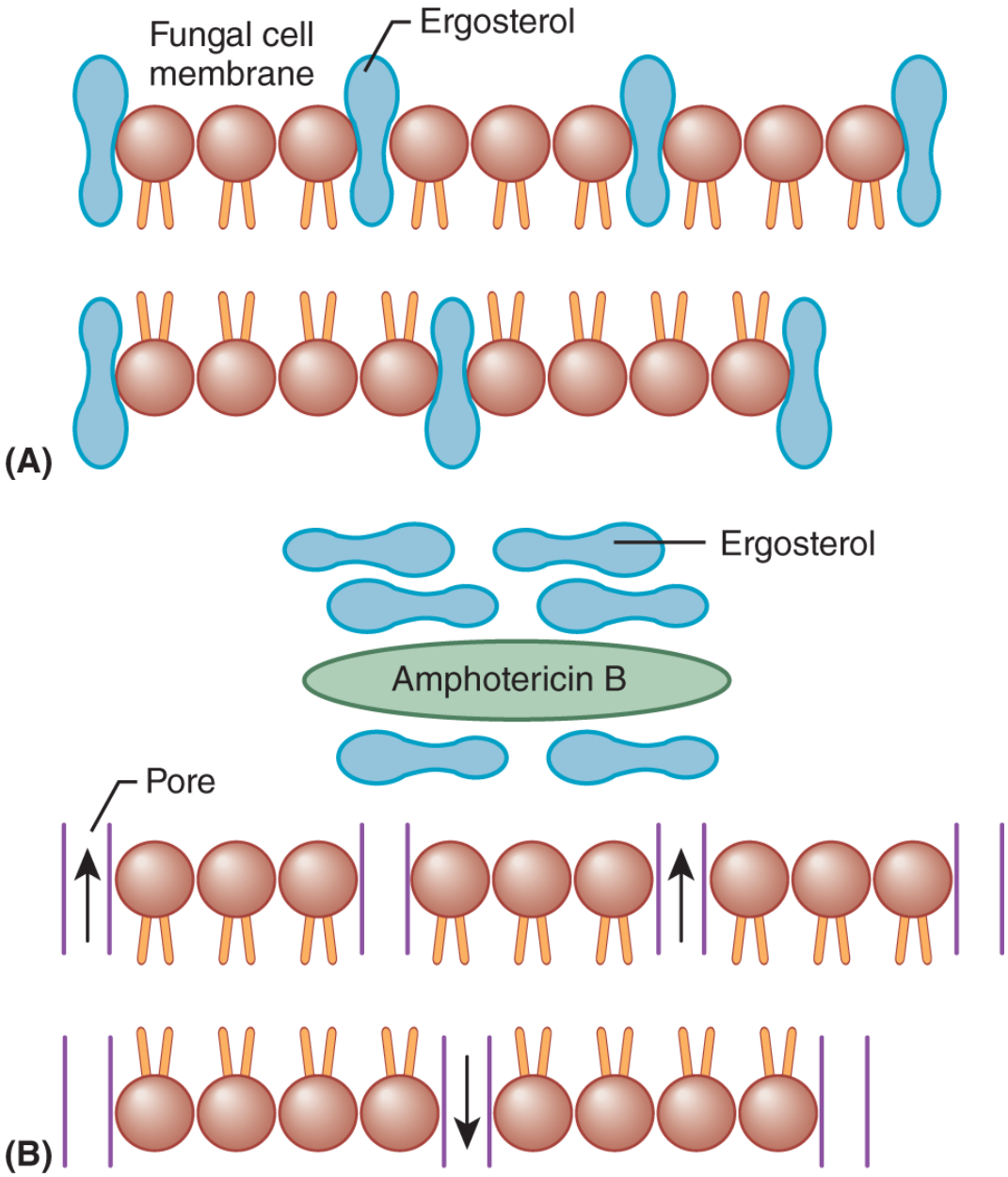


FIGURE10-1 Fungal cell membrane and mechanism of action of amphotericin B.

Created by C Rose; Data from Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition chapter 61 figure 61-2

Description

Adverse effects: The most common side effects with aerosolized therapy include cough, shortness of breath, bronchospasms, and wheezing. Patients may also experience nausea, vomiting, and taste alterations. Side effects are more common with amphotericin deoxycholate, and therefore, the lipid complex formulation is

preferred. The drug is minimally systemically absorbed, and therefore, significant side effects have not been seen with inhaled therapy. *Special considerations*: May cause bronchospasm and the use of a bronchodilator is recommended before administration.

Antiviral Drugs

Ribavirin and zanamivir are two antiviral drugs currently approved for administration by aerosol. Ribavirin is indicated only for use in the severely ill infant or a child who has a known respiratory tract infection caused by RSV. Zanamivir is used for the treatment and prophylaxis of influenza infection.

RSV infections can range from asymptomatic to severe and life threatening. It is the most common cause of bronchiolitis and pneumonia in preterm infants and infants less than 6 months of age during winter months. Immunocompromised patients including adults are also at risk of developing this infection, which is associated with significant morbidity and mortality. The symptoms can range from cough, pneumonia, and wheezing leading to respiratory failure. Touching surfaces contaminated by the virus and then touching the nasal mucosa or eyes with contaminated hands can transmit infection. Palivizumab is a systemically administered monoclonal antibody indicated for the prevention of RSV, which will not be discussed here. Ribavirin has serious adverse effects even when administered by aerosol and is rarely used because recent studies have questioned its benefit for acute RSV infections.

Influenza virus is also a seasonal virus occurring typically from November through March or April. Influenza A and B virus types can cause morbidity and death in any population, but patients with chronic conditions and individuals who are not vaccinated are most susceptible. Vaccination is the best prevention again the influenza virus. Zanamivir is administered by DPI for adults and children 5 years of age and older and is indicated for treatment of uncomplicated influenza and only when symptoms have been present for 2 days or less.

Viruses are microorganisms that consist of either RNA or DNA genes. They are packaged in a capsid. The capsid is a protein shell that covers the genetic material of a virus RNA or DNA. Some viruses also have a lipid outer layer envelope (**Figure10-2**). Proteins containing spikes are found protruding from the surface of the virus that are used to attach to receptors on host cells. A complete virus particle is called a virion. The virus cleaves off a small part of its own RNA or DNA and injects into a healthy host cell. The virus uses the host cell to replicate its own genetic material. Influenza A and B virus types, RSV, HIV, and hepatitis A, C, D, and E viruses are examples of human RNA viruses. Hepatitis B virus, herpes simplex virus, varicella-zoster virus, and cytomegalovirus are examples of human DNA viruses. Most antiviral agents affect the viral replication process, inhibiting the release of the virus into the host cell cytoplasm or outside of the host cell.

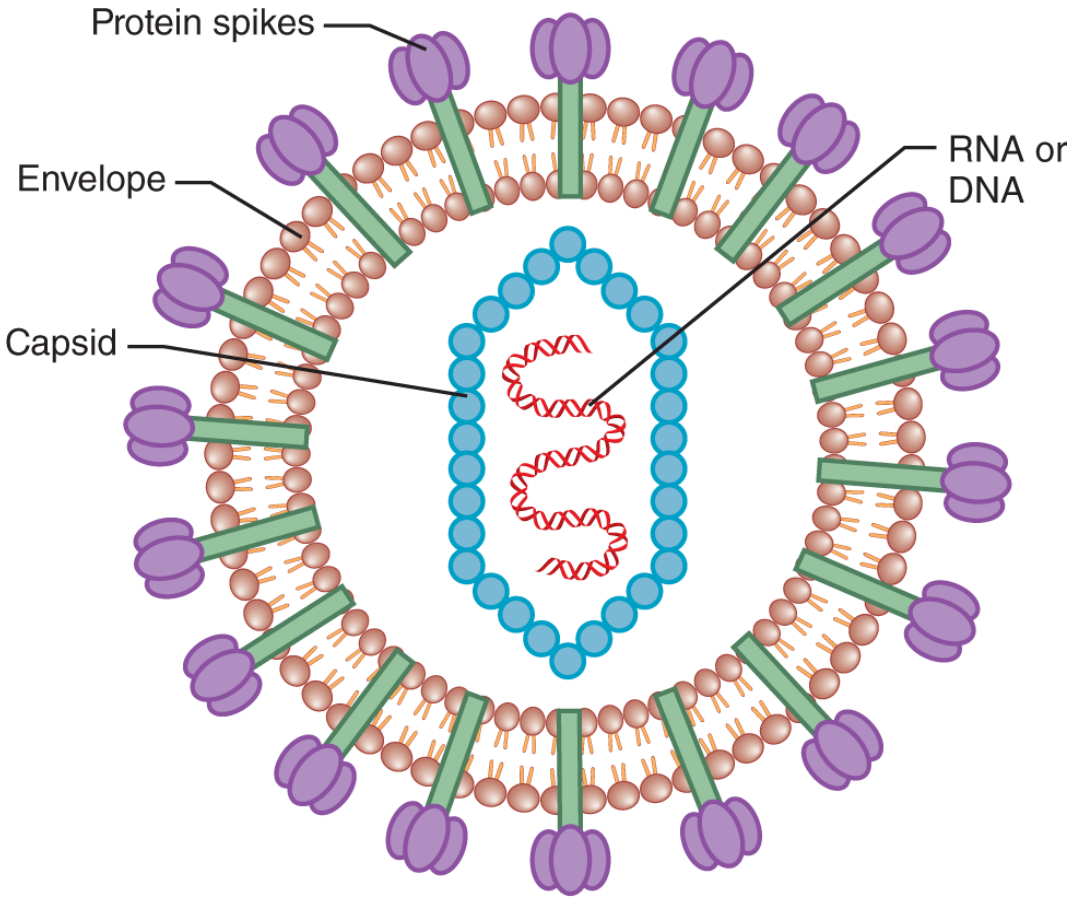


FIGURE10-2 Basic structure of a virion.

Description

Ribavirin (Virazole)

Ribavirin is an antiviral agent with activity against RSV, influenza A and B virus types, and herpes simplex virus. It is available as an aerosolized formulation as well as in a tablet/capsule and oral solution. It is a toxic agent that frequently causes adverse effects to the patient and can cause toxic effects to exposed healthcare workers. *Indication*: The inhalation solution is indicated for use in infants and young children with lower respiratory RSV bronchiolitis or pneumonia to reduce the severity and duration of symptoms. It should only be used and reserved for use in severely ill hospitalized patients. The American Academy of Pediatrics does not recommend the use of ribavirin in children with bronchiolitis. The oral therapy is used in combination with interferon alfa for the treatment of hepatitis C. *Mechanism of actions*: The exact mechanism of action of ribavirin is unknown, but it may inhibit viral RNA synthesis and cellular reproduction. *Dosage and administration*: Inhaled ribavirin is administered as a 20-mg/mL solution. It is available as 6 g of powder that must be diluted with 75 mL of sterile water for injection in the original glass vial. It should only be used with the small particle aerosol generator-2 (SPAG-2) nebulizing system as a continuous administration for 12–18 hours/day. It may also be given as 2 g (over 2 hours) every 8 hours (three times daily). The reconstituted solution should be transferred to the SPAG-2 reservoir and further diluted to a final volume of 300 mL with sterile water for injection. For a 12-hour delivery period, 190 µg/L of air is required. It should not be mixed with any other aerosol agents. In non–mechanically ventilated patients, it can be delivered via an infant oxygen hood, facemask, or oxygen tent from the SPAG-2. In mechanically ventilated patients, dose and administration is the same with a SPAG-2 aerosol generator. The patient's ET tube should be suctioned every 1–2 hours and peak pulmonary pressures should be monitored. A heated-wire connective tubing and bacteria filters in the expiratory limb of the system must be used to minimize the risk of ribavirin precipitating in

the system and subsequent ventilator dysfunction. The SPAG-2 instructions should be consulted before use in a ventilator circuit. *Adverse effects*: Ribavirin has been associated with adversely affecting multiple organ systems. It may cause respiratory deterioration in patients with obstructive lung disease, dyspnea, pneumothorax, apnea, pulmonary edema, and chest tightness. Effects in the cardiovascular system include cardiac arrest, bradycardia, hypotension, and tachycardia. Anemia is the most frequent hematologic side effect that occurs more severely with the oral formulation. Rash and conjunctivitis may also occur.

NEED TO KNOW

Aerosolized ribavirin is only used for severely ill patients with RSV infection owing to its questionable efficacy and significant adverse effects.

Special considerations: Aerosolized ribavirin can deposit in the tubing of a ventilator circuit and may result clogging the ventilator circuit. This has been attributed to several infant deaths. To avoid this complication, patients and ventilator tubing should be monitored frequently. This drug is teratogenic and is known to cause birth defects. It should not be administered to any pregnant patients, and pregnant healthcare workers should avoid exposure to patients being administered this medication. The exposure to healthcare workers caring for patients receiving the drug via oxygen hood or tent is the highest and lowest exposure in patients on MV. Using a negative pressure room with adequate room ventilation, using scavenging devices, and wearing appropriate fitted masks can minimize environmental exposure. The National Institute for Occupational Safety and Health (NIOSH) recommends double-gloving, a protective gown, and eye/face protection for administration of a powder or solution for inhalation or an aerosol treatment; if there is potential for inhalation, respiratory protections is recommended.

NEED TO KNOW

Aerosolized ribavirin is a known teratogen. Care should be taken to avoid environmental exposure to all healthcare workers, especially healthcare workers who may be pregnant.

Zanamivir (RelenzaDiskhaler)

Zanamivir is an antiviral agent with activity against the influenza virus. It has activity against influenza A and B virus types. It should not be used as a substitute for vaccinations. Influenza antiviral treatment has been shown to shorten the duration of fever and symptoms. It may also reduce complications from influenza, and early treatment of hospitalized adult patients has been reported to reduce death. Clinical benefit is the greatest when treatment is administered within 48 hours of symptom onset. The Centers for Disease Control recommend antiviral treatment as soon as possible in patients with suspected influenza who are hospitalized, have severe illness, or are at high risk of complications. *Indication*: Zanamivir is indicated for the treatment of influenza in patients 7 years of age and older who have been symptomatic for no more than 2 days. It can also be used for prevention of influenza in patients 5 years of age and older.

Mechanism of action: Zanamivir is a neuraminidase inhibitor that blocks viral release from infected cells and limits systemic infection. Neuraminidase is an enzyme responsible for releasing viral particles from the host cells and stimulates virus spread via the respiratory tract. *Dose*: Zanamivir is administered by oral inhalation only using the diskhaler device. The medication comes in blister packs containing 5-mg per blister. Each dose is two blisters. If a bronchodilator is usually used, administer the bronchodilator before zanamivir administration. For the treatment of influenza, the dose is 10 mg inhaled twice daily (12 hours apart) for 5 days. On day 1 of treatment, two doses should be administered as long as there are 2 hours between doses. The recommended dose for prophylaxis is 10 mg once daily for 10 days (can be longer depending on certain outbreaks). *Adverse effects*: The most common side effects include headache, cough, rhinitis, and sore throat. This agent may cause bronchospasm, which is more common and severe in patients with asthma and chronic obstructive lung

disease (COPD). Allergic reactions, skin rashes, and anaphylaxis have been reported with use, as well as seizures, hallucinations, and abnormal behaviors are reported. *Special considerations*: Zanamivir should not be used in patients with underlying airways disease (e.g., COPD and asthma) because of risk of bronchospasm. Zanamivir should not be administered to patients on MV. This agent can decrease the effectiveness of the live attenuated influenza vaccine if taken 2 days before or 2 weeks after vaccine administration.

NEED TO KNOW

Zanamivir is indicated for the treatment or prevention of influenza but should not be administered or prescribed in patients with asthma or COPD. This population is at risk for severe bronchospasm with use of this drug.

Antiprotozoal Drugs

The only antiprotozoal drug administered by aerosol is pentamidine. This agent is indicated only for treatment of PCP, a pneumonia seen in immunosuppressed (i.e., post organ-transplant) and HIV patients caused by the *P. jirovecii* fungus. Even though pentamidine treats protozoan species, *P. jirovecii* is actually a fungus. Studies have demonstrated the effectiveness of aerosolized pentamidine as a prophylactic agent for HIV-associated PCP. Trimethoprim-sulfamethoxazole (TMP-SMX) is the preferred first-line prophylactic agent for PCP. PCP prophylaxis is recommended in patients with a CD4 T-lymphocyte (CD4) count less than 200 cells/mm^3. The clinical manifestations of PCP are acute onset of progressive dyspnea, fever, cough, and chest tightness. Hypoxia can range from mild-to-severe in patients who are intolerant to TMP-SMX; aerosolized pentamidine is one of the second-line options. Aerosolized pentamidine is not as effective as IV pentamidine or TMP-SMX in the treatment of PCP infection and should not be used for this indication.

Studies also have shown, however, that factors such as breathing pattern and pulmonary function (which are considered of primary

importance in many aerosol therapies) are less important than the quality of aerosol provided in the nebulization of pentamidine. The major factor influencing pentamidine deposition in the lungs is aerosol delivery, with the Respirgard® II nebulizer (manufactured by Marquet) delivering between 2.5 and 5 times as much drug as other nebulizers studied.

NEED TO KNOW

Bronchospasm and cough are the most common side effects of aerosolized pentamidine.

Pentamidine Isoethionate (NebuPent)

Indication: Aerosolized pentamidine is indicated for the prophylaxis and of PCP. It should not be used to treat PCP because it is less efficacious than other recommended treatments and is associated with relapse of infection. *Mechanism of action*: The mechanism of action is not fully understood but is known to inhibit RNA, DNA, and protein synthesis. *Dose*: NebuPent is marketed as a dry powder with 300 mg per vial; reconstitute with 6 mL sterile water for injection (do not use normal saline because this will cause the powder to precipitate). For PCP prophylaxis, administer 300 mg dissolved in 6 mL sterile water once every 4 weeks. The drug should be nebulized in a specialized micro-nebulizer approved for administration of pentamidine (Respirgard II Nebulizing System™). The treatment will take about 30–45 minutes. Administer pentamidine at a flow rate of 5–7 L/min from a 40- to 50-pound-per-square-inch oxygen or air source. *Adverse effects*: Bronchospasm, bad taste, and cough are the most common side effects experienced in patients receiving aerosolized pentamidine. These effects were controlled by the use of an inhaled bronchodilator. Burning sensation in back of throat and mild hypoglycemia have been reported following aerosol administration. Serious systemic side effects, seen with parenteral pentamidine, have been rarely noted with aerosol administration of the drug, but patients should still be monitored for hypotension, hyperglycemia, hypocalcemia, anemia, thrombocytopenia, leukopenia, QT

prolongation, and pancreatitis. *Special considerations:* Administration of bronchodilator before treatment is indicated if the patient has a history of smoking or asthma (or has previously reacted to pentamidine). Scavenger systems and strict isolation should be used with all aerosolized pentamidine treatments. Pentamidine may degrade in a heated environment; therefore, nebulization via ultrasonic or heated nebulizer is not recommended. It can be considered as an alternative agent for prophylaxis in pregnant women. It was found to be embryo-lethal but not a teratogen.

Limitations of Aerosolized Antimicrobials

It is critical for the respiratory care practitioner to be well-educated in the use of appropriate antimicrobial drugs by aerosol or instillation. Aerosolized administration of antibiotics is an attractive option in order to achieve high concentrations of drugs to the lungs in patients who are colonized or infected with microorganisms but limit systemic absorption. There remain many limitations and disadvantages of aerosol administration of antimicrobials. Bronchospasm is a frequent adverse reaction to inhaled antimicrobials, and the drug may be inactivated by combining with DNA strands in the infected sputum. There is little consensus regarding the optimal nebulization technique for mechanically ventilated patients or dosages that are appropriate for this route of delivery in drugs where aerosolized administration is not FDA-approved. The respiratory care department and its medical director should develop protocols for the aerosol administration of these drugs. The aerosolized drug also enters the ambient air, so that practitioners or other patients may be exposed; this phenomenon actually may lead to increased nosocomial infections (by allowing resistant organisms to proliferate) or to the development of sensitivity or adverse effects to the drug by those exposed. Risks to visitors or healthcare providers should be minimized by the use of scavenger systems whenever possible. In summary, the limitations and disadvantages of aerosolized antimicrobials are as follows:

Case Study 10-2

HIV Status

John R. is a 28-year-old male who was confirmed as having positive HIV status for the past 4 years. He was well until recently when he began to experience increased fatigue and weight loss.

History and Physical Examination

History: The patient has had the usual childhood diseases and is allergic to penicillin and sulfonamide antibiotics.
Social history: IV drug use during age period 20–24 years. Quit smoking 3 years ago.

Vital signs: Heart rate, 80 beats/min; respiratory rate, 20 breaths/min; blood pressure, 110/80 mm Hg; and temperature, 37.2°C.
Respiratory: Breath sounds clear to auscultation. SpO_2 = 94%.

Laboratory Values

Chest radiograph: Few scattered bilateral interstitial infiltrates.
Blood chemistry: Glucose, blood urea nitrogen, and creatinine within normal limits.
Electrolytes: Within normal limits.
Immunodiagnostic studies: CD4+ lymphocytes = 160/mm^3.

Questions

1. What are the indications for administering pentamidine aerosol to this patient?
2. What factors are important in selecting equipment for delivery of the drug by aerosol?
3. What precautions should be taken to minimize risk to the care provider?
4. What adverse effects may occur in a patient who is given pentamidine aerosol?

1. Bronchospasm is a common adverse reaction.
2. Drug may be inactivated by sputum proteins.
3. Drug may not be deposited at desired (infected) site because of improper dose or the administration technique used.
4. Dosages of all aerosolized antimicrobials have not been established.
5. Optimal delivery and equipment techniques have not been determined.
6. Ambient air may be contaminated by drug (exposing other personnel, patients, and visitors to the antimicrobial).
7. Antimicrobial resistance may develop.

Because many anti-infective agents are not approved by the FDA for administration by inhalation, the practice of medicine is an evolving art, in which the clinical experiences of both physician and practitioner will be used for decision making. If there is a significant question regarding the appropriateness of aerosol delivery of an anti-infective agent, experimental protocols should be developed. Patients should be informed of the experimental nature of this route of administration and a written informed consent form should be developed and utilized. All available resources for such decisions should be used, including the hospital formulary and clinical pharmacist, attending

physician, consulting medical staff (including the respiratory care medical director), and an institutional review board.

Review Questions

1. List the three most common indications for the use of antimicrobial drugs by aerosol administration.
2. List five disadvantages or limitations of delivering antimicrobial drugs by aerosol route.
3. What is the most common adverse reaction to the administration of aerosolized antimicrobials?
4. Describe tobramycin, including its primary clinical uses as an aerosol, contraindications, adverse effects, dosage, and special considerations (if any).
5. Describe colistin, including its primary clinical use as an aerosol, contraindications, adverse effects, dosage, and special considerations (if any).
6. Describe two antiviral drugs that have been approved for use by aerosol route, including (a) brand names and (b) clinical indications (i.e., spectrum and specific diseases/conditions for which they are used).
7. Describe one antiprotozoal drug that has been successfully given by aerosol route, including (a) brand name, (b) clinical indications (i.e., spectrum and specific diseases/conditions for which it has been used), (c) contraindications, (d) adverse reactions or side effects, (e) dosage, and (f) special considerations (if any).

Posttest

For each of the following questions, try to select the one best answer from the choices given.

1. Which of the following drugs is an antifungal agent?
   a. Amphotericin B
   b. Aztreonam
   c. Colistin
   d. Ribavirin
2. Which of the following is a common side effect associated with aerosolized antibiotics?
   a. Hypoglycemia
   b. Bronchospasm
   c. Sinusitis
   d. Euphoria
3. Which of the following drugs may be useful in treating colonized *Pseudomonas* in the CF patient?
   a. Ribavirin and pentamidine
   b. Colistin and amphotericin B
   c. Aztreonam and tobramycin
   d. Ribavirin and tobramycin
4. Which of the following is not an appropriate clinical indication or rational for the use of an aerosolized antimicrobial?
   a. To deliver the antimicrobial directly to the respiratory tract (e.g., infected/colonized sputum).
   b. To reduce the severity of systemic side effects.
   c. As an adjunct (additional) therapy when systemic administration of antimicrobials has been unsuccessful.
   d. To avoid the development of drug sensitivity.
5. Which of the following drugs is appropriately aerosolized in order to prevent PCP?
   a. Pentamidine
   b. Ribavirin
   c. Tobramycin

   d. Colistin
6. A 12-year-old boy with CF has copious and purulent secretions, and sputum sample analysis confirms a *Pseudomonas* infection. He is currently receiving dornase alfa (DNase) once a day and 2.5 mg albuterol every 4 hours. Which of the following is an appropriate modification of his care plan?
   a. Administer 3 mL 10% acetylcysteine (Mucomyst®) every 4 hours.
   b. Add 300 mg aerosolized tobramycin (TOBI®) twice a day.
   c. Increase dornase alfa frequency to every 4 hours.
   d. Increase albuterol dosage to 5 mg per treatment.
7. Which nebulizer device is approved for use with nebulized TOBI for this patient?
   a. PARI-LC PLUS nebulizer device
   b. Any nebulizer device should be sufficient because this is an FDA-approved medication
   c. Small particle aerosol generator (SPAG-2) nebulizing system
   d. Respirgard II Nebulizing System
8. A 9-year-old child who recently had a bone marrow transplant is given an aerosol treatment with 300 mg pentamidine (NebuPent) for the prevention of *P. carinii* pneumonia. The patient developed some wheezing during the treatment and then experienced some shortness of breath, wheezing, and a dry cough after the treatment. Which of the following should the respiratory therapist recommend?
   a. Change to ribavirin (Virazole) for the next treatment, given 4 weeks later.
   b. Reduce the dosage of pentamidine to 100 mg and give the next treatment in 2 weeks.
   c. Administer two puffs of albuterol before the next 300 mg pentamidine treatment, given 4 weeks later.
   d. Administer two puffs of albuterol before the next treatment and change to tobramycin (TOBI), wait 2 weeks before the next treatment.
9. Which of the following would be potential consequences of improper administration procedures causing environmental

exposure, when using aerosolized ribavirin in a hospitalized patient?

a. Increases the risk of infection to the patient
b. Increases risk of bronchospasms to the patient
c. Increases the risk of a pregnant nurse giving birth to a baby with a birth defect
d. Decreases the effectiveness of the drug

10. Which of the following would put a patient at risk of fatal lung toxicity from aerosolized colistin?

a. Administration using the PARI-LC PLUS nebulizer
b. Administering albuterol before administration
c. Administering 160 mg every 12 hours
d. Reconstitution of the colistin solution more than 24 hours before administration

References/Recommended Readings

Arnold HM, Sawyer AM, Kollef MH. Use of adjunctive aerosolized antimicrobial therapy in the treatment of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* ventilator-associated pneumonia. *Respir Care*. 2012;5(8):1226-1233.

Athanassa ZE, Markantonis SL, Fousteri MZF, et al. Pharmacokinetics of inhaled colistimethate sodium (CMS) in mechanically ventilated critically ill patients. *Intensive Care Med.* 2012;38:1779-1786.

Boeckh M, Englund J, Li Y, et al. Randomized controlled multicenter trial of aerosolized ribavirin for respiratory syncytial virus upper respiratory tract infection in hematopoietic cell transplant recipients. *Clin Infect Dis*. 2007;44:245-249.

Centers for Disease Control and Prevention. Seasonal influenza (flu): influenza antiviral medications: summary for clinicians. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed September 22, 2018.

Conneally E, Cafferkey MT, Daly PA, et al. Nebulized amphotericin B as a prophylaxis against invasive aspergillosis in granulocytopenic patients. *Bone Marrow Transplant.* 1990;5(6):403-406.

Connor TH, MacKenzie BA, DeBord DG, et al. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2016. 2016. Cincinnati, OH: US Department of Health and Human Services; Centers for Disease Control and Prevention; National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/docs/2016-161/default.html. Updated September 2016. Accessed October 1, 2018.

Czosnowski QA, Wood GC, Magnotti LJ, et al. Adjunctive aerosolized antibiotics for treatment of ventilator associated pneumonia. *Pharmacotherapy.* 2009;29(9):1054-1060.

Drew R, Dodds Ashley E, Benjamin DK, et al. Comparative safety of amphotericin B lipid complex and amphotericin B deoxycholate as aerosolized fungal prophylaxis in lung-transplant recipients. *Transplantation.* 2004;77:232-237.

Druyts E, Thorlund K, Wu P, et al. Efficacy and safety of pegylated interferon alfa-2 or alfa-2b plus ribavirin for the treatment of chronic hepatitis C in children and adolescents: a systematic review and meta-analysis. *Clin Infect Dis.* 2013;56(7):961-967.

Falagas M, Trigkidis K, Vardakas K. Inhaled antibiotics beyond aminoglycosides, polymyxins and aztreonam: a systemic review. *Int J Antimicrob Agents*. 2015;45:221-233.

Fink J, Ari A. Aerosol delivery to intubated patients. *Expert Opin Drug Deliv*. 2013;10:1077-1093.

Katzman M, Meade W, Iglar K, et al. High incidence of bronchospasm with regular administration of aerosolized pentamidine. *Chest.* 1992;101(1):79.

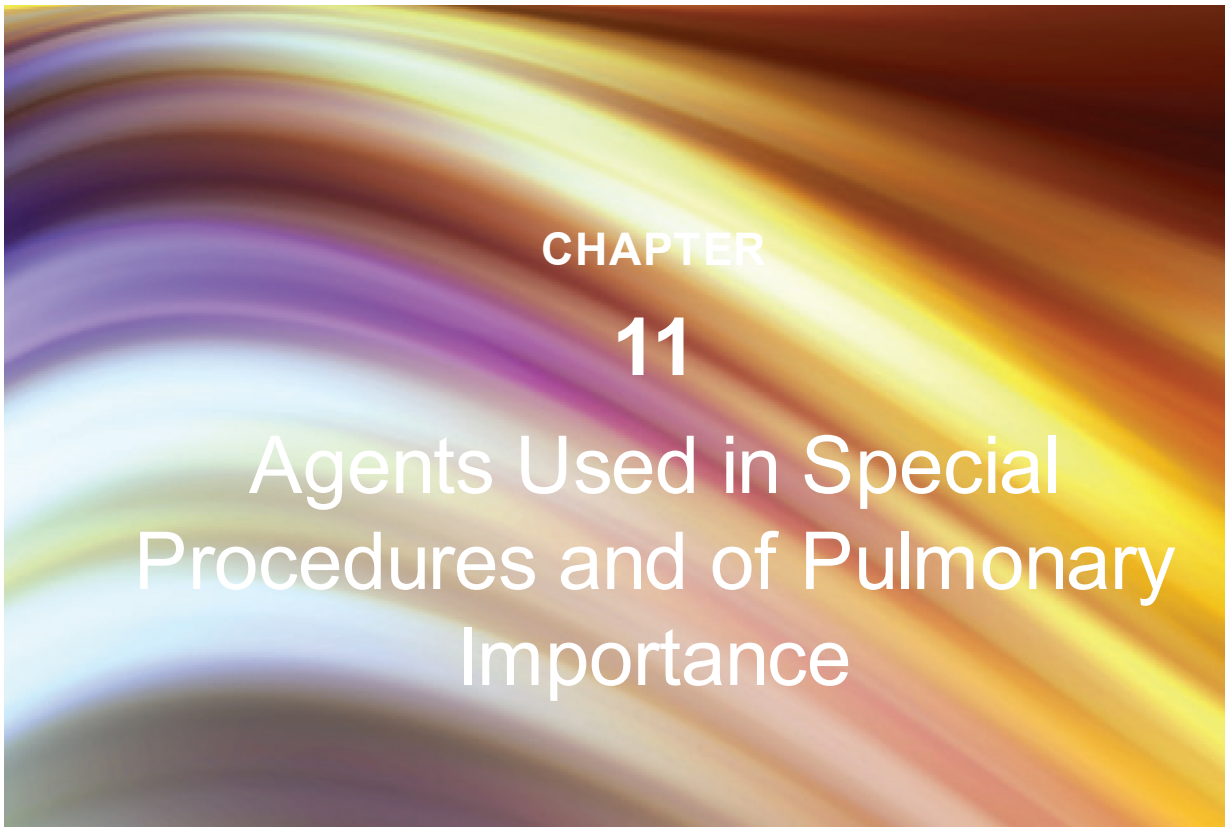
Kofteridis DP, Alexopoulou C, Valachis A, et al. Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator associated pneumonia: a matched case-controlled study. *Clin Infect Dis.* 2010;51(11):1238-1244.

Le J, Ashley ED, Neuhauser MM, et al. Consensus summary of aerosolized antimicrobial agents: application of guideline criteria. *Pharmacotherapy.* 2010;30(6):562-584.

Leoung GS, Feigal DW Jr, Montgomery AB, et al. Aerosolized pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia. *N Engl J Med.* 1990;323:769.

Lim L, Ly N, Anderson D, et al. Resurgence of colistin: a review of resistance, toxicity, pharmacodynamics and dosing. *Pharmacotherapy.* 2010;30:1279-1291.
Lu Q, Luo R, Bodin L, et al. Efficacy of high-dose nebulized colistin in ventilator-associated pneumonia caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Anesthesiology.* 2012;117:1335-1347.
Lu Q, Yang J, Liu Z, et al; The Nebulized Antibiotics Study Group. Nebulized ceftazidime and amikacin in ventilator-associated pneumonia caused by *Pseudomonas aeruginosa. Am J Respir Crit Care Med.* 2011;184(1):106-115.
Luyt CE, Clavel M, Guntupalli K, et al. Pharmacokinetics and lung delivery of PDDS-aerosolized amikacin (NKTR-061) in intubated and mechanically ventilated patients with nosocomial pneumonia. *Crit Care.* 2009;13(6):R200.
Michalopoulis A, Fotakis D, Virtzili S, et al. Aerosolized colistin as adjunctive treatment of ventilator associated pneumonia due to multi-drug resistant Gram-negative bacteria: prospective study. *Respir Med.* 2008;102(3):407-412.
Mogayzal PJ, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines, chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187:680-689.
Montgomery AB, Feigal DW Jr, Sattler F, et al. Pentamidine aerosol versus trimethoprim-sulfamethoxazole for *Pneumocystis carinii* in acquired immune deficiency syndrome. *Am J Respir Crit Care Med.* 1995;151(4):1068-1074.
Murphy RL, Lavelle JP, Allan JD. Aerosol pentamidine prophylaxis following *Pneumocystis carinii* pneumonia in AIDS patients: results of a blinded dose-comparison study using an ultrasonic nebulizer. *Am J Med.* 1991;90(4):418.
Palmer LB, Smaldone GC, Chen JJ, et al. Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. *Crit Care Med*. 2011;36(7):2008-2013.
Patel T, Eschenauer G, Stuckey L, et al. Antifungal prophylaxis in lung transplant patients. *Transplantation*. 2016;100:1815-1826.
Quieffen J, Hunter J, Schechter MT, et al. Aerosol pentamidine-induced bronchoconstriction: predictive factors and preventive therapy. *Chest.* 1991;100(3):624.
Ralston SL, Leiberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics.* 2014;134:e1474-e502.
Rattanaumpawan P, Lorsuttitham J, Ungprasert P, et al. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by gram-negative bacteria. *J Antimcrob Chemother*. 2010;65(12):2645-2649.
Restrepo MI, Keyt H, Reyes LF. Aerosolized antibiotics. *Respir Care*. 2015;60:762-773.
Schneider MM, Hoepelman A, Eeftinck J, et al. A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus infection. *N Engl J Med*. 1992;327:1836-1841.
Smaldone GC, Dickinson G, Marcial E, et al. Deposition of aerosolized pentamidine and failure of *Pneumocystis* prophylaxis. *Chest*. 1992;101:82-87.
Smaldone GC, Fuhrer J, Steigbigel RT, et al. Factors determining pulmonary deposition of aerosolized pentamidine in patients with human immunodeficiency virus infection. *Am Rev Respir Dis*. 1991;143:727-737.
Smith S, Rowbotham NJ, Regan KH. Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis (review). *Cochrane Database Syst Rev*. 2018;(3):CD001021. doi:10.1002/14651858.CD001021.pub3

Stockmann C, Robers J. Clinical pharmacokinetics of inhaled antimicrobials. *Clin Pharmacokinet*. 2015;54:473-492.
Tay GT, Reid DW, Bell SC. Inhaled antibiotics in cystic fibrosis (CF) and non-CF bronchiectasis. *Semin Respir Crit Care Med*. 2015;36:267-286.
Vardakas KZ, Voulgaris GL, Samonis G, et al. Inhaled colistin monotherapy for respiratory tract infections in adults without cystic fibrosis: a systematic review and meta-analysis. *Int J Antimicrob Agents*. 2018;51:1-9.
Ventre K, Randolph AG. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. *Cochrane Database System Rev.* 2007; (1):CD000181.
Waskin H. Toxicology of antimicrobial aerosols: a review of aerosolized ribavirin and pentamidine. *Respir Care*. 1991;36:1026.
Wood GC, Boucher BA. Aerosolized antimicrobial therapy in acutely ill patients. *Pharmacotherapy*. 2000;20:166-181.
Wood C, Swanson JM. An update on aerosolized antibiotics for treating hospital-acquired and ventilator-associated pneumonia in adults. *Ann Pharmacother*. 2017;51:1112-1121.
Wood GC, Underwood EL, Croce MA, et al. Treatment of recurrent *Stenotrophomonas maltophilia* ventilator-associated pneumonia with doxycycline and aerosolized colistin. *Ann Pharmacother*. 2010;44(10):1665-1668.



© Anna RubaK/ShutterStock, Inc.

OUTLINE

Introduction
Special Procedures
  Bronchoscopy
  Medications Used for Airway Hyperresponsiveness
Pulmonary Vasodilators
  Inhaled Vasodilators in Acute Hypoxemia
Respiratory Stimulants
  Apnea of Prematurity
Smoking Cessation
  Smoking Cessation Methods
  Pharmacologic Therapy for Smoking Cessation
  General Considerations of Smoking Cessation

Objectives

After completion of this chapter and its learning activities, you will be able to:

1. Describe the purpose of lidocaine use during a bronchoscopy.
2. Compose a plan for the use of lidocaine during bronchoscopy including strength, route of administration, and maximum dose.
3. List drugs used in performing “bronchial challenge” pulmonary function studies, including generic names, actions, contraindications, and side effects/hazards.
4. Discuss the role and differences between methacholine and mannitol when used for bronchial challenge testing.
5. Create a plan for using inhaled nitric oxide and inhaled epoprostenol as selective vasodilators, dosage, and method of administration and monitoring for adverse effects.
6. Describe the use of respiratory stimulants in neonatal care and the most common adverse effects associated with each.
7. Discuss smoking cessation strategies, and given a patient case be able to recommend appropriate pharmacologic smoking cessation therapy and instructions for use.

KEY TERMS

Airway hyperresponsiveness (AHR)
Bronchial provocation
Bronchial provocation testing
Bronchoscopy
Inhaled nitric oxide (INO)
Nicotine replacement therapy (NRT)

Introduction

This chapter discusses the pharmacology of agents used in the assessment, treatment, and prevention of pulmonary conditions.

There are several areas of respiratory care practice in and out of the critical care setting that involve medication administration. These areas include special procedures such as bronchoscopy, bronchial challenge testing, and assessment of airway hyperresponsiveness. Inhaled pulmonary vasodilator agents such as nitric oxide and epoprostenol are used to assess pulmonary arterial responsiveness as well as used therapeutically in patients with pulmonary hypertension in the critical care setting. There are other pulmonary vasodilators currently approved for the chronic treatment of pulmonary hypertension, which require appropriate inhalation technique to maximize effectiveness. A respiratory care practitioner (RCP) should be familiar with the pharmacology of these agents and the procedures involved in administration. Pharmacologic smoking cessation therapies play a major role in patient's ability to quit smoking and prevent worsening of lung function. The RCP should be familiar with the available agents in order to educate patients on appropriate therapy.

Special Procedures

An RCP may serve as an assistant during a bronchoscopy procedure. It would be important for any assistant to be knowledgeable on the medication therapy used for preparation of the patient and administration of aerosolized medications and drug administered down the bronchoscope during the therapeutic procedure. A trained RCP may be responsible for direct challenge testing to determine airway hyperresponsiveness using methacholine. A trained individual needs to take into account administration and safety procedures when conducting this test.

Bronchoscopy

It is common for the RCP to assist the pulmonary team in performance of various pulmonary diagnostic procedures. A **bronchoscopy** is the direct visualization of the tracheobronchial tree by a rigid or flexible scope and is a potentially hazardous procedure and requires careful patient monitoring to ensure patient comfort and safety. This procedure allows the clinician to visualize the upper and lower respiratory tract for the diagnostic management of several pulmonary diseases involving the airways and lungs. Continuous pulse oximetry, end-tidal CO_2 monitoring, and electrocardiographic monitoring are included as standard recommendations in the most current AARC Clinical Practice Guideline for assisting with bronchoscopy. Analgesic and sedative medications may be used to improve patient tolerability of the procedure. The mucosal membranes may become irritated during the procedure and lead to excessive coughing or bronchospasm. Knowledge of aerosolized medication delivery, treatment of respiratory complications, and management of mechanical ventilation are essential in assisting in this procedure.

Medications Used During Bronchoscopy

A bronchoscopy may be performed without sedative agents but patient approval and tolerance will improve with sedative therapy. Benzodiazepines are the preferred class of sedative agents used in this procedure. Midazolam is most commonly used because of its fast onset of action and short duration of action. Opioids may also be used to improve patient comfort and also for their antitussive properties. Fentanyl is recommended because of its quick effect and short duration of action. Benzodiazepine and opioids are discussed in Chapters 12 and 14.

NEED TO KNOW

Midazolam and fentanyl are the most commonly used sedative and analgesic agents during a bronchoscopy procedure because of their quick onset and short duration of action.

The insertion of the bronchoscope may be traumatic and may stimulate laryngospasm, bronchospasm, mucosal edema, and coughing. To avoid many of these side effects, a preprocedure small-volume nebulizer treatment may be given with an aerosolized local anesthetic. The use of a topical anesthetic before the procedure has been shown to decrease coughing, gagging, the need for sedation during the procedure, and patient distress. The most commonly used and recommended medication for this purpose is topical lidocaine. Lidocaine is a local anesthetic and antitussive, working to suppress the cough reflex during bronchoscopy. It stops both the initiation and the conduction of nerve impulses. It is available in various preparations such as a gel, topical solution, and injectable solution. It can be administered using various methods during a bronchoscopy. The administration techniques include topical instillation, transtracheal injection, local nerve block, nebulized solution, and “spray-as-you-go.” Injection and nerve blocks are not commonly used. Lidocaine 1%, 2%, or 4% solutions are used most commonly with the 1% strength showing similar efficacy at reducing coughing when administered down a bronchoscope compared with 2% strength. When

administered down the bronchoscope, peak effect occurs at 15–30 minutes. Doses of lidocaine used during this procedure may vary among institutions. About 10–20 mL of 1% lidocaine is commonly used by instilling or trickling down the bronchoscope. Lidocaine 4% may be used for nebulization using 5 mL at a time. A total lidocaine dose over the course of the whole procedure should not exceed 4–5 mg/kg. Lidocaine carries significant toxicity that may result in oral paresthesia, seizures, coma, and cardiac arrhythmias. The total dose of lidocaine used during the procedure should be carefully monitored.

NEED TO KNOW

The total dose of lidocaine used during a procedure should not exceed 4–5 mg/kg. This should be recorded and the total dose used should be monitored throughout the duration of the procedure. If this dose is exceeded, it may lead to seizures, coma, or cardiac arrest.

Epinephrine has a favorable vasoconstrictive (alpha) effect that limits bleeding during and after a procedure. Diluted epinephrine may be injected into a bleeding vessel if this occurs during the procedure. Epinephrine's mechanism of action is further discussed in Chapter 3. If the patient is known to have a reactive airway disease such as asthma or chronic obstructive pulmonary disease (COPD), pretreatment with a combination of albuterol/ipratropium (described in Chapter 6) may avoid postprocedure complications, and if wheezing occurs, an aerosolized short-acting bronchodilator such as albuterol and ipratropium should be given.

If a therapeutic bronchoscopy is being performed to remove mucous plugging from the airways, the physician may request a mucolytic/mucokinetic agent such as hypertonic saline, 10% or 20% acetylcysteine, and (rarely) dornase alpha. These medications are further described in Chapter 8. Patients often experience hypoxemia during bronchoscopy, and most institutions have protocols that recommend oxygen therapy for up to 4 hours following the procedure. If laryngospasm occurs, evidenced by stridor, aerosolized racemic epinephrine should be administered.

Case Study 11-1

Diagnostic Bronchoscopy

Mr. A is a 47-year-old Hispanic man who presented several days ago at his physician's office complaining of "trouble swallowing, noisy breathing and I can't breathe when I sleep." Questioning revealed a slow onset of symptoms over the past year. Mr. A. has been referred to the pulmonary diagnostics lab for a flexible fiberoptic bronchoscopic examination.

History and Physical Exam

Work history: The patient is a well-developed Hispanic man who works as a development technician in a chemical plant. He has held this job for 10 years. In his job, he is exposed to various chemical compounds, some of which are newly developed and whose properties are poorly, if at all, understood. Although Mr. A. uses appropriate protective devices and clothing, occasional spills and circumstances expose him to these chemicals.
Vital signs: Heart rate, 86 beats/min; blood pressure, 126/82 mm Hg; respiratory rate, 18 breaths/min; and temperature, 37°C oral.
Cardiovascular: Within normal limits.
Respiratory: Audible stridor on both inspiration and expiration. Visibly delayed filling and emptying on right side. Reduced breath sounds in right lung. Forced expiration reveals wheezing and delayed breath sounds on right. *Impression:* Right bronchial obstruction of unknown origin.

Laboratory Values

Chest radiograph: Apparent right mainstem mass. Evidence of air trapping on right—hyperinflated with slight mediastinal shift to left. *Impression:* Right mainstem mass.
Arterial blood gases: On room air—pH = 7.45; PCO_2 = 46 torr; PO_2 = 94 torr; HCO_3^- = 24.1 mEq/L.

Hospital Orders

Diagnostic Bronchoscopy

The physician asks you to set up for a bronchoscopy in the outpatient endoscopy laboratory.

Questions

1. If a bronchodilator is needed, which type of bronchodilator would you suggest and why?
2. For what reason would a preprocedure local anesthetic be given? What medications may be used for this and what are the usual route, dosage, and method of administration?
3. Should the patient also receive some type of antianxiety or sedative medication before bronchoscopy? If so, what medication(s) might be recommended?
4. If the patient received 10 mg/kg of topical lidocaine during the procedure, which adverse effects should you carefully monitor this patient for?

Medications Used for Airway Hyperresponsiveness

Bronchial provocation testing is a procedure done in the pulmonary function laboratory to provide the physician with information regarding the reactivity of the patient's airway when exposed to an irritant. This testing provides both pathophysiologic and clinical information about a patient's pulmonary disease by testing for the degree of **airway hyperresponsiveness (AHR)**, which can contribute to the diagnosis of asthma. This challenge may be conducted by directly or indirectly stimulating the airways. The direct stimuli act on the smooth muscle receptors and the indirect stimuli act by involving pathways that involve release of mediators from inflammatory cells. Pulmonary function laboratories typically maintain specific protocols for the performance of such provocation testing and describe the procedure in detail. These tests are not performed in children. Before testing, baseline spirometry must be performed. Bronchodilators should be immediately accessible during testing in the event of severe reactions and may be given after testing to enhance return of normal pulmonary function. Resuscitation equipment should also be readily available, and personnel should be certified in cardiopulmonary resuscitation and able to recognize and respond appropriately if severe or life-threatening reactions occur.

The two most common drugs used for this challenge testing are methacholine and mannitol. Histamine is sometimes used for **bronchial provocation** but usually only after a methacholine challenge. Methacholine is a direct stimulus for airway hyperresponsiveness, whereas mannitol is an indirect stimulus. Some patients exhibit AHR to methacholine but not to mannitol, whereas others respond to mannitol but not to methacholine. A positive methacholine-challenge test may indicate asthma, but it may not be definitive. A positive mannitol-challenge test suggests underlying airway inflammation and may be more specific for identifying asthma.

None of these tests is an absolute diagnostic for the presence of asthma and the ultimate diagnosis is made by the patient's physician. This chapter describes methacholine (the most commonly used provocation agent) and mannitol.

Methacholine

Methacholine is a parasympathomimetic agent, meaning that it mimics or imitates the effects of the parasympathetic nervous system. It is used only to induce bronchoconstriction for diagnostic testing, it has no therapeutic indication. When used as an aerosol agent, its primary effect is direct stimulation of bronchoconstriction and increased bronchial gland secretion. The onset of effect is within 30 seconds to 2 minutes and lasts up to 45 minutes unless a bronchodilator is administered, which can shorten its effect. Methacholine-challenge testing begins with the most dilute solution. The patient receives five inhalations of the most dilute solution, followed within 5 minutes by a forced vital capacity (FVC) measurement. The study continues using progressively more concentrated solutions until the patient's forced expiratory volume in one second (FEV_1) is reduced by 20% or the patient has received the maximum dosage which is 188.9 total cumulative units. Some patients who do not respond to a methacholine challenge will respond to histamine, a major mediator of inflammatory reactions. The general clinical indication for such testing is to diagnose reactive airway disease in patients who do not have clinically apparent asthma. Methacholine is contraindicated in patients with active wheezing, severe airflow limitation, patients who have had a myocardial infarction or stroke in the last 3 months, uncontrolled hypertension (SBP > 200 or DBP > 100). Caution should be used in pregnant or breastfeeding patients. Patient receiving cholinesterase inhibitors or β-blockers may be at a higher risk of bronchoconstriction. Patients receiving any type of bronchodilator may lead to decreased activity of this agent. Adverse reactions are rare and include headache, dizziness, and throat irritation.

NEED TO KNOW

Methacholine (Provocholine®) is a cholinergic drug used to induce bronchoconstriction for diagnostic testing; it has no therapeutic uses. Methacholine-challenge testing begins with the most dilute solution and is terminated when a reduction in FEV_1 of 20% from baseline occurs.

Mannitol

The use of dry-powder capsules containing mannitol is another agent that can be used to assess airway hyperresponsiveness. Inhaled mannitol is no longer available in the United States but may still be used in other countries. Mannitol is an osmotic agent that increases airway osmolarity, which leads to release of inflammatory mediators from mast cells, thus indirectly stimulating bronchoconstriction. A positive methacholine-challenge test may indicate asthma, but it may not be definitive. A positive mannitol-challenge test suggests underlying airway inflammation and may be more specific for identifying asthma.

Mannitol is provided in dry-powder capsules of 0.5 mg to 160 mg. Testing begins with 0.5 mg and continues with dosages of 10, 20, 40, 80, and lastly 160 mg administered three times in a row. An FVC test is done 60 seconds after each inhalation, and the test is ended when the patient shows a 10% reduction in FEV_1 between consecutive doses or when the patient has received the maximum dosage (635 mg). If the patient exhibits an overall reduction in FEV_1 of 15% at the maximum cumulative dose of 635 mg, this is considered a positive test, suggestive of asthma. Some patients exhibit AHR to methacholine but not to mannitol, whereas others respond to mannitol but not to methacholine. Mannitol should not be administered for AHR in patients with severe airflow limitation, uncontrolled hypertension, or a recent myocardial infarction or stroke. The use of bronchodilators and inhaled corticosteroids will decrease the airway sensitivity to mannitol. The most common adverse effects include coughing, chest tightness, headache, throat irritation, rhinorrhea, nausea, and vomiting.

Pulmonary Vasodilators

There are multiple pulmonary vasodilators now available. **Inhaled nitric oxide (INO)** and the prostacyclin epoprostenol are used for the treatment of assessment of pulmonary hypertension as well as in the treatment of pulmonary hypertension and acute respiratory distress syndrome (ARDS). There are two other synthetic prostacyclin analogs available for inhaled use in the treatment of pulmonary hypertension. The acute and chronic use of these agents will be discussed in this section.

Inhaled Vasodilators in Acute Hypoxemia

There are a variety of underlying conditions and mechanisms that can lead to hypoxemia in critically ill patients. Mechanistically, ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch is the most common. Hypoxemia can also lead to persistent pulmonary hypertension, typically resulting in continued right-to-left shunting of blood. Providing systemic vasodilators to relieve the $\dot{V}/\dot{Q}$ mismatch has been shown to worsen the clinical condition because the widespread vasodilation improves circulation to unventilated lung units (increasing the $\dot{V}/\dot{Q}$ imbalance). Providing INO or epoprostenol matches the vasodilator to ventilated lung units, thus improving the $\dot{V}/\dot{Q}$ matching and resulting in improved oxygenation with few (if any) systemic side effects.

Nitric Oxide

Nitric oxide is a naturally occurring substance that promotes vasodilation. Nitric oxide (NO) is a gas naturally produced in the body. NO stimulates soluble guanylate cyclase to form cyclic guanosine monophosphate (cGMP), which leads to vascular smooth muscle relaxation. When NO is inhaled, vasodilation occurs primarily in the pulmonary vessels with minimal to no systemic vasodilation. It has become an essential therapy for patients who develop life-threatening

pulmonary hypertension due to acute hypoxemia or underlying pulmonary hypertension in pediatric and adult patients. The approved use for INO is primarily in the neonatal intensive care unit, but there has been success in using INO in adults as well. In addition to pulmonary hypertension, INO has also been used in adult patients with an acute lung injury/ARDS, after lung transplantation, right-sided heart failure, and in sickle cell disease. It can also be used during cardiac catheterization for acute vasodilator testing to determine capacity of pulmonary vasodilation in patients with pulmonary hypertension. INO is only FDA-approved for the treatment of term or near-term newborns with acute hypoxic respiratory failure associated with pulmonary hypertension. The AARC Clinical Practice Guideline regarding INO therapy recommends a trial of INO in newborns ≥ 34 weeks' gestation that require mechanical ventilation and demonstrate a P_aO_2 of less than 100 torr while breathing 100% oxygen. An alternative indication is an oxygenation index of .25 in newborns ≥34 weeks' gestation.

Dosage and administration: Initial starting dose of INO is a concentration of 20 parts per million (ppm). Doses up to 80 ppm have been used with minimal clinical improvement. Following the initiation of INO at this concentration, clinical improvement is measured by an improvement in the oxygenation index or P_aO_2. If improvement is not seen within 30–60 minutes of initiating INO therapy, it should be discontinued. If improvement in oxygenation is seen, the concentration of INO should be reduced to 10 ppm and the patient should be monitored for changes in S_pO_2, oxygenation index, mean arterial pressure (MAP), or pulmonary artery pressure (PAP). If these indexes remain stable or show less than 10% change after 15 minutes, INO concentration may be reduced to 5 ppm. Further weaning is accomplished using these clinical indicators at each increment (from 5 ppm to 3 ppm to 1 ppm). Nitric oxide is provided to mechanically ventilated newborns via the INOvent™ delivery system. This system provides a constant nitric oxide concentration to the inspiratory limb of the ventilator circuit.

The expected outcome of utilizing INO is the ability to maintain oxygenation status at a reduced F_iO_2. As INO improves oxygenation, reductions in F_iO_2 should be made. INO should not be abruptly discontinued because a rebound pulmonary hypertension may occur. To minimize the adverse effects of this rebound phenomenon, patients should be maintained on the lowest effective dose (i.e., 5 ppm or less) and weaned to a concentration of 1 ppm for at least 1 hour before discontinuation of INO. If clinical improvement is such that INO may be discontinued, the F_iO_2 should be increased immediately before removing the INO. There are institution-specific weaning protocols designed for RCPs to assist in the weaning and discontinuation of INO.

NEED TO KNOW

INO should be weaned from 20 ppm to the lowest effective dose and continued weaning should occur as the patient's condition allows. Patients should be weaned to a level of 1 ppm before discontinuing INO.

Adverse effects and hazards: The primary hazards of INO therapy are rebound pulmonary hypertension due to abrupt discontinuation of therapy, as previously discussed, and the development of methemoglobinemia. NO diffuses into red blood cells and when combined with hemoglobin forms methemoglobin. Both of these hazards are avoidable by using appropriate INO protocols. The lowest effective concentration of INO should be used, and even when the dosage is low, INO must be weaned and the patient supported with increased F_iO_2 at discontinuation. Methemoglobinemia is unlikely in therapeutic dosage ranges (less than 40 ppm) but this should be monitored. If the methemoglobin level exceeds 5%, the INO concentration should be reduced or discontinued. When NO is exposed to high concentrations of oxygen gas, nitric dioxide (NO_2) is formed, which may lead to lung tissue injury and pulmonary edema. Using the lowest effective dose for the shortest time period clinically necessary is important to prevent these adverse effects.

Although not a clinical hazard, it is imperative that the RCP and all care givers exercise great caution in handling the equipment and cylinders associated with INO therapy and the INOvent to prevent waste and unnecessary expense.

Epoprostenol Sodium (Flolan, Veletri)

Epoprostenol, a metabolite of arachidonic acid, is a naturally occurring prostaglandin with potent vasodilating properties that also inhibits platelet aggregation. It is a strong vasodilator in all vascular beds, but when administered as an aerosol, it will target vasodilation in the pulmonary vessels. There has been clinical interest in using epoprostenol in an aerosolized formulation as an alternative to INO in adults with ARDS because it is therapeutically equivalent in improving oxygenation and less costly than INO. Inhaled epoprostenol is currently used as part of a salvage therapy for patients with ARDS who exhibit refractory hypoxemia and increased pulmonary vascular resistance. It can also be used for pulmonary hypertension, acute right heart dysfunction, and hypoxemia related to pulmonary vasoconstriction. This section will discuss only the inhalation administration of epoprostenol. It is available in IV formulation as well for the chronic management of pulmonary hypertension.

Dosage and administration: Flolan® is a salt that is reconstituted with a glycine buffer diluent. The active drug is provided in 0.5-mg and 1.5-mg vials and the diluent in 50 mL vials. Due to the quick onset of action (1–2 minutes) and duration of action (3–5 minutes), epoprostenol is administered as a continuous inhalation dosed at 10–50 ng/kg/min. Dosing is based on ideal body weight and can be titrated by 10 ng/kg/min every 15–30 minutes as tolerated based on improvement to the patient's Pa_{O_2}/F_{iO_2}. Many institutions have institution-specific initiation, titrating, and discontinuation protocols for the RCP.

Nebulizers that have been successfully used for administration of inhaled epoprostenol are the Aeroneb® Solo Nebulizer System and MiniHeart™ Nebulizer. The nebulizer is placed in-line with the mechanical ventilator circuit, and two disposable non-HME filters are

placed on the expiratory limb of the ventilator proximal to the water trap. Subsequent dosing and concentration decisions are based on patient response. If no significant clinical response is seen within 30 minutes, the medication should be discontinued. If the patient shows clinical improvement, frequent assessment and subsequent downward titration of the epoprostenol concentration should be continued.

Adverse effects: The solution for nebulization has a tendency to accumulate in ventilator tubing and may impair ventilator valve function. Frequent changing of expiratory filters is usually required and the ventilator must be closely monitored for increases in peak airway or end-expiratory pressures. The half-life of epoprostenol is 6 minutes and if abruptly stopped can lead to rebound pulmonary hypertension. The most common dose-related physiologic side effect is hypotension but flushing, gastrointestinal (GI) complaints, and musculoskeletal pain may occur uncommonly when the drug is given by aerosolized route. Thrombocytopenia may be rarely seen with the aerosolized formulation. As with use of INO, epoprostenol must be weaned by titration to avoid a rebound pulmonary hypertensive response.

Iloprost (Ventavis)

Iloprost is a synthetic analog of prostacyclin indicated for the treatment of chronic pulmonary arterial hypertension (PAH). It has been studied and shown beneficial in patients with idiopathic (unknown cause) pulmonary hypertension, PAH associated with connective tissue disease. It has been shown to improve exercise tolerance, improve symptoms, and prevent deterioration of condition or worsening of heart failure symptoms. It dilates the pulmonary arterial vascular beds and affects platelet aggregation.

Dose and administration: Iloprost inhalation solution should only be inhaled using the I-neb adaptive aerosol delivery (AAD) system (**Figure 11-1**). This system uses vibrating mesh technology to deliver the medication, which analyzes the patient's breathing patterns and only pulses aerosol during inspiration. The starting dose is 2.5 µg and

can be increased to 5 µg and administered six to nine times per day (more than every 2 hours) while awake. The maximum dose is 45 µg daily (5 µg nine times daily). It should not be mixed with other medications. Treatment times last 5–10 minutes and can be adjusted to a more concentrated solution to shorten treatment times. The inhalation solution comes in a 10-µg/mL or 20-µg/mL glass ampule that is opened and instilled into the I-neb AAD device before each dose.

FIGURE 11-1 I-neb adaptive aerosol delivery system for iloprost.

Courtesy of Philips Respironics.

Adverse effects: The most common side effects are flushing, cough, and headache. Jaw pain, hypotension, insomnia, chest pain, nausea/vomiting, and dizziness are also reported with use. Patients with a history of reactive airway disease may experience

bronchospasm with use of iloprost. Because of the changes in platelet aggregation, nose bleeds and hemoptysis may also occur with iloprost use.

Treprostinil (Tyvaso)

Similar to iloprost, treprostinil is also a prostacyclin analog that directly causes pulmonary and systemic arterial vasodilation and inhibition of platelet aggregation. It is indicated in patients with pulmonary arterial hypertension in patients with idiopathic/inherited or PAH associated with connective tissue disease. In studies, treprostinil has been shown to improve exercise capacity (increase 6-minute walk distance). It is available in an oral, intravenous, subcutaneous, and inhaled formulation with similar efficacy. Only the inhaled formulation will be discussed here.

Dose and administration: Inhaled treprostinil should only be used with the Tyvaso Inhalation System, which consists of an ultrasonic pulsed delivery device (**Figure 11-2**). Each daily dose of medication comes in a clear ampule that should be transferred to the medicine cup within the nebulizer device. The initial dose is three breaths (18 µg) per treatment, four times daily while awake. As tolerated, the number of breaths can be increased with each treatment to a maximum of nine breaths (54 µg) four times daily. The patient should be instructed how to assemble, clean, and administer treprostinil inhalation solution into the nebulizer device.

FIGURE 11-2 Treprostinil (Tyvaso) ultrasonic nebulizer system.

Courtesy of United Therapeutics Corporation.

Adverse effects: The most common adverse reactions reported in clinical studies are cough, throat irritation, headache, flushing, nausea/vomiting, and muscle and jaw pain. Treprostinil increases risk of bleeding owing to its inhibition on platelet aggregation.

Respiratory Stimulants

Drugs that stimulate the central respiratory center or reduce central apnea have become useful. Both premature and term newborns may experience apneic episodes that respond to appropriate drug therapy and benefit from respiratory stimulants.

Apnea of Prematurity

Apnea of prematurity results from undeveloped respiratory control. Transient episodes of apnea and bradycardia may occur in newborns, more commonly in premature neonates. Neonates born at 30–31 weeks and neonates weighing less than 1 kg have a higher incidence of apnea than do infants born at an older gestational age. Methylxanthines (such as theophylline, previously discussed in Chapter 5) may be useful as a central nervous system (CNS) and respiratory stimulant and increase respiratory drive and diaphragm contraction. However, these drugs have a narrow therapeutic index, which is even narrower in newborns. Caffeine citrate is a CNS stimulant that also stimulates respiration and may be useful when administered intravenously to infants with episodes of apnea.

Caffeine and Theophylline in Newborns

Caffeine citrate and theophylline are both methylxanthines used to reduce apneic episodes of premature infants. Both agents improve respiratory function and decrease extubation failure but caffeine has been found to have less adverse events than theophylline. Caffeine has a quicker onset of action than does theophylline. The dose of caffeine citrate used in neonates is a 20-mg/kg intravenous loading dose followed by a maintenance dose of 5 mg/kg/day. Theophylline is given as an oral loading dose of 5–6 mg/kg followed by an oral maintenance dose of 1.5 mg/kg every 12 hours. In infants, theophylline is metabolized to caffeine, resulting in increased serum

levels of caffeine. Serum caffeine and theophylline levels must be closely monitored when used in newborns. Plasma caffeine levels should be maintained in the range of 5–20 μg/mL, and serum theophylline should be maintained between 6 and 13 μg/mL. In these ranges, toxicity should not occur. Signs of excess serum caffeine or theophylline levels include tachycardia, tachypnea, tremors, nausea, vomiting, diarrhea, irritability, and feeding intolerance. Theopylline is associated with more severe adverse effects, including seizures, tachyarrhythmias, and feeding intolerance.

Smoking Cessation

Respiratory therapists are often involved in providing smoking cessation resources for patients and their families. Smoking is a complex behavior, and when a patient decides to quit smoking, or is living in an environment where others smoke, initiating a conversation about smoking cessation is good practice. The AARC has issued position statements regarding the role of the respiratory therapist as a role model and as a patient-educator in health promotion and disease prevention.

Smoking Cessation Methods

There is no single best method of smoking cessation. Smoking is considered to be a highly addictive behavior, and there are many approaches to help patients and/or their family members quit. Nicotine is the single most addictive agent found in cigarettes. Up to 70% of smokers report that they would like to quit, but have been unable to do so successfully. Many smokers quit for short periods of time but then start smoking when life events or stressors overcome their resolve to break the habit. Smokers need assistance from healthcare professionals to quit. Patients are twice as likely to quit if they receive assistance from a physician and more than 2.5 times as successful when they receive assistance from more than two or more healthcare professionals. There are three classes of smoking cessation therapies approved for this indication. All patients should be offered pharmacotherapy to quit smoking except if they are pregnant, are breastfeeding, have contraindications, or are adolescents. All approved therapies are more effective than placebo and are considered first line.

Smoking cessation programs, educational materials, and behavioral counseling are available through many agencies (i.e., American Cancer Society, American Lung Association, and American Heart Association). Regardless of the specific program followed, the

key to success for most smokers is to make the commitment to quit and then develop the strategy that will work for them. Most smokers have a host of behaviors that are associated with smoking, and so identifying these and eliminating or developing substitutions for them will usually be necessary.

Pharmacologic Therapy for Smoking Cessation

While the smoker is working on changing smoking behaviors, the use of nicotine replacement will allow patients to gradually reduce the physical addiction to smoking. Buproprion (Zyban) is a nonnicotine oral tablet also used for depression but is an effective form of smoking cessation therapy. Another pharmacologic approach to smoking cessation is the drug varenicline (Chantix®), which blocks receptors in the brain to interfere with the smoker deriving pleasure from the effects of nicotine. Whether or not a nicotine-replacement or nicotine-blocking drug is used, social and psychological supports during this effort are essential to success. Quit Line services are available through all 50 states and provide counseling as well as free medication therapy. The nationwide toll-free number (1-800-QUIT-NOW) [1-800-784-8669] is available to assist smokers in finding resources and support to quit. There are also resources available in different languages.

Nicotine Replacement Products

It is not necessary for the RCP to know all available dosages of nicotine replacement products, but therapists should have knowledge of hazards and side effects of these products. **Nicotine replacement therapy (NRT)** is available as both over-the-counter (OTC) and prescription-only products. Since some forms of NRT are now available over the counter, therapists should be aware of potential adverse effects from their misuse and discuss the effective use of these agents. All NRT deliver nicotine at lower concentrations and at a slower absorption than do cigarettes. All are effective therapies

compared with placebo but the choice of formulation will depend on patient preference and specific patient factors. There are certain populations where NRT should be used with caution. The risks and benefits should be weighed with the patient's physician in cases of patients with underlying cardiovascular disease and recent myocardial infarction (within last 2 weeks), severe angina, serious arrhythmias, pregnancy, and woman who are breastfeeding. Nicotine is pregnancy category D, and this distinction indicates it may cause birth defects to an unborn fetus (but so does smoking). Patients should not smoke while they are using NRTs. The most common side effects from all NRTs are dizziness, insomnia, vivid dreams, headache, nausea, and muscle aches and stiffness.

Nicotine Patches

Transdermal nicotine delivers a constant dose of nicotine through the skin. Available over the counter in varying strengths, transdermal patches were one of the earliest forms of nicotine replacement. The patches are available in 21-mg, 14-mg, and 7-mg doses. Patients that smoke >10 cigarettes a day should start with 21 mg and ≤10 cigarettes should start at a14-mg strength. Recommended method is to use the initial dosage patch for 6 weeks, then use a weaker patch for another 2 weeks, and the final lowest dose for 2 weeks.

Patches should be placed on a clean, dry area of hairless skin on the torso (below the neck and above the waist) and should be replaced at least every 24 hours. Patients should never have more than one patch applied at the same time.

The most common side effect from the patch is skin irritation and redness. Changing the site of patch application and using OTC hydrocortisone cream on the irritation should alleviate this effect. Patients should not smoke while using the nicotine patch unless the physician has approved it. If side effects occur, patients should try a different brand of patch or a different form of NRT, reduce the dosage of nicotine in the patch, and reduce or refrain from smoking. If vivid dreams occur, the patient can be instructed to remove the

patch before bed and replace with another as soon as the patient wakes up.

NEED TO KNOW

If a patient complains of side effects such as itching and redness from a nicotine patch, the RCP should suggest rotating the patch location. If CNS symptoms such as disturbed sleep or vivid dreams occur, it may be necessary to remove the patch before sleep and put on another as soon as the patient awakens.

Nicotine Gum

Nicotine gum is available over the counter in 2-mg and 4-mg dosages. Patients who typically smoke 25 or more cigarettes per day, smoke within 30 minutes of awakening, or have trouble not smoking in restricted areas should probably start with the 4-mg dose. The 2-mg dose can be used for all other patients. The gum should be chewed every 1–2 hours for 6 weeks, then 2–4 hours for the next 3 weeks, and one piece every 4–8 hours during the final 3 weeks. The maximum daily dosage is 24 pieces per day for 6–12 weeks with a recommended maximum of 6 months. The technique for using nicotine gum is important: Gum should be chewed just enough to release the nicotine and result in a tingling or peppery taste. When this occurs, “park” the gum inside the cheek until the sensation fades, then repeat the chewing–parking cycle on and off for 20–30 minutes. Patients should not eat or drink (except water) for 15 minutes before or after chewing. Nicotine gum has the advantage of providing the nicotine sensation on an as-needed basis, when the craving for a cigarette occurs.

Side effects that are specific to the gum formulation of NRT include throat irritation, dyspepsia, mouth soreness, stomatitis, hiccups, and jaw pain from chewing.

Nicotine Lozenges

Nicotine lozenges are available over the counter in 2-mg and 4-mg dosages. Like nicotine gum, the dosage is selected according to how soon after waking the first cigarette is usually smoked. A 4-mg dose

should be used to start for patients who smoke their first cigarette within 30 minutes of waking. A 12-week program is recommended, using one lozenge every 1–2 hours for 6 weeks, then one lozenge every 2–4 hours during weeks 7–9, and tapering to one lozenge every 4–8 hours for the last 3 weeks of therapy. Maximum dosages of no more than 5 lozenges in 6 hours or 20 lozenges per day are recommended. Patients should not eat or drink (except water) for 15 minutes before using a lozenge. When a lozenge is used, it should be allowed to fully dissolve, it should not be bitten or chewed and swallowed. Patients should not smoke while using nicotine lozenges.

Side effects of nicotine lozenges include nausea, heartburn, hiccups, coughing, and sore throat.

Nicotine Inhalers

Inhalers are available only by prescription only in the United States. The delivery system is a cartridge with a mouthpiece that resembles a cigarette, providing the nicotine in a manner similar to smoking and mimics the hand-to-mouth cues used when smoking cigarettes. The nicotine is vaporized and quickly absorbed through the oral mucosa. Recommended usage is 6–16 cartridges per day or at least 6 cartridges/day for up to 6 months. The most common side effects of nicotine inhalers include coughing, throat irritation, rhinitis, and GI upset. The nicotine inhaler may cause bronchospasms in patients with asthma or chronic pulmonary disease. Other forms of NRT may be preferred in these patients. Caution should be exercised in disposing of cartridges because there may be enough residual nicotine to harm children or pets that could handle them. If licked or touched to mucus membranes in the eyes or mouth, local irritation and stimulant effects of nicotine could occur.

Nicotine Nasal Spray (Nicotrol NS)

Nicotine nasal spray is available only by prescription. The nasal spray delivers a dosage of nicotine directly to the nasal mucosa where it is rapidly absorbed. Since nicotine is absorbed more rapidly than do other formulations, there is the risk of dependence with this form.

This delivery method is very convenient and easy to use when the urge to smoke occurs. The spray is usually prescribed for no longer than a 3-month period and should not be used for longer than 6 months. It is dosed as one spray in each nostril, up to 10 sprays/hour, and maximum 80 sprays/day. Side effects of using the nicotine nasal spray include nasal irritation and congestion and can also cause changes in taste and smell. As with the nicotine inhalers, containers must be carefully stored and disposed of to avoid risk to children or pets. Even “empty” spray bottles may contain enough nicotine to irritate skin or mucous membranes or cause CNS stimulation. The nasal spray is not recommended in patients with allergies, rhinitis, sinusitis, or nasal polyps. It can cause bronchospasms in patients with asthma or severe reactive airway disease and should be used with caution or avoided.

NEED TO KNOW

The nicotine inhaler and nasal spray formulations may cause bronchospasms in patients with reactive airway disease (asthma and COPD). Other formulations of nicotine replacement are preferred in these patients.

Varenicline Tartrate (Chantix®)

Varenicline (Chantix) is a smoking-deterrent medication that is thought to block nicotine binding to the α4-β2-nicotinic acetylcholine receptors in the brain. Blocking these receptors prevents nicotine from stimulating the reinforcement and reward experienced by smoking. At the same time, varenicline also stimulates nicotinic receptors and dopamine activity to reduce withdrawal symptoms and cravings. Theoretically, if the patient cannot experience the pleasure he has derived from smoking, he will lose the desire to smoke and smoking cessation will be more easily accomplished. Smoking cessation with the use of varenicline also requires a systematic approach and social support.

A stepwise approach to smoking cessation is used when varenicline is prescribed. As with any smoking cessation attempt, the

smoker must first decide he or she wants to quit. The first step is to set a “quit date” and start taking the varenicline one week before actually stopping or reducing smoking. The dosage is titrated beginning 1 week before smoking cessation. Dosage on days 1–3 is 0.5 mg once a day. Dosage on days 4–7 is 0.5 mg twice daily. Starting on day 8, and continuing until smoking cessation is accomplished, the dose is 1 mg twice daily. Usual length of treatment with varenicline is 12–24 weeks. Tablets should always be taken with at least 8 ounces of water and after eating to reduce nausea. If the patient has successfully stopped smoking after the 12-week period, an additional 12-week period of varenicline use is recommended to increase the long-term success and reduce likelihood of relapse. The most common side effects include nausea, dyspepsia, headache, and sleep disturbances (including insomnia and abnormal dreams). Psychological side effects include depression, hostility, agitation, and suicidal ideation. There is the potential for impaired ability to drive or operate machinery due to CNS depression.

Varenicline has been demonstrated to increase the likelihood of smoking cessation for as long as 1 year when compared with treatment with a placebo. Use with caution in the elderly, and dosage adjustments are needed in patients with renal insufficiency. Patients with cardiovascular disease may be at a higher risk of developing a myocardial infarction or stroke when on varenicline and may not be the preferred agent. Patients should be informed to discontinue therapy is they experience new or worsening depressive symptoms or mood changes.

Buproprion (Zyban)

Buproprion is a dopamine and norepinephrine reuptake inhibitor that may also act as a nicotine receptor antagonist. A prescription is required for use. It was first approved for the treatment of major depressive disorder and was later found to be successful for smoking cessation. Buproprion was shown to successfully increase cessation rates over placebo and have similar rates of success compared with NRT.

Buproprion therapy should be started 1–2 weeks before a scheduled quit date to achieve steady blood concentrations. It is dosed as a 150-mg extended-release oral tablet daily for 3 days and then 150 mg twice daily for 7 to 12–24 weeks. It may cause insomnia and dry mouth. The second dose should be taken 8 hours after the first dose and as far from bedtime as possible to reduce incidence of insomnia. It should not be used in patients with a history of seizures, bipolar disorder, or an eating disorder or if a monoamine oxidase (MAO) inhibitor was used in the past 14 days. It should be avoided in pregnancy.

General Considerations of Smoking Cessation

Regardless of the method used to quit smoking, with or without pharmacologic therapy, there are several physiologic changes that are expected to occur when a patient stops smoking or reduces smoking. Nicotine is a stimulant, which for the smoker provides an increase in metabolic rate. Many smokers actually fear weight gain if they quit smoking more than they fear the risks of pulmonary disease, heart disease, or cancer. When a smoker quits smoking, food also tends to taste better, thus there is a likelihood that caloric intake may increase. The oral gratification of smoking may be replaced by eating, posing another possible risk of weight gain. Encouraging the smoker to increase his exercise level while reducing smoking will help avoid the possibility of weight gain. Many smokers substitute noncaloric oral stimulation (i.e., chewing on toothpicks or plastic spoons) or low-calorie sugar-free hard candy as tactics to avoid increasing their food intake.

Some smokers will experience an increase in sputum production for a period of time while reducing their smoking and even after they have quit. This phenomenon should be explained to the patient so it is not misinterpreted as an unusual or negative occurrence. Cigarette smoke paralyzes ciliary activity for up to 30 minutes after smoking, and thus many smokers do not notice a cough during the day but they usually cough in the morning (after the cilia have been able to move

secretions toward the cough receptors). Coughing after or during a smoking cessation program is a sign that ciliary activity is working to cleanse the airways of residual irritants.

Successful smoking cessation often results in beneficial changes in vital signs as well. It is not unusual for the smoker to have a lower heart rate and resting blood pressure after smoking has been reduced or stopped. Many of these changes are less dramatic if a patient uses NRT while reducing his or her smoking.

NEED TO KNOW

Modest weight gain and reductions in resting heart rate and blood pressure are normal consequences of smoking cessation.

Review Questions

1. What special considerations should be observed by the respiratory care practitioner when assisting a physician with a bronchoscopy? (Describe patient assessment and monitoring, as well as equipment that should be available.)
2. Describe lidocaine when used before/during bronchoscopy, including (a) mechanism of actions; (b) contraindications; (c) dosage/preprocedure aerosol; (d) dosage/mid-procedure instillation.
3. Describe the appropriate use of methacholine and mannitol as diagnostic agents, including dosage and any special considerations that should be observed by the RCP when using these drugs.
4. List the clinical indications for and physiologic effects of inhaled nitric oxide (INO).
5. Describe the initial dose range, maximum recommended dose and the dose-related adverse effects.
6. Describe the use of respiratory stimulant drugs in newborns and list two drugs used for infants.
7. Describe the effectiveness of pharmacologic therapy used in smoking cessation.
8. Compare and contrast the similarities and differences in side effects and contraindications for the various formulations of nicotine replacement therapy.
9. Describe the mechanism of action of varenicline and buproprion and assess the limitations of each agent.

Posttest

For each of the following questions, try to select the one best answer from those choices given.

1. Which of the following is an appropriate drug and dosage for use as a topical agent before bronchoscopy?
   a. 4–6 mL of 4% lidocaine
   b. 10–15 mL of 1% lidocaine
   c. 3–5 mL of 2% procainamide
   d. 3 mL of 1% Novocain®
2. Bronchial provocation testing is performed:
   a. to determine which allergens cause bronchospasm in a specific patient.
   b. to determine the degree of bronchospasm caused by a specific allergen in a given patient.
   c. to determine if an asthma attack or bronchospasm can be provoked by external stimuli.
   d. to diagnose reactive airway disease in patients who do not have clinically apparent asthma.
3. Methacholine can be categorized as a:
   a. β-agonist.
   b. parasympathomimetic.
   c. sympathomimetic.
   d. xanthine agonist.
4. What is the recommended dosage of methacholine used during bronchial provocation testing?
   a. Two to three breaths of the strongest solution, followed by measurement of FVC occurs.
   b. Five breaths of each dilution, beginning with the most dilute solution, followed by measurement of FVC after each dilution until 20% reduction of FEV_1 occurs.
   c. 2–3 mL of each solution, beginning with the most dilute solution; test ends when 20% reduction in FVC occurs.
   d. None of these is correct.

5. A patient who has been using a transdermal nicotine patch as part of his smoking cessation program is complaining of insomnia and itching at the site of the patch. He has been using the patch for several weeks and has been weaned to the lowest dose patch. Which of the following is the best suggestion for this patient?
   a. Rotate the location of the patch more frequently and remove the patch at night.
   b. Change to the next higher dose patch, rotate it frequently, and remove it at night.
   c. Place the patch in the lumbar area (just below the waist) during the night.
   d. Discontinue the patch and concentrate on other smoking cessation techniques.
6. Which of the following are appropriate indications for use of the inhaled vasodilators, nitric oxide, and epoprostenol?
   a. Pulmonary hypertension
   b. Acute respiratory distress syndrome
   c. Right-sided heart failure
   d. All of these are correct.
7. Which of the following is NOT adverse effect reported with inhaled epoprostenol use?
   a. Hypotension
   b. Flushing
   c. Jaw pain
   d. Methemoglobinemia
8. Which of the following drugs may be used to stimulate respiration in a newborn with episodes of apnea?
   a. Varenicline and acetazolamide
   b. Caffeine and prostacyclin
   c. Theophylline and caffeine
   d. Mannitol and acetazolamide
9. Which of the following pharmacologic agents used for smoking cessation should be avoided in patients with reactive airway disease due to risk of causing bronchospasm?
   a. Buproprion

b. Nicotine patch
c. Nicotine inhaler
d. Varenicline

10. Which of the following pharmacologic agents used for smoking cessation should be started before the patient quits smoking?
    a. Nicotine patch and buproprion
    b. Varenicline and buproprion
    c. Nicotine gum and varenicline
    d. All agents should not be used when still smoking

References/Recommended Readings

American Association for Respiratory Care. AARC clinical practice guideline: fiberoptic bronchoscopy assisting. *Respir Care*. 1993;38(11):1173-1178, revision and update 2007.

Anderson SD, Charlton B, Weiler JM, et al; A305 Study Group. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. *Respir Res*. 2009;10:4.

Barr FE, Macrae D. Inhaled nitric oxide and related therapies. *Pediatr Crit Care Med*. 2010;11(2 suppl):S30-S36.

Brunton LL, Hilal-Dandan R, Knollmann BC, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 13th ed. New York, NY: McGraw-Hill Medical Publishing; 2018.

Busse WW. The relationship of airway hyperresponsiveness and airway inflammation: airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest*. 2010;138(2 suppl):4S-10S.

Cockcroft DW. Direct challenge tests. *Chest*. 2010;138(2 suppl):18s-24s.

Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med*. 2000;161(1):309-329.

Davis BE, Blais CM, Cockcroft DW. Methacholine challenge testing: comparative pharmacology. *J Asthma Allergy*. 2018;11:89-99.

DeLuca DA, Karpinski J, Kelley K, et al. *Mosby's Drug Reference for Health Professionals*. St. Louis, MO: Mosby Elsevier; 2010.

DiBlasi RM, Myers TR, Hess DR. Evidence-based clinical practice guideline: inhaled nitric oxide for neonates with acute hypoxic respiratory failure. *Respir Care.* 2010;55(12):1717-1745.

Du Rand IA, Blaikley J, Booton R, et al. Summary of the British thoracic society guideline for diagnostic flexible bronchoscopy in adults. *Thorax*. 2013;68:786-787.

Dzierba AL, Abel EE, Buckley MS, et al. A review of inhaled nitric oxide and aerosolized epoprostenol in acute lung injury or acute respiratory distress syndrome. *Pharmacotherapy*. 2014;34(3):279-290.

Ellis A, Sherman J. *Community and Clinical Pharmacy Services: A Step-by-Step Approach.* New York, NY: McGraw-Hill Companies, Inc.; 2013.

Fuller BM, Mohr NM, Skrupky L, Fowler S, Kollef MH, Carpenter CR. The use of inhaled prostaglandins in patients with ARDS. *Chest*. 2015;147(6):1510-1522.

Griffiths MJ, Evans TW. Inhaled nitric oxide therapy in adults. *N Engl J Med*. 2006;353(25):2683-2695.

Hartmann-Boyce J, Chepkin SC, Ye W, et al. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database System Rev*. 2018;5:CD0000146.

Hess DR, MacIntyre NR, Galvin WF, et al. *Respiratory Care: Principles and Practice*. 3rd ed. Burlington, MA: Jones and Bartlett, LLC; 2016.

Khan T, Schnickel G, Ross D, et al. A prospective randomized crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart transplant and lung transplant recipients. *J Thorac Cardiovasc Surg*. 2009;138(6):1417-1424.

Mainland PA, Kong AS, Chung DC, et al. Absorption of lidocaine during aspiration anesthesia of the airway. *J Clin Anesth*. 2001;13(6):440-446.
Mottram C. *Ruppel's Manual of Pulmonary Function Testing.* 10th ed. Maryland Heights, MO: Mosby-Elsevier; 2012.
Sarkar M, Niranjan N, Benyal PK. Mechanisms of hypoxemia. *Lung India*. 2017;34(1):47-60.
Schoen K, Yu T, Stockmann C, et al. Use of methylxanthine therapies for the treatment and prevention of apnea of prematurity. *Pediatr Drugs*. 2014;16(2):169-177.
Siobal MS. Pulmonary vasodilators. *Respir Care*. 2007;52(7):885-899.
Sterk PJ. Airway hyper-responsiveness: using bronchial challenge tests in research and management if asthma. *J Aerosol Med*. 2002;15(2):123-129.
Tabrizi MB, Schinco MA, Tepas JJ. Inhaled epoprostenol improves oxygenation in severe hypoxemia. *J Trauma Acute Care Surg*. 2012;73(2):503-506.
Taylor RW, Zimmerman JL, Dellinger RP, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. *JAMA.* 2004;291(13):1603-1609.
Tobacco Use and Dependence Guideline Panel. *Treating Tobacco Use and Dependence: 2008 Update*. Rockville, MD: US Department of Health and Human Services; 2008.
Torbic H, Szumita PM, Anger KE, et al. Inhaled epoprostenol vs inhaled nitric oxide for refractory hypoxemia in critically ill patients. *J Crit Care.* 2013;28:844-848.
Wahidi M, Jain P, Jantz M, et al. American College of Chest Physicians Consensus Statement on the use of topical anesthesia, analgesia and sedation during flexible bronchoscopy in adult patients. *Chest.* 2011;140(5):1342-1350.
Walmrath D, Schneider T, Schermuly R, et al. Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1996;153(3):991-996.
Yu B, Ichinose F, Bloch DB, et al. Inhaled nitric oxide. *Br J Pharmacol*. 2019;176(2):246-255. doi:10.1111/bph.14512.

Part 3
General Pharmacology

© Winui/Shutterstock

CHAPTER

12

Critical Care Pharmacotherapy and Advanced Cardiac Life Support

Coauthored by Jennifer Hoh, PharmD

© Anna RubaK/ShutterStock, Inc.

OUTLINE

Introduction
Rapid Sequence Intubation
  Pretreatment
  Induction
Critical Care Pharmacotherapy
  Neuromuscular Blockade
  ICU Analgesia and Sedation
  Shock
ACLS: Adult and Pediatrics
  Causes of Cardiac Arrest
  Oxygenation
  Ventilation and Capnography
  Medication Use and Route of Administration
  Rhythm-based Management During Cardiac Arrest
  Post–Cardiac Arrest Care

OBJECTIVES

After completion of this chapter and its learning activities, you will be able to:

1. Identify the steps of rapid sequence intubation and summarize what actions and/or medications are administered at each step.
2. Explain the mechanism of action of neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure.
3. List the medications used for pain management in the intensive care unit and identify possible adverse effects associated with these agents.
4. Assess the indications for deep sedation and light sedation and list appropriate medications for each indication.
5. Explain the rationale between coordinating daily sedation vacations with spontaneous breathing trials.
6. Distinguish between the various types of shock and identify the need for vasopressor therapy.
7. Explain the differences in action and adverse effects between the available vasoactive agents used for shock.
8. Indicate which advanced cardiovascular life support (ACLS) medications can be administered via an endotracheal tube and describe the proper administration technique.
9. Compare the management of pulseless ventricular fibrillation/ventricular tachycardia with pulseless electrical activity/asystole cardiac arrest.
10. Suggest the most appropriate ACLS therapy, including the drug of choice and route of administration, given a patient case study.

KEY TERMS

Advanced cardiovascular life support (ACLS)
Analgesia
Induction
Inotropes
Neuromuscular blocking agent (NMBA)
Pediatric Advanced Life Support (PALS)
Rapid sequence intubation (RSI)
Sedation
Septic shock
Shock
Vasopressor

Introduction

Respiratory care professionals (RCPs) that treat patients in the emergency department (ED) and intensive care unit (ICU) will frequently be involved in treating patients receiving **neuromuscular blocking agents (NMBAs)**, analgesics, and sedatives. These classes of drugs affect breathing and ventilator management. The use of vasoactive agents in management of shock is also covered in this chapter because these are the concepts the RCPs must be knowledgeable about while treating a critically ill patient. RCPs are part of the hospital team and play a major role in cases involving cardiac and respiratory arrests. **Advanced cardiovascular life support (ACLS)** therapeutics are important to understand and be familiar with during these medical emergencies. Endotracheal intubation using **rapid sequence intubation (RSI)** is an important procedure that an RCP should be familiar with because it is used to facilitate emergency airway management.

Rapid Sequence Intubation

RSI is the administration of appropriate medications to facilitate an endotracheal intubation and to reduce adverse effects. It is indicated in patients who require endotracheal intubation and in patients who have an increased risk for aspiration or reflux of gastric contents. The seven steps of RSI, also referred to as the “seven ps,” are summarized in **Figure 12-1**. This section will discuss the medications used for pretreatment and **induction**. Neuromuscular blocking agents such as rocuronium, succinylcholine, and vecuronium are used for paralysis and are discussed in detail later in this chapter.

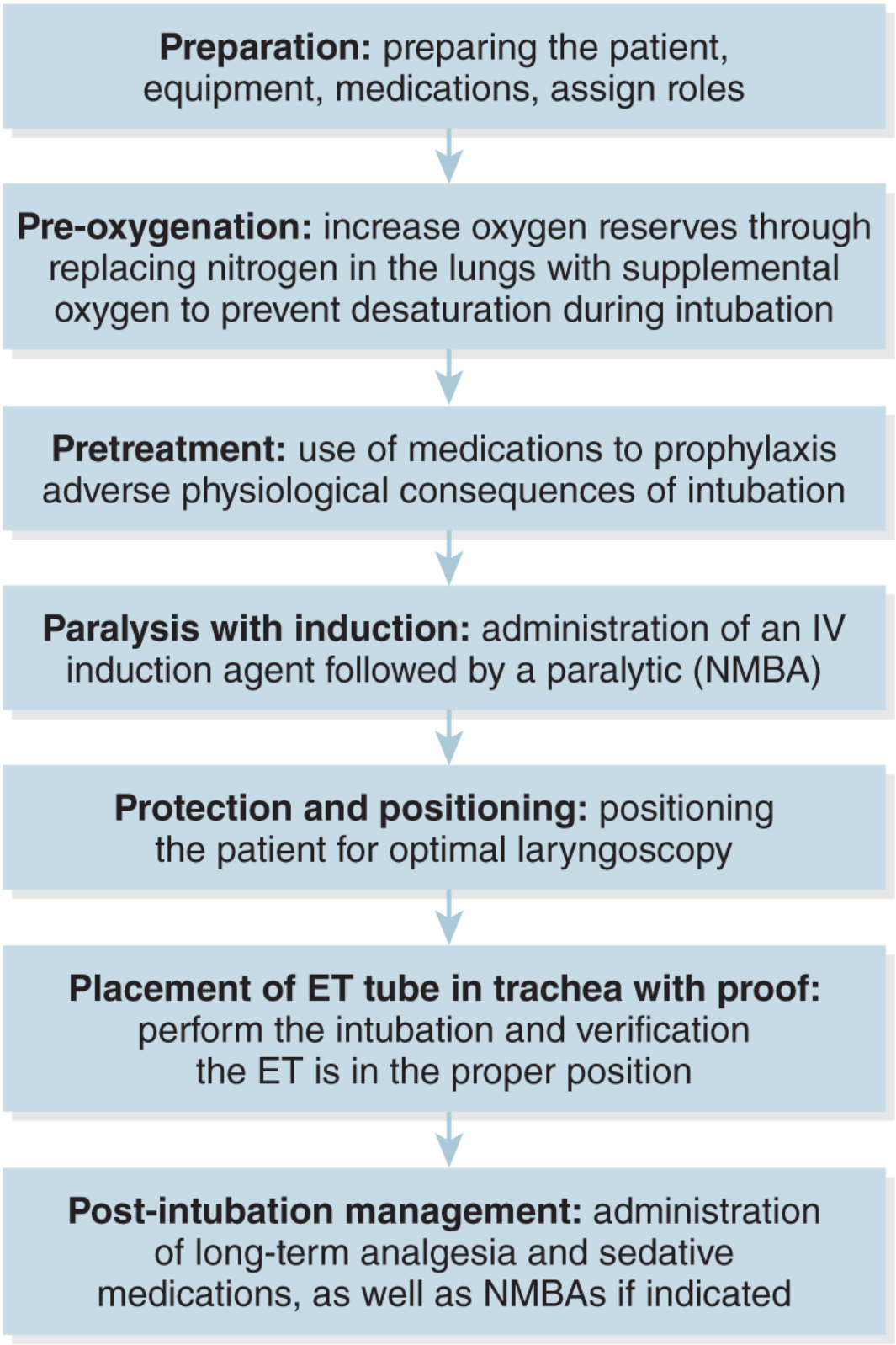


FIGURE 12-1 Steps of rapid sequence intubation (RSI).

Description

Pretreatment

Pretreatment occurs ideally 3 minutes before administration of induction agents and neuromuscular blockade. The purpose of pretreatment is to minimize the pathophysiologic response to intubation. These physiologic responses include a systemic release of catecholamines, which causes an increase in blood pressure and heart rate. Patients at greatest risk for a catecholamine surge include those with increased intracranial pressure (ICP), ischemic heart disease, intracranial hemorrhage, or an aortic aneurysm/dissection. Upper airway reflexes are also stimulated by endotracheal tube placement, which can cause cough and bronchospasm.

In adult patients, lidocaine or fentanyl is recommended for pretreatment. Lidocaine is a class IB antiarrhythmic, which is further discussed in Chapter 13. In RSI, lidocaine prevents an increase of ICP, which can be a sympathetic response to laryngoscopy, as well as it prevents bronchospasm in patients with reactive airway disease. In RSI, it is dosed 1.5 mg/kg intravenous (IV) push and has a very short onset and duration of action. Lidocaine's onset of action is 45–90 seconds and the duration of action is 10–20 minutes after administration. Lidocaine is contraindicated in patients with an amide anesthetic allergy (e.g., mepivacaine, prilocaine, bupivacaine, and ropivacaine), who are severely bradycardic or who have severe heart block.

Fentanyl, an opioid pain medication, can be used for pretreatment to prevent catecholamine release (fentanyl is further discussed in the ICU **Analgesia** and **Sedation** section of this chapter). In RSI, it is dosed 1–3 μg/kg IV push over 30–60 seconds and has a rapid onset of action. Fentanyl is used over other opioids because of its quick onset and short duration of action. At high doses, it may cause chest wall rigidity.

In patients younger than 1 year of age or in children aged 1–5 years who receive succinylcholine, a vagolytic agent such as atropine is recommended for the prevention of reflex bradycardia that may occur secondary to intubation. It also helps to decrease oral

secretions. Atropine is dosed 0.01–0.03 mg/kg IV push. Its onset of action is 2–4 minutes and its half-life is approximately 7 hours.

Induction

The induction phase of RSI produces a state of anesthesia before intubation. It should always precede paralysis owing to the risk of inadequate sedation. The goals of induction therapy are providing rapid sedation, pain control, and amnesia without changes in hemodynamics. The agents used for induction include etomidate, ketamine, propofol, and midazolam, as described in **Table 12-1**. The pharmacologic properties of midazolam and propofol are further discussed in the Sedation section of this chapter.

TABLE 12-1
Rapid Sequence Intubation: Induction Agents

Drug	Dose (mg/kg IV)	Onset(sec)	Duration (min)	Indication
Etomidate	0.3	10–15	4–10	Considered gold standard for RSI Can be used in hypotensive patients Consider alternative if patient with status epilepticus or septic
Ketamine	0.6–2	45–60	10–20	Reactive airway disease Hypotensive Avoid in patients with increased ICP or in hypertensive patients
Midazolam	0.2–0.3	60–90	15–30	Not recommended for routine RSI use Consider use in postintubation sedation
Propofol	1.5–2.5	15–45	5–10	Hemodynamically stable with increased ICP Status epilepticus

ICP, intracranial pressure; RSI, rapid sequence intubation.

Etomidate

Etomidate is an ultra–short-acting nonbarbiturate anesthetic with minimal adverse effects. It works by acting on the gamma-aminobutyric acid type A ($GABA_A$) receptor, blocking neuroexcitation, and causing sedation but without analgesic affects. It has a rapid onset of action with very short duration of action after one dose. The benefit of using etomidate over other agents is that it is safe for

patients with cardiovascular disease. It has minimal cardiac effects, does not cause hypotension, and is safe for patients with an increased ICP. It may cause myoclonic jerks or seizures and pain on injection. Etomidate has also been associated with a decrease in cortisol production and therefore should be used with caution in critically ill patients.

Ketamine

Ketamine works by inhibiting *N*-methyl-D-aspartate (NMDA) receptors. The NMDA receptors normally respond to the excitatory neurotransmitter, glutamate. Ketamine works by inhibiting the action of glutamate. It causes a different type of sedative or hypnotic state called as dissociative state, when compared with other sedatives. Ketamine causes sedation, amnesia, and analgesia, but patients may have their eyes open but may not be able to respond to commands. Ketamine is the only RSI agent that has sedative and analgesic properties. It causes minimal respiratory depression but is optimal for patients with bronchospasms because it also relaxes bronchial smooth muscle and antagonizes the spasmodic effects of histamine. Unlike other sedatives, ketamine inhibits catecholamine reuptake, which causes increases in blood pressure and heart rate that can be beneficial for hypotensive patients, but for patients with myocardial ischemia, ketamine should not be used. As the effects of ketamine wear off, the patients may develop delirium, hallucinations, and nightmares.

Critical Care Pharmacotherapy

RCPs working in an ICU or ED setting will encounter and manage patients requiring sedative and analgesic agents to facilitate pain and decrease anxiety while mechanically ventilated. Uncontrolled pain and anxiety in the ICU may lead to delirium, and thus noncompliance with the ventilator. NMBAs are used as one dose in RSI but also used to improve ventilator compliance and improve mortality in patients with acute respiratory distress syndrome (ARDS) when used as a continuous infusion. Because NMBs will paralyze the diaphragm, it is important for RCPs to be familiar with their short- and long-term effects on respiratory function.

Shock is a common disease state encountered in a critical care setting. The agents used to increase heart rate and blood pressure in the treatment of shock will also be discussed in this section.

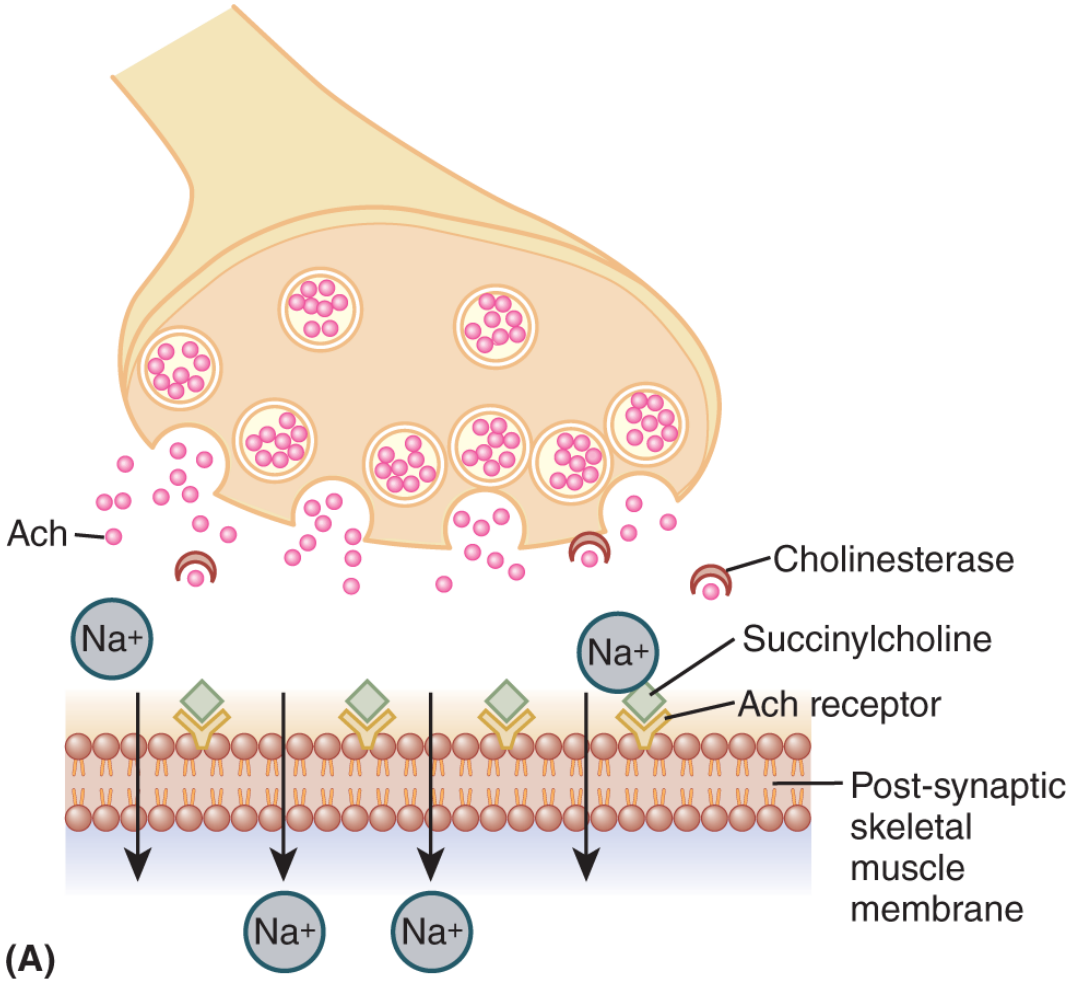
Neuromuscular Blockade

Peripheral acting muscle relaxants are also referred to as NMBAs. These agents interact with nicotinic-2 receptors at the skeletal neuromuscular junction causing muscle weakness and paralysis. There are two classes of NMBAs: nondepolarizing and depolarizing agents. The mechanism of action of each class is discussed in **Table 12-2** and illustrated in **Figure 12-2**. Nondepolarizing and depolarizing NMBs are commonly used in the critical care setting during RSI to facilitate endotracheal intubation and to improve the effectiveness of mechanical ventilation in patients who are “fighting” the ventilator or who require very high peak or mean airway pressures. NMBAs can also be beneficial during surgical procedures to obtain skeletal muscle relaxation in an anesthetized patient so that surgical procedures can be performed more easily.

TABLE 12-2

Classification of Peripheral Acting Muscle Relaxants

Classification	Mechanism of Action	Agents
Nondepolarizing neuromuscular blockers	Compete with acetylcholine for the nicotinic-2 receptor site at the neuromuscular junction	Pancuronium, rocuronium, vecuronium, and cisatracurium
Depolarizing neuromuscular blockers	Cause a persistent depolarization at the motor/endplate so that receptors cannot react with acetylcholine	Succinylcholine



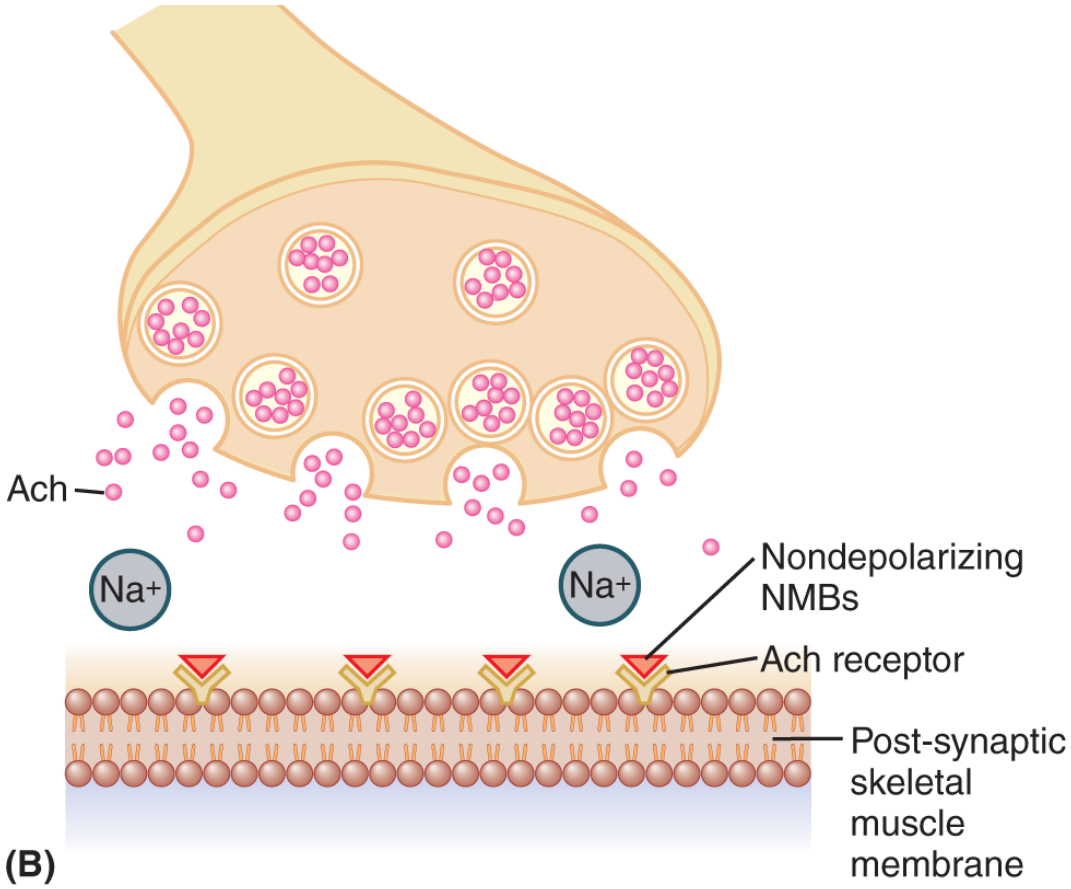


FIGURE 12-2 Mechanism of action of (**A**) depolarizing and (**B**) nondepolarizing neuromuscular blocking agents.

Description

Upon administration of an NMBA, these agents will cause skeletal muscle paralysis, including their intercostal muscles, diaphragm, and extremities. Because of this, patients receiving these agents must be intubated for airway protection. NMBAs do not affect the level of consciousness or a patient's perception of pain. They do not provide analgesia or sedation. Because the patient will be paralyzed and will not be able to communicate, all healthcare providers must be vigilant in providing appropriate sedation, analgesia, and ventilation for these patients.

NEED TO KNOW

Patients receiving NMBAs must be intubated and deeply sedated with the use of sedative and analgesic medications.

NMBAs are administered intravenously and produce a blockade at the neuromuscular site, causing skeletal muscle relaxation within minutes. **Table 12-3** displays the individual onset and duration of action. All NMBAs can cause prolonged skeletal weakness or myopathy when used for a prolonged period of time as continuous infusions in the ICU. This may be worsened when systemic corticosteroids are also used. All patients receiving continuous NMBAs should be administered a lubricant eye drop multiple times a day to prevent corneal abrasions because ocular protective mechanisms are impaired (inadequate eyelid closure and lack of corneal reflexes) that may occur as a result of NMB administration. Table 12-3 includes adverse effects and precautions for each specific agent. There are certain medications and clinical conditions that may enhance the neuromuscular blocking effects of these drugs and some that may antagonize or lessen the effects of these agents (**Table 12-4**).

TABLE 12-3
Properties of Neuromuscular Blocking Agents

Drug	Dose	Onset(min)	Duration (min)	Adverse Effects/Precautions
Atracurium	RSI dose: 0.4–0.5 mg/kg Continuous infusion: 5–20 μg/kg/min	3–5	25–35	Has a toxic metabolite (laudanosine) that can accumulate in organ dysfunction and cause seizures, dose-dependent histamine release, and hypotension Caution use in asthmatics
Cisatracurium (Nimbex)	Continuous infusion: 0.5–10 μg/kg/min	2–3	35–45	
Pancuronium	RSI dose: 0.04–0.1 mg/kg	2–3	60–100	Tachycardia and increased cardiac output Effects prolonged in hepatic/renal impairment Caution in patient with coronary artery disease
Rocuronium (Zemuron)	RSI dose: 1 mg/kg IV	1–2	30–60	Tachycardia Effects prolonged in hepatic impairment
Succinylcholine (Anectine®)	RSI dose: 1.5 mg/kg IV 4 mg/kg IM (max dose 150mg)	1–2	10–15	Histamine release, hypotension, muscle fasciculation, hyperkalemia Do not use in patients with hyperkalemia, glaucoma, or familial history of malignant hypothermia
Vecuronium (Norcuron®)	RSI dose: 0.1 mg/kg IV	2–5	25–30	Hypertension, flushing Effects prolonged in renal impairment

RSI, rapid sequence intubation.

TABLE 12-4
Interactions with Neuromuscular Blocking Agents

Drugs or Clinical Conditions that Enhance Effects	Drugs or Clinical Conditions that Antagonize Effects
Local anesthetics	Antiepileptics (Phenytoin, carbamazepine)
Lidocaine	Theophylline
Antimicrobials (aminoglycosides, colistin/polymyxin B, vancomycin, tetracycline, and clindamycin)	Ranitidine
Cardiac agents (procainamide, quinidine, calcium channel blockers, and β-adrenergic blockers)	Alkalosis
Diuretics	Hypercalcemia
Corticosteroids	Peripheral neuropathy
Lithium	

Dantrolene	
Immunosuppressants (cyclosporine and cyclophosphamide)	
Acidosis	
Electrolyte abnormalities (hypocalcemia, hypokalemia, hyponatremia, and hypermagnesemia)	

Depolarizing NMBAs

Succinylcholine is the only available depolarizing agent. Succinylcholine is used to facilitate endotracheal intubation and to relax skeletal muscle during surgery. It works by acting at the skeletal muscle motor endplate (Figure 12-2). Succinylcholine depolarizes the membrane, mimicking the effects the acetylcholine (Ach) by occupying the Ach receptors. The depolarizing effect lasts longer than with Ach, which leads to initial excitation and quick muscle contractions (fasciculation), followed by flaccid paralysis by blocking neuromuscular transmission (see Figure 12-2). The onset is very quick, 1–2 minutes, and the duration of action is only 10–15 minutes, which makes it an ideal agent for surgery and to facilitate intubation. Succinylcholine is only used as a one-time dose in all clinical situations.

Nondepolarizing NMBAs

There are multiple nondepolarizing NMBAs available for use. They work by competitively blocking Ach on the Ach receptors at the skeletal muscle motor endplate (Figure 12-2). In clinical practice, rocuronium and vecuronium are commonly used during RSI to facilitate endotracheal intubation. Cisatracurium is used in patients with early ARDS or to manage shivering from therapeutic hypothermia. This class of agents may also be used as an IV bolus or continuous infusion in patients with status asthmaticus refractory to other treatments and are profoundly hypoxic and acidotic.

Pancuronium is rarely used owing to its long duration of action and adverse effects.

ICU Analgesia and Sedation

Patients receiving continuous mechanical ventilation often require a variety of analgesic and sedative medications to both improve patient-ventilator synchrony and to treat pain and anxiety associated with procedures and routine ICU care. The respiratory therapist is a key member of the patient-care team and may be the most likely provider to notice patient discomfort that is secondary to the mechanical ventilation. Although the therapist may not be able to administer these medications, it is important to recognize signs of distress that could be because of pain and anxiety and to interact with the nurses and physicians to appropriately treat the patient. Sudden onset of increased peak airway pressures that are not associated with airway obstruction (e.g., severe bronchospasm or the need to be suctioned) could be because of patient anxiety.

The goal for the majority of patients in the ICU is to keep them alert and calm and avoid deep sedation or agitation. A light level of sedation as well as discontinuing all sedative and analgesic agents at least once daily (sedation vacation) has been shown to decrease time on mechanical ventilation and should be coordinated with spontaneous breathing trials (SBTs). The respiratory therapist plays a paramount role in SBT with daily sedation vacations to assess a patients' respiratory drive. Increased amounts of analgesic and sedative medications may be associated with poor SBT performance, which can result in prolonged mechanical ventilation.

Opioids

When managing pain in the critically ill patient, objective measures such as the use of vital signs should not be used alone but rather as a cue for further pain assessment. Scoring tools such as the Critical-Care Pain Observation Tool or Behavioral Pain Scale are the most

reliable pain scales in ICU patients who have scores ranging from 0 to 10; 0 indicating no pain and 10 indicating severe pain. In addition to validated pain scales, the respiratory therapist plays a key role in identifying any patient discomfort or pain that is secondary to the mechanical ventilation. An analgesia-first approach should be practiced when treating pain in the ICU. This involves addressing a patient's pain first before sedative or hypnotic medications are administered.

IV opioids such as morphine, fentanyl, and hydromorphone are recommended first-line agents to treat non-neuropathic pain. These agents are compared in **Table 12-5**. Opioids work by agonizing, or stimulating, mu receptors. Mu receptors are located within the central nervous system (CNS), and to a lesser extent throughout the periphery. When the opioid binds to opioid receptors, the pain response is inhibited, producing an analgesic effect. Respiratory depression, constipation, and increased sedation are possible adverse effects because there are opioid receptors located throughout the periphery and binding is not selective. Respiratory therapists should be conscious of the high risk of respiratory depression and help monitor for any signs of opioid-induced respiratory depression and oversedation.

TABLE 12-5
Opioid Analgesics for Use in Critically Ill Patients

Agent	Equianalgesic Dose (mg)		Onset (min)	Elimination Half-Life(h)	Additional Adverse Effects
	IV	PO			
Fentanyl (Duragesic)	0.1	Not available	1–2	2–4	Less hypotension compared with morphine; accumulates in hepatic impairment
Hydromorphone (Dilaudid)	1.5	7.5	5–15	2–3	Accumulation with hepatic impairment
Morphine	10	30	5–10	3–4	Histamine release; accumulation with hepatic/renal impairment

Adjunctive pain and analgesia agents (discussed in Chapter 14) such as IV acetaminophen and nonsteroidal anti-inflammatory medications (e.g., ibuprofen and ketorolac) can be considered in addition to opioids to decrease overall opioid requirements.

Sedation

After analgesia is managed, patient's need for sedation can be assessed. A light level of sedation should be maintained, where the patient is awake but calm, if the use of sedatives is required. In the ICU, a patient may require light sedation in addition to analgesics to improve synchrony with the ventilator, decrease work of breathing, relieve discomfort, and to treat anxiety. Deep sedation, where the patient is asleep and unarousable, is required when patients are receiving NMBAs, are in prone positioning, and when undergoing certain diagnostic and surgical procedures. Benzodiazepines, propofol, and dexmedetomidine are the most common sedative agents used in the ICU for sedation. Important pharmacokinetic parameters as well as adverse effects of each sedative are given in **Table 12-6**. In the 2018 Society of Critical Care Medicine, Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, and Delirium recommend either propofol or dexmedetomidine over benzodiazepines when continuous sedation is required in mechanically ventilated ICU patients. Both these agents can achieve lighter levels of sedation and a possible shorter time to extubation when compared with benzodiazepines.

TABLE 12-6
Agents Used for Agitation in Critically Ill Patients

Agent	Onset (min)	Elimination Half-Life (h)	Adverse Effects
Dexmedetomidine	5–10	1.8–3.1	Bradycardia and hypotension
Diazepam	2–5	20–120	Respiratory depression and hypotension
Lorazepam	15–20	8–15	Respiratory depression, hypotension, propylene glycol–related metabolic acidosis, and nephrotoxicity
Midazolam	2–5	3–11	Respiratory depression and hypotension
Propofol	1–2	3–12 (after short-term use)	Dose-dependent respiratory depression, hypotension, bradycardia, hypertriglyceridemia, propofol-related infusion syndrome, and pancreatitis

Benzodiazepines

Benzodiazepines such as diazepam, lorazepam, and midazolam are commonly used for their amnestic effects in addition to sedating, hypnotic, and anxiolytic effects. They do not have any analgesic benefits. As a class, benzodiazepines work by binding to and activating gamma-aminobutyric acid (GABA) receptors in the CNS. GABA is an inhibitory neurotransmitter that is responsible for decreasing stimulation in the brain; its effect is enhanced in the presence of benzodiazepines, leading to calmness, sedation, and muscle relaxation.

Propofol

Propofol is a lipophilic medication administered by continuous IV infusion. Its exact mechanism of action is not fully understood but is thought to bind to multiple receptors in the CNS, including GABA to exert its sedative effects. Propofol also exhibits hypnotic, anxiolytic, amnestic, antiemetic, and anticonvulsant effects. As can be seen in Table 12-6, propofol has a short onset of action and duration following short-term administration. Patients receiving continuous infusions of propofol must be on mechanical ventilation. Propofol may also be used for conscious sedation in procedures such as endoscopy and colonoscopy, and for minor surgical procedures under close supervision of a specialized physician. Propofol is made in a lipid emulsion, and patients should be monitored for hypertriglyceridemia and related side effects. Propofol-related infusion syndrome (PRIS) is another adverse effect following high-

dose propofol administration for more than 48 hours. PRIS is characterized by the presence of refractory bradycardia and one or more of the following: metabolic acidosis, rhabdomyolysis, hyperlipidemia, or an enlarged liver. Propofol may also cause hypotension and bradycardia.

Dexmedetomidine

Dexmedetomidine is a continuous IV infusion that can be administered with or without mechanical ventilation because it has a unique mechanism of action. It is an α_2-adrenergic receptor agonist, binding selectively to α_2 to exhibit its sedative properties. It is thought to have an opioid sparing effect, allowing prescribers to use less opioids with co-administration of dexmedetomidine and may prevent or reduce the incidence of delirium in ICU patients. Its use has not been associated with respiratory depression and should be utilized when targeting a light level of sedation in intubated or nonintubated patients.

NEED TO KNOW

Patients receiving continuous infusion propofol must be mechanically ventilated. Dexmedetomidine is the only sedative approved in the United States for administration without mechanical ventilation.

Case Study 12-1

Ventilator Management

Scott is a 33-year-old man admitted to the ED with acute respiratory distress. He has a history of asthma and has been seen in this ED before.

History and Physical Examination

History: Diagnosed with asthma in late teens, no other significant medical or surgical history. He explains that he has been taking Dulera® (e.g., formoterol and mometasone) for the past 8 months and using an albuterol metered-dose inhaler (MDI) as a rescue inhaler. He lost his job about 3 months ago and could not afford to fill his prescription for Dulera, so he has not taken it for several weeks. He has been relying on his MDI, but this morning he was very short of breath and he has inhaled two puffs of albuterol every hour since 6:00 a.m. It is now noon.

Vital signs: Heart rate, 160 beats/min; blood pressure,148/92 mm Hg; respiratory rate, 34 breaths/min; and temperature,37°C.

Clinical appearance: Well-nourished and muscular young man in obvious respiratory distress and using accessory muscles of respiration.

Review of systems: Breath sounds diminished with wheezing in all lung fields. Other systems within normal limits, and no cardiovascular abnormalities seen.

Laboratory Values

Arterial blood gases (on O_2 per cannula at 2 L/min): pH= 7.31; $PaCO_2$ = 52 torr; PaO_2 = 65 torr; and HCO_3^- = 24.1 mEq/L.

ED treatment: An IV is started and methylprednisolone 125 mg is administered. He is started on continuous nebulized albuterol, and 30 minutes later, his breath sounds are more prominent, but his wheezing is more pronounced and he is becoming very fatigued. The decision is made to intubate him, admit him to ICU, and put him on a ventilator. Todd is 178 cm (5' 10") tall and weighs 75 kg (165 lb).

ICU treatment: Todd is placed on a ventilator at a tidal volume of 450 mL, A/C mode at a rate of 10/min, F_iO_2 of 0.40, and positive end-expiratory pressure (PEEP) of 5 cm H_2O. He also receives albuterol 5 mg nebulization every 2 hours. The RN calls you (the respiratory therapist) 90 minutes later because the high-pressure alarm on the ventilator is sounding. When you arrive in ICU, the nurse tells you that she has already tried to suction him and was easily able to pass the catheter but less than 2 mL of secretions were removed. You notice that the peak airway pressure is now exceeding the limit (40 cm H_2O) while it had been delivering normal tidal volumes at peak pressures around 30 cm H_2O before. His breath sounds are almost clear with some expiratory wheezes and no rhonchi. His heart rate is 110 beats/min and his $S_pO_2$has dropped from 94% to 88%. He is agitated and restless.

Questions

1. When Todd was intubated in the ED, what drug was appropriate for short-term musculoskeletal paralysis to perform the intubation?
2. Todd was assessed for pain and it was determined that his agitation is not from pain. Multiple doses of midazolam were administered without an effect. What continuous intravenous agent/s should be initiated for his agitation at this time?
3. As Todd's condition is improving, he is failing SBTs owing to agitation and delirium. The use of a continuous sedative to facilitate extubation has been decided. Which continuous sedative is safe to use in an extubated patient?

Shock

Shock is a medical emergency characterized by tissue hypoperfusion secondary to hypotension. It is reversible state when identified and treated early, but can progress to severe organ dysfunction. There

are four classifications of shock: cardiogenic, distributive, hypovolemic, and obstructive. Patients can exhibit more than one type of shock at a time. Each classification contains several etiologies that are discussed next.

Cardiogenic Shock

Cardiogenic shock (CS) is a low cardiac output state caused by a cardiac disorder with hemodynamic instability. This type of shock occurs when function is impaired in the myocardium, valves, conduction system, or pericardium. Patients in CS typically exhibit hypotension unresponsive to fluid resuscitation. The use of invasive hemodynamic measurements or clinical examination help determine the best treatment of CS. Classic CS can also be referred to as “wet and cold” and is characterized by a poor cardiac contractility, fluid overload, and hypotension.

General CS treatment consists of a **vasopressor** such as norepinephrine or dopamine, which is discussed later in this chapter, or an inotropic agent such as dobutamine or milrinone. **Inotropes** should only be initiated when the patient is hemodynamically stable (SBP >90 bpm) or after revascularization in the case of CS secondary to a myocardial infarction (MI). Milrinone, and to a less extent dobutamine, causes vasodilation, which can result in hypotension.

Distributive Shock

Distributive shock is a hypermetabolic process and is also referred to as vasodilatory shock, because it is characterized by severe peripheral vasodilation. Types of distributive shock include anaphylactic, neurogenic, and septic.

Anaphylactic Shock

Anaphylactic shock is most commonly immunoglobulin-E (IgE)-mediated and is seen in patients with a severe allergic reaction after exposure to allergens such as foods, medications, or insect bites. It

is typically sudden in onset and can rapidly progress to a life-threatening state. It is important to continually assess the patient for respiratory distress and evaluate the need for an advanced airway. Treatment of anaphylactic reactions includes intramuscular (IM) epinephrine to the anterior-lateral thigh. On the basis of patient's response to the initial treatment with epinephrine, repeat IM epinephrine or a continuous IV epinephrine infusion may be indicated.

Other pharmacologic interventions can also be administered on the basis of clinical response. These interventions, further discussed in their respective chapters, include IV fluids, bronchodilators, steroids, H_2 antihistamines, and glucagon.

Neurogenic Shock

Neurogenic shock can result from a spinal cord injury (SCI) or traumatic brain injury (TBI). An SCI can result in a loss of sympathetic innervation causing bradycardia and hypotension. A TBI can cause neurogenic shock from an induced catecholamine and neuroinflammatory response. Initial treatment strategies for neurogenic shock include maintaining perfusion with the use of IV fluids and vasopressors.

Septic Shock

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection that causes organ dysfunction. It can progress to **septic shock**, which is a subset of sepsis with hypotension and is associated with a higher risk of mortality. Treatment begins with initial fluid resuscitation in patients experiencing sepsis-induced hypoperfusion. About 30 mL/kg of an IV crystalloid fluid such as normal saline (0.9%) should be promptly administered.

Broad-spectrum IV antimicrobial agents should also be promptly administered to cover against the most common pathogens that cause septic shock. Causative pathogens include both gram-negative and gram-positive bacteria. Further discussion on microorganisms and antimicrobial agents are discussed in Chapter 16.

Vasopressors should also be initiated to maintain a mean arterial pressure (MAP)>65 mmHg. Norepinephrine is recommended as the first-line agent. Vasopressin or epinephrine can be added to norepinephrine if additional agents are required to reach target MAP.

NEED TO KNOW

Norepinephrine is the first-line vasopressor recommended in septic shock when necessary to maintain a MAP >65 mmHg.

Hypovolemic Shock

Hypovolemic shock results from a decreased intravascular volume. This can be hemorrhagic, resulting from acute blood loss, or nonhemorrhagic. Treatment includes prompt restoration of intravascular volume using IV normal saline or lactated Ringer's solution. In patients with a hemoglobin <7 g/dL or with an active bleed, the use of blood transfusions and products such as packed red blood cells and fresh frozen plasma should be administered.

Obstructive Shock

Obstructive shock can be caused by a pulmonary embolism, pneumothorax, or cardiac tamponade. It is overall characterized by a cardiac or extracardiac process that decreases cardiac compliance and interferes with blood flow to or from the heart. It is characterized by poor oxygenation and perfusion. Management and treatment are dependent on the individual cause.

Vasoactive Agents

Vasoactive agents or vasopressors are used to improve cardiac output and blood pressure, oftentimes in the setting of shock as was previously discussed in the Shock section of this chapter. As a class, vasopressors work by causing constriction of blood vessels, therefore increasing systemic vascular resistance and increasing blood pressure. They work at adrenergic receptors, α_1, β_1, and β_2,

which are located throughout the peripheral and CNS (discussed in Chapter 3). There are also dopaminergic (e.g., D) and vasopressin (e.g., V_1 and V_2) receptors, where dopamine and vasopressin exert their pharmacologic effect. Agents that act on V_1-receptor and α_1-receptor cause vasoconstriction and increase blood pressure. Drugs that act on β_1-receptors increase heart rate and cardiac contractility. Drugs that act on β_2-receptors cause vasodilation.

Vasopressors are typically administered as titratable, continuous IV infusions. **Table 12-7** summarizes each vasopressor agent, the receptors they bind to, and clinical indications. It is important to understand that dopamine's action is dose-related. At low doses, renal and mesenteric vasodilation occurs without affecting heart rate or blood pressure. At somewhat higher doses, cardiac output is increased. At high doses, there is marked peripheral vasoconstriction.

TABLE 12-7
Vasoactive Therapies

Drug	Dosing Range	Receptor Binding					Indication
		α_1	α_2	β_1	β_2	D	
Norepinephrine	0.02–2 μg/kg/min	+++	+++	+++	+/++	0	Shock (distributive, cardiogenic)
Epinephrine	0.01–0.15 μg/kg/min	++	++	++++	+++	0	Cardiac arrest Symptomatic bradycardia Hypotension Anaphylaxis
	0.05–3 μg/kg/min	++++	++++	+++	+	0	
Vasopressin	0.01–0.04 units/min	0	0	0	0	0	Cardiac arrest Shock (distributive, cardiogenic)
Dopamine*	1–3 μg/kg/min	0	0	+	0	++++	Shock (distributive, cardiogenic) Heart failure Symptomatic bradycardia (second line after atropine)
	3–10 μg/kg/min	0/+	0	++++	+	++++	
	>10–20 μg/kg/min	+++	0	++++	+	0	
Phenylephrine	0.5–9 μg/kg/min	+++	+	+	0	0	Hypotension
Inotropes							
Dobutamine	2–20 μg/kg/min	+		++++	++	0	Low cardiac output Shock (cardiogenic)
Milrinone	Loading dose: of 50 μg/kg over 10–60 min Maintenance: 0.25–0.75 μg/kg/min	Phosphodiesterase inhibitor that works by increasing contractility in the myocardium, leading to vasodilation in the vascular smooth muscle by increasing the intracellular concentrations of cAMP					Low cardiac output

+ = mild; ++ = mild-to-moderate; +++ = moderate-to-strong; ++++ = strong.

Adverse effects of vasopressor therapy include hypertension, peripheral/gut ischemia, and tissue necrosis. Agents that act on β_1-receptors cause tachycardia, which may exacerbate patients with tachyarrhythmias. Dobutamine and milrinone may cause excess unwanted hypotension as well. Continuous blood pressure monitoring should always be performed during vasopressor administration.

ACLS: Adult and Pediatrics

Many RCPs pursue certification in ACLS and **Pediatric Advanced Life Support (PALS)** through demonstration of skills and knowledge during American Heart Association–recognized courses. Although respiratory care practitioners are frequently IV-certified and able to administer selected ACLS drugs, several of these agents are useful when instilled directly into an endotracheal tube. RCPs are commonly at the bedside during cardiac arrest, and it is important for them to understand the causes and treatment strategies for this emergency situation. Asystole, pulseless electrical activity (PEA), and ventricular fibrillation (VF)/ventricular tachycardia (VT) are the most common arrhythmias causing cardiac arrest.

When cardiac resuscitation is needed in infants and children, the cause of the emergency is far less likely to be associated with a primary cardiac disease or dysrhythmia. A common cause of bradycardia in infants and children is respiratory failure, and most cardiac arrests in this population are secondary to hypoxia and/or shock.

Causes of Cardiac Arrest

Securing your ABCs (airway, breathing, circulation) and starting high-quality cardiopulmonary resuscitation (CPR) are vital when beginning to resuscitate a patient in cardiac arrest. Identifying the Hs and Ts of ACLS, listed in **Table 12-8**, will help to define possible reversible causes of cardiac arrest. Treating reversible causes with the proper procedure or medication early in the arrest is paramount in obtaining return of spontaneous circulation (ROSC).

TABLE 12-8
Reversible Causes and Treatments of ACLS (Hs and Ts)

H	Hypovolemia	Hypoxia	Hydrogen Ions (Acidosis)	Hyper-/Hypokalemia	Hypothermia
Treatments	Administer IV fluids or blood product	Manage airway Oxygenate	Respiratory: ventilate Metabolic: sodium bicarbonate	Hypo: potassium Hyper: calcium chloride, sodium bicarbonate, insulin	Warming strategies to return body temperature to normothermia
T	**Toxins**	**Tamponade (cardiac)**	**Tension Pneumothorax**	**Thrombosis (Coronary)**	**Thrombosis (Pulmonary)**
Treatments	Individual antidote dependent on overdose	Pericardiocentesis	Needle point decompression	Fibrinolytics Percutaneous coronary intervention	Fibrinolytics Thrombolytics

In infants and children, the most common cause of cardiac arrests is asphyxial arrest, occurring subsequent to prolonged systemic hypoxemia. Severe hypoxemia and hypercarbia lead to acidosis; when not treated early enough or successfully, the child's condition will deteriorate to bradycardia, hypotension, and cardiac arrest (usually asystole).

Oxygenation

During cardiac resuscitation, the importance of early and effective CPR and defibrillation, with proper airway management and oxygenation, cannot be overstated. During effective external cardiac compressions, the cardiac output is only 25–35% of normal (1.25–1.75 L/min); thus, tissue ischemia and hypoxemia are likely. Oxygen is an essential ACLS drug. About 100% oxygen should be administered throughout resuscitation, with pulse oximetry and waveform capnography to monitor the appropriate levels of ventilator support. If a patient achieves an ROSC, oxygen should be administered in sufficient inspired concentrations to achieve an S_pO_2 of ≥94%.

Ventilation and Capnography

Waveform capnography or colorimetric exhaled CO_2 devices should be used to monitor the effectiveness of both ventilation and circulation. Hyperventilation is not routinely recommended owing to

the reduction in cerebral blood flow when arterial Pco_2 levels are too low. Waveform capnography can be used to monitor the endotracheal tube position and also to optimize chest compressions. If P_{ETCO2} levels are less than 10 mm Hg, the most likely cause is inadequate chest compressions during CPR. Normal P_{ETCO2} in adult patients is 35–40 mm Hg, but high-quality chest compressions will only give a P_{ETCO2} of 10–20 mm Hg.

Medication Use and Route of Administration

Preferred routes of drug administration during resuscitation are IV or intraosseous (IO). Insertion of a large-bore needle directly into bone marrow (IO) may be the most effective method of obtaining vascular access in very low-perfusion states. Instillation of epinephrine, atropine, lidocaine, and vasopressin via the endotracheal tube may be indicated as an adjunct or when IV or IO routes cannot be established. The technique for endotracheal administration is outlined next. When this method is used, drugs should be administered at 2–2.5 times the recommended IV dosage and diluted in 5 mL (pediatrics) or 10 mL (adults) of normal saline or distilled water.

Recommended administration technique by instillation during CPR is as follows:

1. Insert a catheter to a point *beyond* the tip of the endotracheal tube.
2. Interrupt cardiac compressions while medication bolus is inserted.
3. Manually ventilate several times to aerosolize and distribute medications.
4. Remove catheter and resume cardiac compressions.

Rhythm-Based Management During Cardiac Arrest

After a witnessed or unwitnessed pulseless cardiac arrest, immediate initiation of high-quality CPR has been shown to improve patient survival. After initiation of CPR, an automatic external defibrillator (AED) to identify the cardiac rhythm will help guide further treatment. The algorithms discussed next (**Figure 12-3**) are used during the resuscitation effort to help obtain ROSC. It is not uncommon for the rhythm to evolve during resuscitation and to switch algorithms.

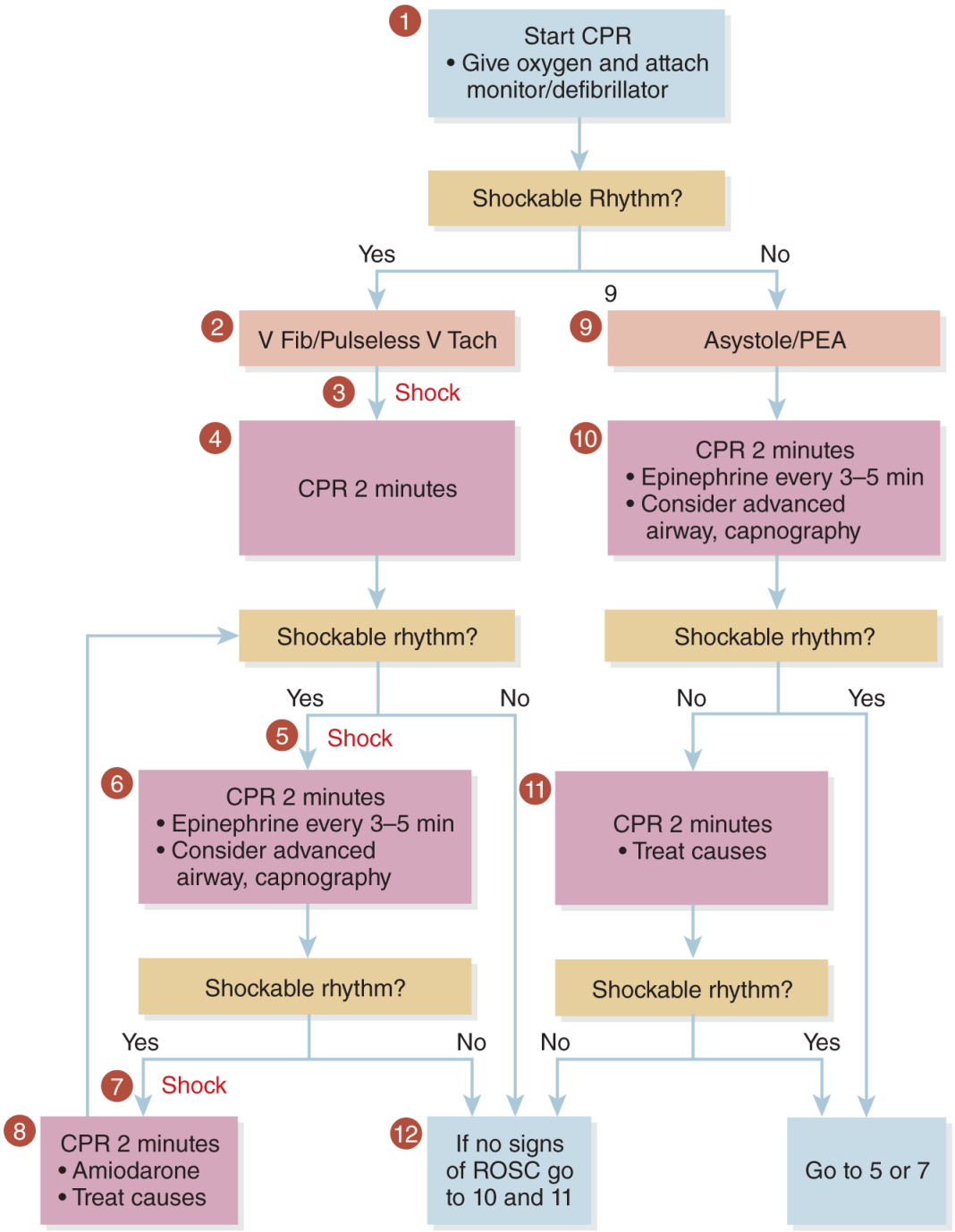


FIGURE 12-3 American Heart Association cardiac arrest algorithm.

Created by C Rose; Data from AHA ACLS Guidelines

Description

When cardiac resuscitation is needed in infants and children, the cause of the emergency is far less likely to be associated with a

primary cardiac disease or dysrhythmia. Only 5–15% of cardiac arrests in children occur from VF or pulseless VT.

PEA/Asystole

PEA and asystole are referred to as nonshockable rhythms. Resuscitation of patients in PEA/asystole includes continuing CPR, maintaining an airway, oxygenating, and identifying any reversible causes with the Hs and Ts discussed in Table 12-8. Every 2 minutes, the cardiac rhythm should be reevaluated using the AED to determine if the rhythm converted and a shock can be administered.

Epinephrine should be administered IV or IO every 3–5 minutes. Epinephrine is the first drug of choice in cardiac arrest because it is an endogenous catecholamine that directly stimulates β_1-receptors to increase cardiac output and α-receptors to increase systemic vascular resistance and blood pressure. Epinephrine dosing for ACLS is indicated in **Table 12-9** and further discussed in the Vasopressor section of this chapter.

TABLE 12-9
Medications Used During Adult and Pediatric Advanced Life Support

Drug	Dose	Drug Action	Clinical Indication in ACLS
Adenosine	(Adult) Initial: 6 mg rapid IV bolus Repeat: 12 mg rapid IV bolus, can repeat twice	Depresses atrial rate and AV-node conduction	Drug of choice for narrow complex SVT
	(Pediatrics) Initial: 0.1 mg/kg (max 6 mg*), Repeat: 0.2 mg/kg (max 12 mg)		
Amiodarone	(Adult) 300 mg IV push If no response, may repeat 150 mg IV push once	Antiarrhythmic	First-line drug for recurrent hemodynamically unstable VT and for VF/pulseless VT unresponsive to shock, CPR, and vasopressor
	(Pediatrics): 5 mg/kg		
Atropine	(Adult) 0.5 mg rapid IV push, may repeat every 3–5 min	Chronotrope	First-line drug for symptomatic bradycardia
	(Pediatrics):0.02 mg/kg		
Calcium chloride Calcium gluconate	(Adult) 0.5–1 g IV bolus over 2–5 min	Serum electrolyte	Reversal of hyperkalemia, treatment of hypocalcemia, hypermagnesemia Calcium channel blocker overdose
	(Pediatrics): 20 mg/kg		
Epinephrine	(Adult) IV bolus: 1mg every 3–5 min	α- and β-agonist; Vasopressor	First-line drug for cardiac arrest from VF, pulseless VT, asystole, and PEA Anaphylaxis Status asthmaticus
	(Pediatrics): 0.01 mg/kg every 3–5 min		
Lidocaine	(Adult) Bolus: 1–1.5 mg/kg IV over 2–3 min May repeat 0.5–0.75 mg/kg, max: 3mg/kg	Suppresses ventricular ectopy	Alternative to amiodarone in cardiac arrest owing to VF/VT; useful in managing stable polymorphic VT
	(Pediatrics): 1 mg/kg		
Magnesium sulfate	(Adult) 1–2 g IV bolus	Serum electrolyte necessary for cardiac rhythm and output	Cardiac arrest owing to torsades de pointe or suspected hypomagnesemia Status asthmaticus (PALS)
	(Pediatrics): 25–50 mg/kg		

ACLS, advanced cardiovascular life support; AV, atrioventricular; CPR, cardiopulmonary resuscitation; PALS, pediatric cardiovascular life support; PEA, pulseless electrical activity; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

*Pediatric weight-based doses should not exceed recommended adult doses.

Pulseless VF/VT

Pulseless VF and VT are considered shockable rhythms. When the AED identifies the rhythm as VF/VT, a shock should be administered. Similar to management of asystole/PEA, the rhythm should be evaluated every 2 minutes and epinephrine should be administered every 3–5 minutes.

For VF/VT rhythms unresponsive to CPR, defibrillation, and vasopressor therapy, amiodarone can be administered. Lidocaine can also be administered as an alternative to amiodarone. Amiodarone, as discussed in Table 12-9 and Chapter 13, is a class III

antiarrhythmic that prolongs the QT exhibiting β-blocking properties affecting calcium, potassium, and sodium channels.

NEED TO KNOW

Epinephrine 1 mg should be administered every 3–5 minutes for PEA/asystole arrest and pulseless VF/VT. It can be administered IV or IO. If administered through the endotracheal tube, the dose should be doubled to 2 mg for adults.

Supraventricular Tachycardia

In emergency cardiac care, up to 25% of the cases of paroxysmal supraventricular tachycardia (PSVT) may be terminated by the use of vagal maneuvers. Stimulating a vagal response will result in slowing the heart rate. The two methods recommended to slow the heart rate in PSVT are the Valsalva maneuver (exhaling against a closed glottis) and carotid sinus massage (simultaneous massage of the carotid bodies). When vagal maneuvers are not successful, synchronized cardioversion or medications are used to control PSVT.

Adenosine is administered by a rapid IV bolus depressing the atrioventricular (AV) and sinus node activity. It can be administered up to three successive times if there is no response within 1–2 minutes. Administration must be rapid, because adenosine's half-life is less than 5 seconds. Side effects including chest pain and a brief period of asystole following administration while terminating the PSVT resolve quickly after administration. Adenosine should not be administered for unstable, irregular, or wide complex tachycardias.

If vagal maneuvers and adenosine fail to terminate the PSVT or the rhythm recurs, longer acting AV nodal blockers such as calcium channel blockers (e.g., diltiazem and verapamil) or β-blockers can be administered. These agents are further discussed in the Cardiology Module of the text, Chapter 13.

Post–Cardiac Arrest Care

After ROSC, the American Heart Association recommends initiation of targeted temperature management to all comatose adult patients after cardiac arrest. Cooling measures should be initiated to maintain a core body temperature between 32°C and 36°C for at least 24 hours after arrest.

Case Study 12-2

Supraventricular Tachycardia or Pulseless VT

A 62-year-old man presents to the ED complaining of palpitations and chest discomfort. He has a history of coronary artery disease and had a stent placed in the past. Patient has no history of other illnesses or disease.

Vital signs: Heart rate, 180 beats/min; respiratory rate, 20 breaths/min; blood pressure, 100/64 mm Hg; and S_pO_2 92% on O_2 at 2 L/min by cannula.

Clinical presentation: Symptoms are mild, and cardiac rhythm is regular and displays supraventricular tachycardia (SVT). IV access is obtained. Vagal maneuver is attempted but not successful, and cardioversion is not recommended at this time.

Patient suddenly becomes unresponsive during assessment. ECG monitor reveals VT and no pulse is present. CPR is initiated and a team is called to assist with the resuscitation. As soon as it is available, a defibrillator is used to deliver a shock and CPR is resumed.

Questions

1. What medication and dose was indicated to treat the initial arrhythmia, SVT?
2. What vasopressor drug and intravenous dose should be administered for VT after the initial shock? How frequently can this medication be given?
3. The patient's intravenous line becomes malfunctioned. What medications used for ACLS can be administered into the endotracheal tube and what dose?

Review Questions

1. List the seven steps of RSI and what actions occur at each phase.
2. What is the purpose of induction? What medications can be used?
3. In what instances should an NMBA be administered to a critically ill patient?
4. Where are opioid receptors located? What are some side effects to monitor for when patients are receiving opioid pain medications?
5. What are some instances in which an ICU patient may require light sedation in addition to analgesics? When is deep sedation indicated?
6. What are some side effects of propofol administration?
7. Name the four classifications of shock.
8. A patient is diagnosed with septic shock. How is septic shock defined and how should a patient with septic shock be treated?
9. What is the difference between ACLS and PALS? What is the most common cause of pediatric cardiac arrest?
10. Describe the use of epinephrine during ACLS? In which rhythms should epinephrine be administered? How frequently?
11. Describe the proper technique for instillation of ACLS medications by endotracheal tube during cardiac resuscitation. What, if any, dosage adjustment should be made for this method of administration?

Posttest

For each of the following questions, try to select the one best answer from the choices given.

1. CPR is being performed on a patient; following intubation and ventilation, the cardiac monitor reveals asystole. Which of the following ACLS drugs is appropriate first?
   a. 1 mL isoproterenol
   b. 1 mg epinephrine
   c. 1 mg atropine
   d. 0.1 mg digoxin
2. When ACLS drugs are to be instilled via endotracheal tube, the dosage should be:
   a. 2 to 2.5 times the standard IV dosage.
   b. the same as the standard IV dosage.
   c. one-half the standard IV dosage.
   d. determined by Starling's law.
3. A respiratory therapist is caring for a patient with a flail chest who is intubated and receiving mechanical ventilation with PEEP. Which of the following medications is the most appropriate recommendation to provide analgesia for his severe pain?
   a. Midazolam (Versed®) IV
   b. Budesonide (Pulmicort®) aerosolized
   c. Morphine IV
   d. Hydrocodone (Lortab®) PO
4. Which of the following side effects of morphine should be monitored by the respiratory therapist?
   a. Hypertension
   b. Tachycardia
   c. Respiratory depression
   d. Tachypnea
5. A 25-year-old man is found unresponsive and requires intubation and mechanical ventilation. The patient is hypotensive and anxious. Which of the following drugs is the most appropriate

agent to facilitate his intubation after pretreatment and induction have been completed?

a. Morphine
b. Vecuronium (Norcuron)
c. Cisatracurium (Nimbex)
d. Midazolam (Versed)

6. Which of the following statements is true regarding the use of skeletal muscle relaxants during mechanical ventilation?
   a. Most NMBAs provide adequate analgesia.
   b. Analgesia and sedation must be provided in addition to NMBA.
   c. Most NMBAs provide adequate sedation but no analgesia.
7. Induction should always follow paralysis in RSI. True or False?
8. Patients receiving NMBAs need to be mechanically ventilated. True or False?
9. Which of the following medications can be used in addition to an analgesic agent to target a light level of sedation? (Select all that apply.)
   a. Propofol
   b. Dexmedetomidine
   c. Acetaminophen
   d. Ketamine
10. A 68-year-old woman (70kg) presents to the ED. She is hypotensive (90/75) and is complaining of pain on urination for the past 3 days, which indicates a bladder infection. Her laboratory results have come back and are significant for an acute kidney injury and her urinalysis is positive, demonstrating a urinary tract infection. She has already been given 2000 mL of normal saline and remains hypotensive. What kind of shock does this patient have?
    a. Septic shock
    b. Cardiogenic shock
    c. Hemorrhagic shock
    d. Anaphylactic shock

References/Recommended Readings

American Heart Association. *Advanced Cardiovascular Life Support Provider Manual*. Dallas, TX: American Heart Association; 2016.

American Heart Association. *Pediatric Advanced Life Support Provider Manual*. Dallas, TX: American Heart Association; 2016.

American Heart Association. Part 7: adult advanced cardiovascular life support. Web-based integrated 2010 & 2015 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. ECCguidelines.heart.org.

Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263-295.

Barrington KJ. Premedication for the endotracheal intubation in the newborn infant. *Paediatr Child Health*. 2011;16(3):159-174.

Campbell RL, Li JTC, Nicklas RA, et al. Emergency department diagnosis and treatment of anaphylaxis: a practice parameter. *Ann Allergy Asthma Immunol*. 2014;113:599-608.

Devlin JW, Skorbik Y, Gelinas C, et al. Clinical practice guidelines for the prevention, and management of pain, agitation/sedation, delirium, immobility and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46:e825-e873.

Dexmedetomidine [package insert].

Frerk C, Mitchell VS, McNarry AF, et al. Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. *Br J Anaesth*. 2015;115(6):827-848.

Gregory T, Smith M. Cardiovascular complications of brain injury. *Contin Educ Anaesth Crit Care Pain.* 2012;12(2):67-71.

Hampton JP. Rapid sequence intubation and the role of the emergency department pharmacist. *Am J Health Syst Pharm*. 2011;68:1320-1330.

Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine for long-term sedation investigators: dexmedetomidinevs midazolam or propofol for sedation during prolong mechanical ventilation. *JAMA.* 2012;307:1151-1160.

Kam PC, Cardone D. Propofol infusion syndrome. *Anesthesia*. 2007;62(7):690-701.

Kee VR. Hemodynamic pharmacology of intravenous vasopressors. *Crit Care Nurse*. 2003;23(4):79-82.

Krausz MM. Initial resuscitation of hemorrhagic shock. *World J Emerg Surg.* 2006;1:14. doi:10.1186/1749-7922-1-14

Kumar P, Denson SE, Mancuso TJ; Committee on Fetus and Newborn, Section on Anesthesiology and Pain Medicine. Premedication for nonemergency endotracheal intubation in the neonate. *Pediatrics*. 2010;125(3):608-615.

MacIntyre NR. The ventilator discontinuation process: an expanding evidence base. *Respir Care*. 2013;58(6):1074-1086.

McManus MC. Neuromuscular blockers in surgery and intensive care, Part 1. *Am J Health Syst Pharm.* 2001;58:2381.

Murray MJ, Cowen J, DeBlock H, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med*. 2002;30:142-156.

Murray MJ, DeBlock H, Erstand B, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med*. 2016;44:2079-2103.

Nimmagadda U, Salem MR, Crystal GJ. Preoxygenation: physiologic basis, benefits, and potential risks. *Anesth Analg*. 2017;124:507.

Overgaard CB, Dzavik V. Inotropes and vasopressors. *Circulation*. 2008;118:1047-1056.

Pathan H, Williams J. Basic opioid pharmacology: an update. *Br J Pain*. 2012;6(1):11-16.

Propofol [package insert].

Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2016;45(3):488-552.

Richards JB, Wilcox SR. Diagnosis and management of shock in the emergency department. *Emerg Med Pract*. 2014;16(3):1-24.

Schmidbauer S, Kneifel HA, Hallfeldt KK. Endobronchial application of high dose epinephrine in out of hospital cardiopulmonary resuscitation. *Resuscitation.* 2000;47:89.

Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-dose nocturnal dexmedetomidine prevents ICU delirium. A randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 2018;97(9):1147-1156.

Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2016;388:1893-1902.

Taylor MP, Wrenn P, O'Donnell AD. Presentation of neurogenic shock within the emergency department. *Emerg Med J*. 2017;34:157-162.

Tomlinson DR, Cherian P, Betts TR, et al. Intravenous amiodarone for the pharmacological termination of haemodynamically-tolerated sustained ventricular tachycardia: is bolus dose amiodarone an appropriate first-line treatment? *Emerg Med J.* 2008;25:15-18.

Upchurch CP, Grijalva CG, Russ S, et al Comparison of etomidate and ketamine for induction during rapid sequence intubation of adult trauma patients. *Ann Emer Med*. 2017;69(1):24-33.

vanDipen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e232-e268. doi:10.1161/CIR.0000000000000525.

Varon AJ, Morrina J, Civetta JM. Clinical utility of a colorimetric end-tidal CO_2 detector in cardiopulmonary resuscitation and emergency intubation. *J Clin Monit*. 1991;7:289-293.

CHAPTER

13

Cardiovascular and Renal Pharmacology

Coauthored by Michael Barros, PharmD

© Anna RubaK/ShutterStock, Inc.

OUTLINE

Introduction
Hypertension
  Factors That Control BP
  Current Therapeutic Approach to Hypertension
Physiology of the Nephron
  Filtration
  Tubular Reabsorption
  Tubular Secretion
  Diuretics and Their Therapeutic Role
Agents for the Treatment of Hypertension
  ACE Inhibitors
  Angiotensin II Receptor Blockers
  Calcium Channel Blockers
  Adrenergic Agents
  Direct-Acting Vasodilator Drugs
Heart Disease
HF and GDMT
  Cardiac Workload

Neurohormonal Activation
ACE Inhibitors
Angiotensin II Receptor Blockers
Angiotensin Receptor-Neprilysin Inhibitor
Beta-Adrenergic Blockers
Aldosterone Antagonists
Hydralazine and Isosorbide Dinitrate
Cardiac Glycosides, Digoxin
Angina and the Effects of Nitrates
Nitrates
Other Categories of Antianginal Drugs
Conduction System of the Heart
Definition and Types of Arrhythmias
Reasons for Converting and Causes of Arrhythmias
Antiarrhythmic Drug Classes
Examples of Antiarrhythmic Drugs
Coagulation Process
Anticoagulant Drugs
Antiplatelet Drugs
Lipids
Drugs Used in Treatment of Hyperlipidemia

OBJECTIVES

After completion of this chapter and its learning activities, you will be able to:

1. Classify the stages of hypertension and discuss the physiologic factors that control blood pressure.
2. Design a plan for the treatment of hypertension by choosing the agents used as first line for the treatment of hypertension.
3. Compare and contrast the mechanism and adverse effects of the first-line drugs used in the treatment of hypertension.
4. Describe the basic physiology of the nephron and how it is related to the pathophysiology of hypertension.
5. Discuss the mechanism of action of each class of diuretics and most common adverse effects and be able to determine the most appropriate class to use for the treatment of pulmonary edema.
6. Define heart failure with reduced ejection fraction (HFrEF) and coronary artery disease.
7. Identify the drug classes used in the treatment of HFrEF and be able to determine which agents decrease the risk of death with use.
8. Define arrhythmia, and list the different types and the most common causes of arrhythmias.
9. Describe four classifications of antiarrhythmic agents, list at least one drug from each of the four classifications, and indicate the overall mechanism of action of these drugs and side effects and contraindications of each agent.
10. Describe the mechanism of action and adverse effects of the antianginal drugs, including appropriate dosing of sublingual nitroglycerin.

11. Briefly review the process of coagulation and how it is affected by anticoagulants.
12. Identify the various injectable and oral anticoagulants and antiplatelet drugs and their respective mechanisms of action.
13. List the categories and drugs generally used in controlling hyperlipidemia and their effects on cholesterol and the most common adverse effects.

KEY TERMS

Afterload
Aldosterone
Angina
Angiotensin II
Arrhythmia
Atherosclerosis
Cholesterol
Chronotropic
Congestive heart failure (CHF)
Coronary artery disease (CAD)
Diastolic blood pressure
Diuretics
Heart failure
Heart failure with reduced ejection fraction (HFrEF)
Hypertension
Inotropic
Low-density lipoprotein (LDL)
Myocardial infarction (MI)
Neurohormonal
Preload
Renin
Sinoatrial (SA) node
Systolic blood pressure
Triglyceride (TG)

Introduction

Heart disease is the major cause of death from illness in the United States. Because respiratory problems often accompany cardiac dysfunction, it is essential that the respiratory care practitioner have some knowledge regarding drugs that are used in treating heart and vascular disease. This chapter discusses drugs used in treating **hypertension**, the role of guideline-directed therapy (GDMT) in the treatment of heart failure (HF), antianginal drugs, and antiarrhythmic agents. This chapter also discusses anticoagulants, antiplatelets, and hypolipidemic drugs (i.e., drugs that lower **cholesterol** and **triglyceride [TG]** levels). As part of the section on antihypertensive drugs, renal function in connection with the use of **diuretics** is discussed.

Specific information regarding indications and dosages of medications used in advanced cardiovascular life support (ACLS) and pediatric advanced life support are provided in Chapter 12.

Hypertension

Hypertension is a condition of elevated blood pressure (BP) and is one of the leading causes of stroke, heart attack, and kidney disease. Classification of high BP is based on both **systolic** and **diastolic blood pressures** (**Table 13-1**). Generally, if the diastolic pressure is 89 mm of mercury (mm Hg) and more or the systolic pressure is more than 139 mm Hg, treatment is usually initiated using antihypertensive drugs. Hypertension is diagnosed when two or more BPs exceed the normal values when the measurements are taken in a seated position and on different days.

TABLE 13-1
Stages of Hypertension

Classification	Systolic Pressure (mm Hg)	Diastolic Pressure (mm Hg)
Normal	<120	<80
Prehypertension	120–139	80–89
Stage 1 hypertension	140–159	90–99
Stage 2 hypertension	>160	>100

The resting BP for the majority of the population will remain relatively stable throughout life, with a tendency to increase only slightly with age. About 10–15% of the population has elevated BP requiring treatment. Of the group that has elevated BP, 90% of the cases have an unknown etiology. This type of hypertension is referred to as primary or essential hypertension. The other 10% of hypertensive cases are called secondary because the elevated pressure is because of an identifiable condition (e.g., kidney disease,

thyroid disease, pheochromocytoma, hormonal disorders, or are caused by other medications).

Although the etiology of primary or essential hypertension is unknown, there are several factors that have been implicated: genetic predisposition, stress, obesity, and excessive salt intake. In order to treat hypertension properly, these factors must be considered along with the proper selection of drugs. Commonly used first-line agents for the management of hypertension include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), diuretics, and calcium channel blockers (CCBs).

Factors That Control BP

In order to control BP through proper drug therapy, as well as other methods, it is important to understand the factors that determine BP. The two primary factors are cardiac output (CO) and peripheral resistance (PR). The CO is the amount of blood pumped by the heart per minute. Factors that make up CO are heart rate (HR) and stroke volume (SV). The formula for cardiac output is: $CO = HR \times SV$. The PR is largely determined by the diameter (vasoconstriction or vasodilation) of the blood vessels, mainly the small arterioles, which are regulated by the sympathetic nervous system (SNS). Therefore, the overall formula for BP is:

$$BP = CO \times PR$$

Antihypertensive drugs lower BP by decreasing the CO or reducing the total PR by decreasing the effects of the SNS or reducing the intravascular fluid volume. The role of calcium is also important and pharmacologically is very complex. Calcium is located in smooth muscles and cardiac myocytes (cells) and is responsible for causing contractions. Drugs such as CCBs reduce the effects of calcium in smooth muscle and result in vasodilation and a lowering of BP.

The kidneys also play a role in hypertension because, with hypertension, there is often a decrease in blood flow to the kidneys as a result of an increase in PR or constriction of the vessels to the kidney. When renal blood flow is reduced, a hormone called **renin** is released into the bloodstream. Through a series of chemical reactions that are triggered by the release of renin, a substance called **angiotensin II**, which is a powerful vasoconstrictor, is released into the bloodstream. Angiotensin II also causes the release of another hormone, **aldosterone**, from the adrenal cortex. With the release of aldosterone, there is an increase in the reabsorption of sodium and water into the bloodstream. This elevates the blood volume and, along with the increased vasoconstriction, causes the BP to be elevated. Normally this renin–angiotensin–aldosterone (RAA) system ensures adequate blood flow to the kidneys. However, in the presence of hypertension, this normal mechanism actually worsens hypertension. Antihypertensive agents that inhibit the RAA system are called ACE inhibitors. ARBs work further down the RAA system and block the effects of angiotensin II.

Current Therapeutic Approach to Hypertension

There are currently a large number of drugs available for treating hypertension. As a result, it has been necessary to establish guidelines for choosing the right drug or drug combination for a particular patient. Current approaches to initiating medications include beginning with one agent or two agents if a patient has stage 1 hypertension or stage 2 hypertension, respectively. When starting with one agent, a few dosing strategies may be utilized. The first strategy includes starting with one drug and titrating to the maximum dose before adding a second drug. A second strategy includes starting one drug and then adding a second drug before achieving the maximum dose of the initial drug; either approach is acceptable. The decision is on the basis of the drug's side effect profile and a patient's willingness to take multiple medications.

Because diuretics have been used clinically for many years, not only in the treatment of hypertension but also for many other clinical problems, the function of the kidneys will be reviewed in order to understand the mechanism of action of various diuretic agents. The clinical uses of other antihypertensive agents will also be discussed, including adrenergic antagonists, central-acting drugs, vasodilators, ACE inhibitors, ARBs, and CCBs.

Physiology of the Nephron

Urine formation is the main function of the kidneys, and the functional unit of a kidney is the “nephron” or kidney tubule. Each kidney contains millions of nephrons and each nephron comprises several segments: the glomerulus, the proximal convoluted tubule (PCT), the loop of Henle, the distal convoluted tubule (DCT), and the collecting duct (**Figure 13-1**). The formation of urine involves three basic processes: filtration, tubular reabsorption, and tubular secretion.

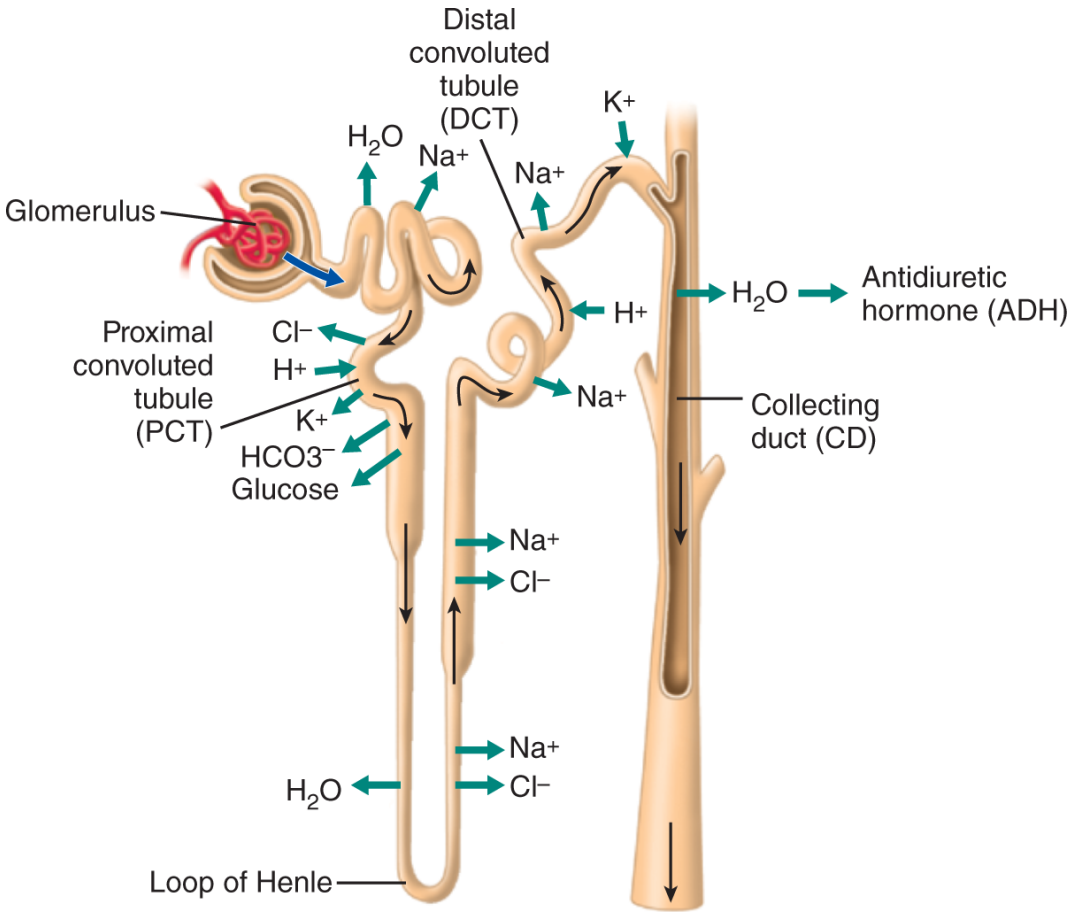


FIGURE 13-1 Function of the nephron.

Description

Filtration

Most of the substances in the blood are filtered through the glomerulus. As the blood flows through the glomerulus, it filters small molecules, wastes, and water into the tubules. The substances that are not filtered usually include large molecules, plasma proteins, and blood cells (e.g., red blood cells, white blood cells, and platelets). These substances stay in the blood vessels.

Tubular Reabsorption

Most of the ions and nutrients that are filtered by the glomerulus are reabsorbed back into the blood along the various segments of the nephron. The most important ion that is reabsorbed is Na^+, with 99% being reabsorbed. The main extracellular ion of the body is the sodium ion, and, with the absorption of large amounts of sodium, an osmotic gradient is established that attracts water. Because sodium ion concentrations are higher in the blood, water is attracted by osmosis. Therefore, the conservation of water in the body is directly related to the reabsorption of the sodium ion.

Along the length of the nephron, the reabsorption of sodium ion occurs by two mechanisms: (1) cation exchange among sodium ion, hydrogen ion, and potassium ion and (2) anion transport by chloride ion. The exchange between sodium and hydrogen occurs in the PCT and in the DCT. The exchange between sodium and potassium occurs in the DCT. In the loop of Henle, chloride ion is actively reabsorbed and sodium follows the chloride ion. When the renal tubules reabsorb the sodium ions by the described mechanisms, an osmotic gradient is established with a high concentration of sodium in the blood. Because of the higher concentration of sodium in the blood, water also is reabsorbed. In addition to being reabsorbed by osmosis, water is reabsorbed in the collecting duct under the influence of antidiuretic hormone and aldosterone. It is important to understand reabsorption mechanisms of sodium and water because diuretics increase urine volume by inhibiting or altering these mechanisms.

Tubular Secretion

The main secretory functions of the nephron have already been mentioned regarding the cation exchange among sodium, hydrogen, and potassium. In addition to hydrogen and potassium exchange, weak acids and weak bases are also secreted into the renal tubules. These substances are the products of normal cell metabolism and are delivered to the kidneys for excretion. As mentioned in Chapter 2, many drugs that are weak acids and weak bases are also secreted through the kidneys. The secretion of hydrogen ion should be emphasized as another major function of the tubular secretion. By secreting excess hydrogen ion in the urine, the kidney becomes a major organ controlling blood pH. The probable source of hydrogen for secretion can be seen in the following equation:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

This reaction occurs in the renal tubule cells and is under the control of the enzyme carbonic anhydrase (CA). If the CO_2 level in the blood is elevated, the above-mentioned reaction shifts to the right and hydrogen ion is excreted in exchange for sodium. The reabsorbed sodium then is paired with bicarbonate ion (HCO_3^-), which is part of the important sodium bicarbonate buffer system of the blood (see Figure 13-1).

Diuretics and Their Therapeutic Role

Diuretics are agents that increase urine volume. As long as the kidneys are capable of normal function, diuretics can be administered to increase urine formation by increasing glomerular filtration or, more commonly, by preventing reabsorption of sodium and water. Diuretics are used in the treatment of hypertension to reduce blood volume and peripheral edema. In addition, diuretics can be used for pathologic conditions involving fluid retention and edema such as chronic HF.

NEED TO KNOW

Patients with **congestive heart failure (CHF)** may exhibit moist crackles, suggesting pulmonary edema. These patients may benefit from the administration of a diuretic.

As mentioned earlier, diuretics are one of the first-line agents in the treatment of hypertension. There are five classes of diuretics available on the basis of the mechanism of action (**Table 13-2**); however, thiazides are the diuretics of choice for hypertension. The following discussion lists the classes of diuretics along with the mechanism of action and examples of drugs. These classes include thiazide and thiazide-like diuretics, loop diuretics, potassium-sparing diuretics, osmotic diuretics, and CA inhibitors.

TABLE 13-2
Diuretics Classes and Mechanism of Action

Category	Drug	Typical Dose Ranges	Mechanism of Action
Thiazide and thiazide-like	Chlorothiazide (Diuril®)	250–1000 mg IV or PO twice daily	Prevent Na^+ and Cl^- reabsorption at distal tubule
	Hydrochlorothiazide (Microzide®)	12.5–50 mg PO daily	
	Chlorthalidone (Hygroton®)	12.5–200 mg PO daily	
	Metolazone (Zaroxolyn®)	2.5–20 mg PO daily	
Loop	Furosemide (Lasix®)	20–80 mg IV or PO once or twice daily (may give higher doses)	Blocks Na^+, Cl^-, and K^+ exchange at loop of Henle
	Bumetanide (Bumex®)	0.5–2 mg twice daily (max 10 mg)	
	Torsemide (Demadex®)	10–20 mg PO daily (max 200 mg/day)	
	Ethacrynic acid (Edecrin®)	50–200 mg PO in 1–2 divided doses or 0.5–1 mg/kg/dose IV	
Potassium-sparing	Spironolactone (Aldactone®)	12.5–50 mg PO daily (max 200 mg)	Blocks aldosterone
	Triamterene (Dyrenium®)	50–100 mg PO twice daily (max 300 mg/day)	Blocks Na^+ reabsorption at distal tubule
	Amiloride (Midamor®)	5–20 mg PO daily	
Osmotic	Mannitol (Osmitrol®)	0.25–1 g/kg/dose IV q6–8h as needed	Osmosis

Thiazide and Thiazide-like Diuretics

These agents comprise the largest and most widely used group of diuretics and have a similar mechanism of action regarding diuresis. These diuretics prevent reabsorption in the DCT of the nephron, causing a relatively potent diuresis. The main adverse effects of these drugs include hypotension, dizziness, light-headedness, and electrolyte abnormalities such as hyponatremia, hypomagnesemia, and hypokalemia. Thiazides can also increase uric acid and should be used with caution in patients with uncontrolled gout. Thiazides are efficacious and widely used in hypertension management. Examples of the thiazide diuretics are chlorothiazide (Diuril®) and hydrochlorothiazide (Microzide®). Examples of thiazide-like diuretics are chlorthalidone (Hygroton®) and metolazone (Zaroxolyn®).

Loop Diuretics

Loop diuretics are the most potent of the diuretics and can cause significant water loss by preventing the reabsorption of sodium and chloride in the loop of Henle. They are organic acids but are unaffected by acid–base balance. These agents are extremely potent and are used when fluid retention/edema is present or in place of a thiazide diuretic for hypertension when they are ineffective. Although these agents can be used for hypertension, they are not considered first-line agents within the diuretic class and are more commonly used for treating peripheral edema and acute pulmonary edema. They can be given orally but are commonly used intravenously for the treatment of acute pulmonary edema and fluid overload from HF in an inpatient setting because of the quick onset of action. The adverse effects of these drugs are similar to those of the thiazides except that, in high doses, they can cause ototoxicity (i.e., damage to the 8th cranial nerve), loss of calcium, and renal failure when water loss is significant. Examples of loop diuretics are bumetanide (Bumex®), ethacrynic acid (Edecrin®), furosemide (Lasix®), and torsemide (Demadex®).

NEED TO KNOW

Furosemide (Lasix®) is often used to reverse pulmonary edema associated with fluid overload or acute HF.

Potassium-Sparing Diuretics

As the name implies, these agents are diuretics that prevent exchange of sodium and potassium in the collecting tubules. They promote sodium excretion and potassium reabsorption. Spironolactone and eplerenone are aldosterone antagonists. They block aldosterone receptors of the distal tubules in the kidney. This mechanism increases the excretion of sodium and chloride but not potassium. Agents such as triamterene and amiloride block sodium channels in the DCT resulting in sodium excretion and retention of potassium. These agents create mild diuresis and they are not routinely used for hypertension; however, these agents are good to use with other diuretics to decrease potassium loss. Spironolactone and eplerenone have added benefits in HF. Adverse effects include hyperkalemia and elevations in serum creatinine. Spironolactone has some affinity toward progesterone and androgen receptors and may cause gynecomastia (i.e., breast growth); this side effect is not observed with eplerenone, and it is a good alternative to spironolactone if this side effect occurs.

Examples of potassium-sparing diuretics are eplerenone (Inspra®), spironolactone (Aldactone®), triamterene (Dyrenium®), and amiloride (Midamor®).

Osmotic Diuretics

The osmotic diuretic mannitol (Osmitrol®) is used as an adjunct in treating low urine output and anuria (i.e., scanty or no urine formation). It is filtered by the glomerulus but not reabsorbed by the renal tubules. Mannitol is a large molecule and, by the process of osmosis, attracts water into the tubules, causing a mild diuresis that does not affect electrolyte and acid–base balance. In addition, mannitol is used in treating cerebral edema and glaucoma. The drug

has relatively few side effects, but can cause an increase in plasma volume and can cause CHF.

NEED TO KNOW

Mannitol may be indicated as a diuretic in clinical situations involving increased intracranial pressures caused by cerebral edema.

CA Inhibitors

These drugs create a diuretic action by inhibiting the enzyme CA. By inhibiting the enzyme CA, there is less hydrogen available to exchange with sodium; therefore, less sodium is reabsorbed. These agents also cause excretion of potassium and bicarbonate. Thus, water remains in the tubule and is excreted, which produces a moderate diuresis. These diuretics are more commonly used in the treatment of edema and glaucoma but may be used systemically in the treatment of metabolic alkalosis. In glaucoma, CA inhibitors are administered as topical eye drops and work by decreasing the formation of aqueous humor (i.e., fluid in the eye). The main adverse effects include problems with acid–base balance and, because these drugs are related to sulfonamides, various allergic reactions and blood dyscrasias (e.g., low white blood cells, red blood cells, and platelets). An example of a CA diuretic is acetazolamide (Diamox®).

Case Study 13-1

Acute Pulmonary Edema

A nurse on the medical unit calls the respiratory therapist for an arterial blood gas and patient evaluation for respiratory distress.

History and Physical Examination

History: Patient was admitted 3 days ago for an exacerbation of chronic obstructive pulmonary disease (COPD). Temperature was 38.6°C on admission and he had difficulty clearing his airway of copious amounts of purulent sputum.

Hospital Course

Patient has been receiving an IV antibiotic since admission and has received IV fluids to improve his hydration and help mobilize secretions. He has had S_pO_2 levels between 91% and 93% on oxygen per nasal cannula at 2 L/min and had been receiving DuoNeb® small-volume nebulizer treatments with airway clearance maneuvers every 4 hours while awake. He has been responding well to this therapy with improvement in dyspnea and breath sounds. When the therapist sees the patient to evaluate, she notes the following:
Vital signs: HR, 120 beats/min; BP, 160/95 mm Hg; respiratory rate, 25 breaths/min; and temperature, 37.5°C.
Clinical appearance: Breathing is somewhat labored in semi-fowler's position. S_pO_2 now reading 88% on nasal cannula at 2 L/min.
Breath sounds: Scattered wet crackles bilaterally.
The therapist reviewed the patient chart for fluid balance and found the following I and O's:

	Intake	Urine Output
Day 1 (admitted at 1000)	2.50 L	800 mL
Day 2	4.3 L	1.50 L
Day 3 (through 1000)	1.8 L	700 mL

Questions

1. Should the therapist give a DuoNeb treatment to relieve the respiratory distress?
2. What could be causing the drop in S_pO_2 and what would be the most appropriate medication class suggested to correct this, and route of administration?
3. What is the mechanism of the agent that was used to treat this patient and what are the common side effects?

Agents for the Treatment of Hypertension

There are multiple classes of agents used for the treatment of hypertension. There are agents that are preferred first-line therapies owing to their effectiveness, side effect profiles, and benefit to treat other cardiovascular or renal conditions. Thiazide diuretics, ACE inhibitors, ARBs, and dihydropyridine CCBs are considered first-line agents for the treatment of hypertension. Other drug therapies listed below may be used second- or third-line for hypertension but may be more effective to treat other cardiovascular disorders. Agents such as α-blockers, hydralazine, and minoxidil are rarely used and may cause an increased risk of side effects.

ACE Inhibitors

ACE inhibitors are used for various cardiovascular diseases and are very effective for hypertension. These agents are considered first line for treating hypertension and they remain one of the cornerstone agents in the treatment of **heart failure with reduced ejection fraction (HFrEF)**. They are also used in diabetic nephropathy and chronic kidney disease owing to their renoprotective effects. They can be used in chronic kidney disease but should be stopped if kidney function worsens acutely on these agents. These agents work by suppressing the RAA system. They inhibit the enzyme ACE, which is responsible for the conversion of angiotensin I to angiotensin II. As previously discussed, angiotensin II is a potent vasoconstrictor and promotes the release of aldosterone, which causes sodium and water retention. By inhibiting the formation of angiotensin II, vasodilation occurs and sodium and water retention decreases. Common side effects include cough, renal failure in certain patients, hyperkalemia, and angioedema. ACE inhibitor–induced cough presents as a dry, hacking-type cough that does not resolve with cough suppressants. It is not a life-threatening adverse effect but can be bothersome for the patient. Angioedema can be life-threatening and manifest as swelling

of the tongue, lips, or upper airway requiring endotracheal intubation until it resolves. If patients develop angioedema attributed to an ACE inhibitor, it is contraindicated for these patients to ever be placed on an ACE inhibitor again. Examples of ACE inhibitors are captopril (Capoten®), enalapril (Vasotec®), and lisinopril (Prinivil®, Zestril®). **Figure 13-2** describes the RAA system and how ACE inhibitors affect it.

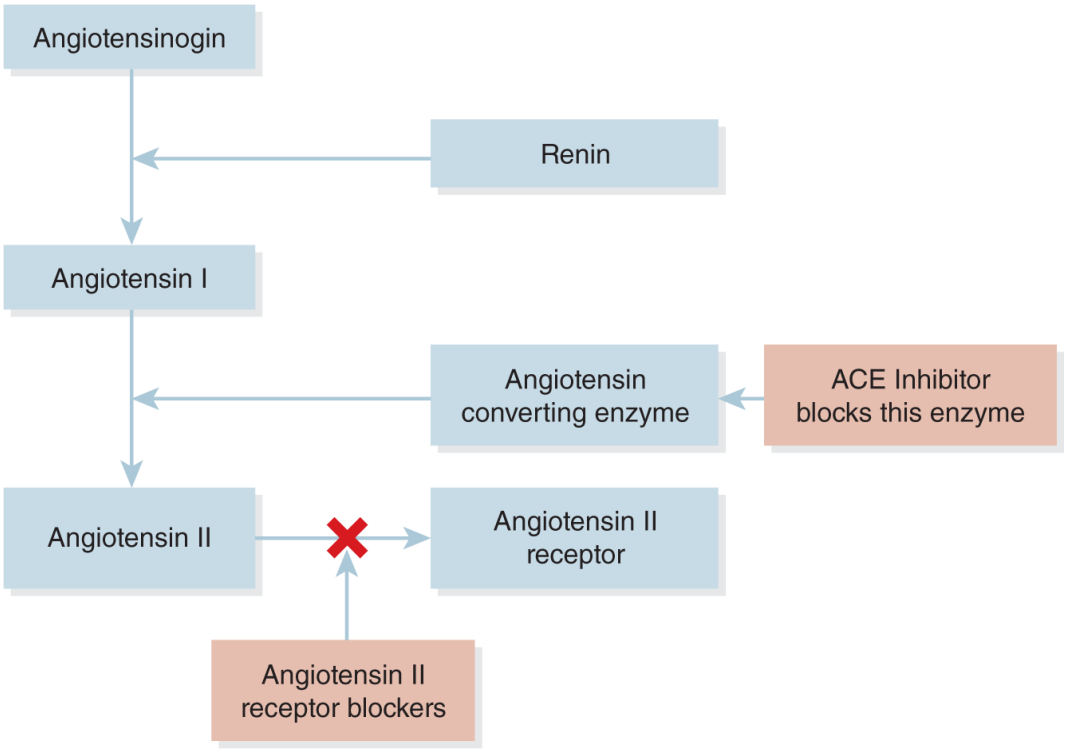


FIGURE 13-2 Mechanism of action of ACE inhibitors and angiotensin II receptor blocking agents.

Description

NEED TO KNOW

ACE inhibitors can cause a life-threatening side effect called angioedema. Angioedema can manifest as swelling of the lips, tongue, and, in some cases, upper airway, requiring intubation. Patients who experience this reaction should not be rechallenged on an ACE inhibitor again.

Angiotensin II Receptor Blockers

ARBs, much like ACE inhibitors, are widely used for cardiovascular diseases and are very effective for hypertension. These agents are also considered first-line agents for hypertension and they are used in place of an ACE inhibitor for the treatment of HFrEF if a contraindication to an ACE inhibitor exists. They are also used for diabetic nephropathy and chronic kidney disease because of their renoprotective effects. They can be used in chronic kidney disease but should be stopped if kidney function worsens acutely on these agents. These agents also work along the RAA system but they have an added benefit over ACE inhibitors in that they do not cause cough. They block the binding of angiotensin II at the receptor site, thereby inhibiting the effects of angiotensin II (Figure 13-2). The resulting effects will be vasodilation and a reduction in sodium and water retention, much like the ACE inhibitors. Examples of ARB include irbesartan (Avapro®), losartan (Cozaar®), and valsartan (Diovan®). Side effects are similar to ACE inhibitors, except they do not cause cough and are less likely to cause angioedema. An ARB may be started in select patients that develop angioedema while on ACE inhibitors; but careful monitoring and patient selection is needed.

Calcium Channel Blockers

The CCBs are subdivided into two classes: dihydropyridine and non-dihydropyridine CCB. Depending on the agent selected, different cardiovascular diseases may be treated successfully. The non-dihydropyridine CCBs are widely used for various cardiovascular diseases including **angina**, HR control in atrial fibrillation, and hypertension. The dihydropyridine CCBs are widely used for hypertension and are considered first-line agents. When selecting a CCB for hypertension, the dihydropyridine CCBs are preferred as these agents primarily cause vasodilation by inhibiting the movement of calcium ions across the cell membranes, especially in the vascular smooth muscle. The non-dihydropyridine CCBs primarily exert their effects by decreasing the influx of calcium ions into the cardiac

muscle. Examples of the dihydropyridine CCBs are amlodipine (Norvasc®) and nifedipine (Adalat CC®, Nifedical XL®, Procardia®, and Procardia XL®). Examples of the non-dihydropyridine CCBs are verapamil (Calan®) and diltiazem (Cardizem®). The most common adverse effects of the dihydropyridine CCBs include peripheral edema, headache, and hypotension. The most common adverse effects of the non-dihydropyridine CCBs include bradycardia, hypotension, edema, and constipation (verapamil).

Adrenergic Agents

This group of drugs lowers BP by reducing sympathetic activity to the heart and/or blood vessels, thus reducing CO and/or PR.

Alpha-1-Receptor Antagonists

These agents are used for hypertension; however, they are not considered first-line agents because more effective agents are available. These agents are more widely used for the treatment of benign prostatic hyperplasia. These agents exert their BP lowering effects by blocking postsynaptic α_1-adrenergic receptors. The result is dilation of both arterioles and veins. These agents also block α_1-receptors in the prostate and bladder neck causing smooth muscle relaxation. Examples of α_1-receptor antagonists include doxazosin (Cardura®), prazosin (Minipress®), and terazosin (Hytrin®). Common adverse reactions include dizziness, headache, and orthostatic hypotension. They should not be used in patients with angina, HF, or a recent **myocardial infarction (MI)** because they can worsen heart function.

Alpha-2-Receptor Agonists

These agents are used for hypertension, but should only be considered as a last-line agent when BP remains elevated despite taking recommended first-line agents. These agents are extremely

potent and cause a profound drop in BP. These agents are centrally acting vasodilators and they exert their pharmacologic effect by stimulating α_2-receptors in the brain stem. The result is a reduction in sympathetic outflow from the central nervous system and a decrease in PR, HR, and BP. An example of an α_2-receptor agonist is clonidine (Catapres®). Major adverse reactions include central nervous system depression, constipation, drowsiness, bradycardia, and rebound hypertension if abruptly stopped. These agents should not be recommended for patients with suspected compliance issues owing to rebound hypertension that may occur when abruptly stopped.

Beta-Adrenergic Antagonists

These agents, commonly referred to β-blockers, compromise one of the most widely used cardiovascular agents. Although these drugs are not first-line agents for hypertension, they are considered excellent first-line agents for patients with cardiovascular indications, such as HFrEF, MI, **coronary artery disease (CAD)**/angina, and atrial **arrhythmias**. Beta-blockers competitively block the response to β-adrenergic stimulation at the β-receptor. This results in a decrease in HR, myocardial contraction, BP, and myocardial oxygen demand. Beta-blockers can be selective to the β_1-receptor and others are nonselective (**Table 13-3**), meaning that they will antagonize both β_1- and β_2- (pulmonary) receptors. Caution should be exercised when using nonselective β-blockers in patients with asthma because of bronchoconstriction (may also occur with selective agents at higher doses) or a decrease in effect with β_2-agonists such as albuterol. Examples of β-blockers include atenolol (Tenormin®), carvedilol (Coreg®), labetalol (Normodyne®), metoprolol succinate (Toprol XL®), metoprolol tartrate (Lopressor®), nadolol (Corgard®), and propranolol (Inderal®). Common adverse reactions include bradycardia, sexual dysfunction, fatigue, lethargy, worsening HF symptoms, and bronchoconstriction.

TABLE 13-3
Beta-Selectively of Available β-Adrenergic Antagonists

Cardioselective β_1-Blockers	Non-Cardioselective β-Blockers
Atenolol	Carvedilol (β_1, β_2, α_1)
Metoprolol tartrate/succinate	Labetalol (β_1, β_2, α_1)
Bisoprolol	Nadolol (β_1, β_2)
Nebivolol	Propranolol (β_1, β_2)
	Timolol (β_1, β_2)

NEED TO KNOW

Patients with asthma requiring therapy with beta-adrenergic antagonists should only use β_1-selective agents such as metoprolol, atenolol, bisoprolol, or nebivolol. The use of nonselective beta-blockers may induce bronchospasms or lead to uncontrolled asthma symptoms.

Direct-Acting Vasodilator Drugs

These agents work by causing direct vasodilation of the arterioles. These agents are potent and are considered last line for patients who are not able to achieve adequate BP despite taking first-line agents. Examples include hydralazine (Apresoline®) and minoxidil (Loniten®). Common adverse reactions include tachycardia, hypotension, edema, lupus-like syndrome (hydralazine), and hirsutism (minoxidil).

Heart Disease

The most common diseases of the heart are **heart failure** and CAD. HF is a complex syndrome that impairs the ability of the ventricle to fill with or eject blood. This can be divided into HF with preserved ejection fraction or HFrEF. HFrEF is caused by a loss of contractility of the cardiac muscle that leads to an inefficient pump. If the heart pumps less blood than it receives, the blood volume increases inside the chambers, causing enlargement. When there is less blood pumped to the rest of the body, many organs receive less blood flow. The kidneys, which are very sensitive to the amount of blood volume, react by functioning less efficiently, leading to fluid retention and a generalized edema throughout the body. This is often referred to as congestive heart failure (CHF). When the left side of the heart fails, fluid accumulates in the lungs, causing pulmonary edema. When the right side of the heart fails, fluid accumulates in the body organs, particularly the lower extremities. The most common form of right-sided HF is cor pulmonale, a condition that is commonly found in patients who develop HF secondary to pulmonary disease such as COPD.

CAD is the result of decreased flow to the coronary circulation and is associated with several cardiovascular diseases:

- **Atherosclerosis**: Hardening (fibrosis) of the arteries, which cause a narrowing of all the vessels, especially the coronary arteries. One type of arteriosclerosis is caused by accumulation of fatty plaques in the wall of the arterioles and is known as atherosclerosis. This eventually causes a narrowing of the vessel diameter and leads to a decrease in blood flow to the coronary arteries and a decrease in cardiac efficiency.
- **Angina pectoris**: A clinical term for chest pain that is the result of insufficient coronary blood flow, resulting from a decreased level of oxygen availability for cardiac contraction. Angina is often

an early warning sign of decreased blood flow and/or oxygen supply to the heart.

- **MI**: A “heart attack” that is a result of an occlusion (coronary occlusion) of the blood supply to the cardiac muscle leading to an infarct (muscle tissue death). If the infarct involves a large area of the heart, sudden death will result. If the area of infarct is of a lesser degree, the dead tissue is replaced with fibrous connective tissue and the efficiency of the heart is greatly decreased. (Remember, cardiac cells cannot undergo mitosis and thus cannot regenerate lost tissue.)

HF and GDMT

The lifetime risk of developing HF is 20% for Americans 40 years of age and older, with more than 650,000 new HF cases diagnosed every year. The mortality risk steadily increases each year after diagnosis, and so it is imperative that patients receive drug therapy that has been shown to decrease mortality and improve symptoms; refer to **Table 13-4** for drug classes with proven mortality (decrease chance of death) benefits in HFrEF. The American College of Cardiology/American Heart Association (ACC/AHA)guidelines have been recently updated and the Task Force recommends that most patients with HFrEF should receive GDMT including an ACE inhibitor, an ARB, or an angiotensin receptor-neprilysin inhibitor (ARNI), a β-blocker, and an aldosterone antagonist. Diuretics should be recommended if patients have evidence of fluid retention. Digoxin can be beneficial to decrease hospitalizations for HF, and hydralazine and isosorbide dinitrate are recommended as additional therapy for symptomatic self-described African American patients on optimal therapy with other GDMT therapy or in non–African American patients who cannot be given ACE inhibitor, ARB, or ARNI because of intolerances. In order to comprehend the role of the many agents utilized in HFrEF, an understanding of **afterload**, **preload**, and **neurohormonal** activation is required.

TABLE 13-4
Drug Classes Shown to Reduce Death When Used in Heart Failure

Drug Class	Mortality Data
ACE inhibitor	Yes
ARB	Yes
ARNI	Yes

Beta-blockers	Yes
Aldosterone antagonists	Yes
Hydralazine/isosorbide	Yes
Diuretics	No
Digoxin	No

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor.

Cardiac Workload

A common finding in HF is an increase in workload and a decrease in CO. As discussed in the Hypertension section of this chapter, CO can be determined by the following equation: CO = HR × SV. There are four major determinants that effect CO, which include preload, afterload, contractility, and HR. However, this section will only discuss the role of afterload and preload on CO.

- *Afterload* is tension that develops in the ventricular wall as systole (when the heart ejects blood) occurs. Afterload is affected by systemic vascular resistance (SVR), or how constricted blood vessels are in the body. In HFrEF, the left ventricle is characterized by a decreased ability of the heart to contract. Therefore, the higher the SVR, the lower the amount of blood that is able to be ejected to the rest of the organs in the body owing to the ventricle's inability to overcome the resistance. Arterial vasodilators play an important role in HFrEF because they help to decrease SVR and in turn increase stroke volume in patients with severe ventricular dysfunction.
- *Preload* is the volume of blood in the ventricles at the end of diastole (filling). The volume is maximal at the end of diastole (filling of the heart). Preload may be increased in HF leading to fluid accumulating the lungs. Preload may be reduced by

decreasing peripheral venous volume and by peripheral venous dilation. This is accomplished with the use of diuretics and venous vasodilators.

Neurohormonal Activation

With a reduction in CO comes circulatory changes and compensatory mechanisms that lead to changes in HR and cardiac contractility, salt and water retention, and constriction of peripheral blood vessels. These alterations are meant to maintain cardiovascular homeostasis and this is commonly referred to as neurohormonal activation. Although these changes are initially beneficial, they end up becoming detrimental in the long run and pharmacotherapy is used to minimize these effects. The compensatory mechanisms that occur include activation of the SNS and activation of the RAA system. Activation of the sympathetic system occurs early in the course of the disease. Increased levels of norepinephrine (NE) are released and this sustained activation and release leads to negative effects on the heart, kidneys, and peripheral vasculature. Increased SNS stimulation to the kidney leads to a reduction in renal blood flow because of peripheral vasoconstriction of the afferent arteriole. This results in the release of renin, which is ultimately responsible for the formation of angiotensin II, a potent vasoconstrictor. Angiotensin II also promotes the release of aldosterone from the adrenal glands. Activation of the RAA system leads to increased sodium and water retention and vasoconstriction, all of which affect the pathogenesis of HF. As such, drugs such as ACE inhibitor, ARBs, ARNI, diuretics, and aldosterone antagonists all play a role in decreasing the deleterious effects of the RAA system.

Activation of the SNS is also harmful to the heart because NE decreases β_1-receptor sensitivity on the surface of myocardial cells. Overtime, this leaves the myocyte less responsive to adrenergic stimulation and further decreases myocardial contractility. Agents such β-blockers help to upregulate the β_1-receptors, and cardiac glycosides, such as digoxin, help to decrease SNS outflow.

ACE Inhibitors

ACE inhibitors represent one of the cornerstone agents in treating HFrEF. These are considered first-line agents for HFrEF and they should be initiated promptly and continued indefinitely. ACE inhibitors decrease mortality and improve symptoms by blocking the detrimental effects of angiotensin II and aldosterone. ACE inhibitors can produce cough and angioedema and caution should be exercised when given to patients with low BP, renal insufficiency, or elevated potassium (>5.0 mEq/L). **Table 13-5** lists examples of ACE inhibitors, along with recommended doses used in HFrEF.

TABLE 13-5
ACE Inhibitors and Common Doses Used in Heart Failure

ACE Inhibitor	Initial Dose	Maximum Dose
Captopril	6.25 mg TID	50 mg TID
Enalapril	2.5 mg BID	10–20 mg BID
Fosinopril	5–10 mg daily	40 mg daily
Lisinopril	2.5–5 mg daily	20–40 mg daily

ACE, angiotensin-converting enzyme.

Angiotensin II Receptor Blockers

The efficacy of ARBs are similar to ACE inhibitors and they have been found to decrease mortality and morbidity in clinical trials. These agents are recommended in patients with HFrEF who are intolerant to ACE inhibitors because of cough and angioedema. These agents also block the effects of angiotensin II and aldosterone. Unlike ACE inhibitors, these agents do not inhibit the breakdown of bradykinin and are associated with a lower risk of angioedema and cough. Caution should be exercised when given to patients with low systemic BP,

renal insufficiency, or elevated potassium (>5.0 mEq/L). **Table 13-6** lists examples of ARBs, along with recommended doses used in HFrEF.

TABLE 13-6
Angiotensin II Receptor Blockers (ARBs) and Common Doses Used in Heart Failure

ARBs	Initial Dose	Maximum Dose
Candesartan	4–8 mg daily	32 mg daily
Losartan	25–50 mg daily	50–150 mg daily
Valsartan	20–40 BID	160 mg BID

Angiotensin Receptor-Neprilysin Inhibitor

Neprilysin is an endopeptidase that degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. The drug sacubitril blocks the effects of neprilysin and increases the endogenous vasoactive peptides resulting in the following effects: reduction in neurohormonal activation, vascular tone, cardiac fibrosis, and sodium retention and an increase in diuresis. Combined inhibition of angiotensin II and neprilysin was superior to either approach alone in studies. Sacubitril/valsartan (Entresto®) was found to have a significantly lower risk of mortality and hospitalization when used in HF. Guidelines recommend that an ARNI replace an ACE inhibitor or ARB to further reduce morbidity and mortality. Use of an ARNI is associated with hypotension and a very low risk of angioedema. Caution should also be exercised when given to patients with renal insufficiency or elevated potassium (>5.0 mEq/L). An ARNI should not be administered concomitantly with ACE inhibitors because of the increased risk of angioedema. Before

initiating an ARNI, patients must wait 36 hours when switching from or to an ACE inhibitor.

NEED TO KNOW

Sacubitril inhibits neprilysin and increases endogenous vasoactive peptides. When switching from an ACE inhibitor to an ARNI, patients must wait 36 hours after stopping the ACE inhibitor to prevent the risk of angioedema.

Beta-Adrenergic Blockers

Along with an ACE, ARB, or ARNI, β-blockers are essential first-line agents in HFrEF. Treatment with β-blockers improves systolic function and reduces symptoms. There are three approved β-blockers for HFrEF. In clinical trials, these agents decreased hospitalizations and mortality. The three approved β-blockers are bisoprolol, carvedilol, and metoprolol succinate. These agents are recommended for all patients to reduce morbidity and mortality. Although these agents are beneficial in HFrEF, they may exacerbate HF with initiation or dose titration and should be performed in stable patients. Beta-blockers should not be initiated during an acute exacerbation and should be deferred until the patient's condition improves. **Table 13-7** lists the approved β-blockers, along with doses used in HFrEF.

TABLE 13-7
Beta-Adrenergic Blockers and Common Doses Used in Heart Failure

Beta-Blocker	Initial Dose	Maximum Dose
Bisoprolol	1.25 mg daily	10 mg daily
Carvedilol	3.125 mg BID	25–50 mg BID
Metoprolol succinate	12.5–25 mg daily	200 mg daily

Aldosterone Antagonists

Spironolactone and eplerenone and have been underutilized in the past; however the use of these agents has been increased because of their expansion in the guidelines. These agents have been found to decrease mortality and hospitalizations and improve symptoms. Aldosterone antagonists exert minimal diuresis; however, researches have speculated that aldosterone antagonists reduce aldosterone-induced vascular damage and myocardial fibrosis. Guidelines recommend the addition of an aldosterone antagonist in all patients, despite their level of symptoms, taking an ACE inhibitor or ARB and β-blocker. Before initiation, renal function and potassium must be assessed. These agents should not be used if the serum creatinine is more than 2.5 mg/dL in men or more than 2.0 mg/dL in women and the potassium should be less than 5.0 mEq/L to avoid renal insufficiency and hyperkalemia.

Hydralazine and Isosorbide Dinitrate

These agents were one of the first vasodilators studied in HFrEF. In past clinical trials, African American patients did not have as good a response to ACE inhibitor as did Caucasian patients, but had a better response to hydralazine–isosorbide than did Caucasian patients. One landmark study showed that the addition of hydralazine–isosorbide to standard HF therapy decreased mortality and reduced HF hospitalizations. Hydralazine is a direct-acting arteriolar vasodilator and decreases afterload, whereas isosorbide dinitrate is a venous vasodilator and decreases preload. Guidelines recommend this combination to reduce mortality and morbidity for symptomatic self-described African American patients on background optimal therapy. It is also a reasonable alternate for patients who cannot take ACE inhibitor or ARBs because of intolerances. **Table 13-8** lists the common doses used in HFrEF.

TABLE 13-8

Combination Doses of Hydralazine and Isosorbide Dinitrate in Heart Failure		
Hydralazine/Isosorbide Dinitrate	**Initial Dose**	**Maximum Dose**
Fixed-dose combination	37.5 mg hydralazine/20 mg isosorbide dinitrate TID	75 mg hydralazine/40 mg isosorbide dinitrate TID
Hydralazine/Isosorbide dinitrate	25–50 mg hydralazine/20–30 mg isosorbide dinitrate TID	100 mg hydralazine/40 mg isosorbide dinitrate TID

Cardiac Glycosides, Digoxin

The cardiac glycosides are a group of drugs found in a number of plants (foxglove). Because of their natural source, these drugs have been used in a variety of medicines for hundreds of years. As early as 1785, there was published information describing the use of foxglove to treat dropsy (edema) and other diseases. It is currently used to treat arrhythmias and HFrEF. In the past, the beneficial effects of digoxin in the treatment of HFrEF were thought to be because of an increase in the force of the heart's contraction (**inotropic** effect). However, digoxin has other effects aside from the inotropic effect. Digoxin has beneficial neurohormonal and autonomic effects caused by restoring the balance between sympathetic and parasympathetic outflow. Digoxin has a narrow therapeutic index with much toxicity that requires monitoring. Several studies in the past evaluating digoxin have confirmed a clinical benefit, including a reduction in hospitalizations. However, there is no reduction in mortality, and recently, newer studies have shown possible increase risk of death with the use of digoxin. Therefore, the use of digoxin has decreased over time.

Digoxin

Cardiac glycosides specifically, digoxin, combine with a receptor in the cardiac muscle called sodium/potassium adenosine

triphosphatase. When the drug combines with this receptor site, the “normal cellular pump” is inhibited, which results in an increase in accumulation of intracellular sodium ions. With the increase of intracellular sodium, through a number of membrane mechanisms, there is also an increase in intracellular calcium. This increase in the amount of calcium greatly enhances the contractile apparatus and increases the strength of contraction of the myocardium (positive inotropic effect). The increase in the force of contraction occurs in both a normal and a failing heart, but the force of contraction is greatly increased in a failing heart. Digoxin also binds to receptors in vagal afferent fibers thus sensitizing baroreceptors, resulting in a reduction of sympathetic outflow and an increase in parasympathetic stimulation of the heart. Adverse effects are frequent and range from minor to severe (even death). It is estimated that 25% of hospitalized patients who are treated with digoxin suffer signs of toxicity. Some of these signs include: (1) alteration of cardiac rhythm and conduction, or even complete heart block; (2) all types of arrhythmias; (3) conduction disturbance; (4) gastrointestinal effects, including nausea, vomiting, diarrhea, and abdominal pain; (5) neurologic effects, including headache, muscle weakness, facial pain, delirium, hallucinations, and convulsions; and (6) visual disturbances, including blurred vision and color blindness. Blood levels are routinely checked to determine if toxic levels are present. Therapeutic digoxin levels depend on the indication, but a target level of 0.5–1.0 ng/mL for HFrEF and 0.8–1.2 ng/mL for atrial fibrillation are considered appropriate. Renal function should be monitored to determine appropriate dosing, and electrolytes, especially potassium, should be monitored periodically because abnormalities can cause digoxin toxicity.

NEED TO KNOW

Digoxin has toxicities that may affect the heart, gastrointestinal tract, and central nervous system. Monitoring of blood levels of this drug should be routinely conducted to assure toxicity will not occur.

Angina and the Effects of Nitrates

Angina pectoris is a painful sensation that occurs as a result of ischemia (lack of oxygen to the cardiac muscle). It usually is precipitated by anything that increases oxygen need, such as exercise/stress, excitement, or digestion of a heavy meal. This type of angina, because it is predictable, is classified as stable angina. It usually is relieved by rest or terminating the activity that has caused it. Because the heart has no pain fibers, angina is a referred type of pain that probably is mediated through the autonomic nervous system. An individual feels the pain in mid-chest and often radiating to the left shoulder and the arm and neck, but the pain also can occur in the right shoulder and arm, depending on the site of myocardial ischemia.

The major types of drugs that improve the flow of oxygen to the myocardium, particularly in the stable type of angina, are the drugs that cause peripheral and coronary vasodilation. These drugs are called nitrates and cause relaxation and vasodilation that occur in the coronary vessels as well as in all the vessels of the body. The vasodilation causes an overall decrease in BP and a decrease in cardiac work. By decreasing cardiac work load, there is less oxygen demand on the myocardium and thus a decrease in pain. Nitrates may be used for chronic therapy and for acute relief of chest pain.

Nitrates

- Nitrates are very effective and are perhaps the most important drugs in relieving acute attacks of angina. However, certain undesirable adverse effects can occur, including throbbing headache, flushing of the face, dizziness, postural hypotension, and gastrointestinal irritation. The most commonly used nitrate for relieving acute attacks of angina is nitroglycerin. Patients

administer this sublingually for a total of three doses in 5-minute intervals. Patients should contact 911 after the first dose.

- There are many forms of nitrates available and they are administered according to the patient's need. It should be noted that repeated administration of these agents leads to development of tolerance, which occurs rather rapidly if the medication is used too often. In order to avoid tolerance, some cardiologists use intermittent therapy (i.e., drug-free periods). Nitrates such as isosorbide dinitrate (Isordil®) and isosorbide mononitrate (Imdur®) are used daily for chronic relief of angina symptoms.
- **Table 13-9** lists examples of nitrates, along with available dosage forms, onset of action, and duration.

TABLE 13-9
Available Nitrate Agents

Drug	Dosage Form	Onset of Action	Duration
Nitroglycerin	IV	Immediate	3–5 min
Nitrol®	2% Ointment	15–30 min	7 h
Nitrostat®	Sublingual	1–3 min	25 min
Nitro-Bid®	Transdermal	30 min	10–12 h
Isosorbide dinitrate (Isordil®)	PO	60 min	8 h
Isosorbide mononitrate (Imdur®)	PO	30–45 min	12–24 h

NEED TO KNOW

Anginal pain may be described as a burning or heavy sensation of the chest and may be accompanied by shortness of breath. These symptoms are also common in patients experiencing a MI, so immediate treatment and transport to a medical facility is indicated if symptoms do not respond to rest and/or the administration of medications such as nitroglycerin. Nitroglycerin should be administered sublingually every 5 minutes for a total of three doses. Patients should contact 911 after taking the first dose.

Other Categories of Antianginal Drugs

In addition to the nitrates, there are other agents that are used either alone or with the nitrates in treating angina. These drugs are the β-blockers, CCB, and ranolazine (Ranexa®).

Beta-Blockers in Angina

The β-blockers decrease HR, reduce BP, and decrease cardiac contractility without any major effect on CO. These effects decrease the amount of cardiac work and, therefore decrease the oxygen demand by the myocardium. Beta-blockers are used in long-term treatment of angina and are particularly effective in increasing tolerance to angina that is brought on by exercise.

CCBs in Angina

The CCBs decrease the influx of calcium ions into the cardiac muscle as well as the vascular smooth muscle. In the vascular smooth muscle, the vasodilation decreases venous return and thus causes less cardiac work and oxygen demand. In addition, the CCBs have been shown to dilate the larger coronary arteries and decrease vasospasm, which is another mechanism of angina symptoms.

Ranolazine (Ranexa)

Ranolazine (Ranexa) is a newer agent used in chronic angina. This agent is typically given in combination with β-blockers, CCBs, and nitrates in patients who continue to experience angina symptoms despite receiving those agents. The mechanism of action is not clearly understood but it is believed to inhibit inward sodium channels in ischemic cardiac myocytes. This reduces intracellular sodium concentrations and the calcium influx via Na^+–Ca^{2+} exchanges. Decreased intracellular calcium leads to improved blood flow through the heart. Additionally, ranolazine improves angina symptoms without changing HR or BP. This agent is particularly useful for patients who cannot take or tolerate higher doses of β-blockers, CCBs, and nitrates because of hypotension. Major adverse reaction is prolongation of the QT interval on electrocardiogram (ECG). Patients should have a baseline ECG and periodically throughout therapy. It may also cause constipation, nausea, dizziness, and headaches. It is contraindicated in patients with severe liver disease or cirrhosis.

NEED TO KNOW

Ranolazine decreases angina symptoms without lowering HR or BP. This agent can cause life-threatening arrhythmias.

Conduction System of the Heart

The heart is dependent on the continual contraction of the myocardium. The blood supply to the heart is carried by coronary arteries that branch from the aorta immediately after the aorta leaves the left ventricle. Normally, the blood flow to the coronary arteries is dependent on the force of contraction of the myocardium, and any interference with normal blood flow to the heart results in decreased efficiency and contraction. The constant supply of blood to the heart and to the rest of the body is under the control of a specialized conduction system of the heart. One of the unique characteristics of this system is that it creates and maintains its own rhythm (autorhythmicity). This characteristic enables the heart to initiate and maintain its own rate of contraction.

The normal rate of contraction is initiated by a specialized group of cells called the **sinoatrial (SA) node**. When the SA node depolarizes or fires a signal, the impulse is spread over both atria to the atrioventricular (AV) node. The AV node then causes depolarization of the ventricles. The impulse from the AV node then travels through the bundle of His, located in the intraventricular septum, through the left and right bundle branches, and into the Purkinje fibers (**Figure 13-3**).

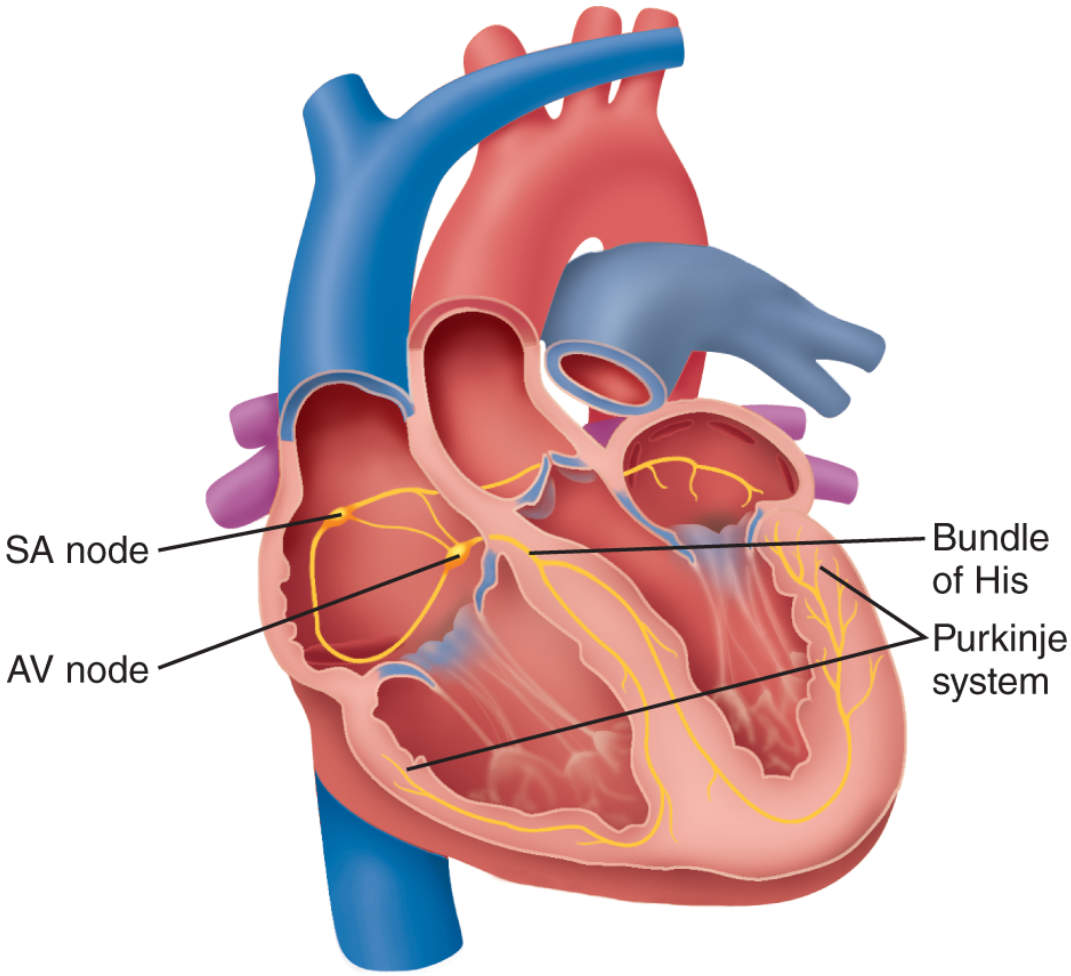


FIGURE 13-3 Conduction system of the heart.

It is through this conduction system that the contraction of the chambers of the heart is coordinated. Although the heart has its own conduction system, the SA node also receives nerve supply from both divisions of the autonomic nervous system. The sympathetic nerves release NE, which increases HR (positive **chronotropic** effect) and increases the force of contraction (positive inotropic effect). The parasympathetic nerves release acetylcholine, causing a decrease in HR (negative chronotropic effect) and a decrease in force of contraction (negative inotropic effect). With the opposite effects of both autonomic divisions, the homeostatic balance of the body regarding blood supply is maintained.

Because of the electrical activity of the heart, characteristic wave forms known as the ECG can be recorded to evaluate normal as well

as pathologic conditions of the heart.

Definition and Types of Arrhythmias

An arrhythmia is an irregularity or loss of rhythm of the electrical activity in the heart. Throughout this chapter, the term arrhythmia will be used to denote an irregularity or loss of cardiac rhythm.

Arrhythmias may be manifest in the diseased heart as well as the normal heart through the influence of exercise or drugs. The severity of symptoms may range from mild palpitations to complete cardiac arrest identified by an ECG. Both the atria and the ventricles develop arrhythmias. Generally, most arrhythmias occur when there is a defect in the AV node causing abnormal impulse formation, or a defect in conduction, or both. The automatic firing of the AV node (pacemaker) is under the influence of the proper balance between sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}). Each ion plays a significant role in the cardiac action potential (nerve impulse). When an arrhythmia occurs, there is a disturbance in one or all of these ions. The overall action of the majority of the antiarrhythmic drugs is to correct the movement or imbalance of these ions and thus restore proper function.

There are a number of arrhythmias that occur in the atria, the ventricles, and ectopic foci (a beat is one that is triggered by an area other than the SA node). Arrhythmias that originate in the atria or around the AV node are referred to as “supraventricular arrhythmias” (above the ventricles). The most serious type of arrhythmia is “ventricular fibrillation,” which, if not treated immediately, causes cardiac arrest and death. **Table 13-10** lists some common types of arrhythmias, their location, and characteristic HRs (beats/minute).

TABLE 13-10
Types of Arrhythmias

Arrhythmia	Location	Rate (beats/min)
Tachycardia	Atria/ventricle	>100

Atrial flutter (supraventricular)	Atria	200–350 atrial rate
Atrial fibrillation (supraventricular)	Atria	>300 atrial rate
Ventricular fibrillation	Ventricle	>300–400 (uncoordinated contractions, no cardiac output or pulse)
Premature contractions	Atria/ventricle	Variable
Bradycardia	Atria/ventricle	<60

Reasons for Converting and Causes of Arrhythmias

There are many reasons for converting cardiac arrhythmias:

1. They may be a signal or warning of a potential problem, or, more likely, a problem that already has occurred.
2. They cause extreme anxiety and fear in the patient.
3. They may indicate an infarction has occurred.
4. They can greatly decrease the efficiency of the heart.
5. They decrease O_2 delivery to the heart.

Antiarrhythmic Drug Classes

In general, there are four classifications of antiarrhythmic agents, and the various drugs are classified on the basis of overall mechanism of action. Class I drugs are the sodium channel blockers, class II drugs are β-blockers, class III drugs are potassium channel blockers, and class IV drugs are the CCBs. The most commonly used classification system is the Vaughan Williams Classification of Antiarrhythmic Drugs.

Class I

The class I antiarrhythmics are further divided into three subgroups on the basis of their specificity for sodium channels: Ia, Ib, and Ic.

- Class Ia: These agents block both sodium and potassium channels, resulting in a decrease in depolarization and prolongation of the repolarization phase. Prolongation of the repolarization phase increases the QT interval and places the patient at risk for arrhythmias, especially torsades de pointes. Because of their side effect profile, the use of these agents has fallen out of favor. These drugs should be used in caution or require a dose reduction in renal or liver impairment. They may worsen symptoms of HF. Examples include disopyramide (Norpace®), quinidine (Quinaglute®), and procainamide (Pronestyl®)
- Class Ib: These agents block sodium channels but cause a much less significant decrease in depolarization compared with the class Ia agents. These agents are used only for ventricular arrhythmias and are seldom used. These drugs should be avoided or used with caution at a reduced dose in patients with liver impairment. They may also worsen symptoms of HF. Examples include lidocaine (Xylocaine®) and mexiletine (Mextil®).

NEED TO KNOW

Class Ia antiarrhythmics block both sodium and potassium channels. These drugs may prolong the QT interval and cause torsades de pointes, a potentially fatal arrhythmia.

- Class Ic: These agents block sodium channels and decrease depolarization. They are used for supraventricular arrhythmias and are contraindicated in patients with structural heart disease. Propafenone may increase the risk of death if used in patients with HF. Propafenone may cause bronchospasm and is contraindicated in patients with uncontrolled severe obstructive lung disease. Examples include flecainide (Tambocor®) and propafenone (Rythmol®).

NEED TO KNOW

Propafenone is a class Ic antiarrhythmic that is contraindicated for use in patients with uncontrolled bronchospasms or uncontrolled severe obstructive lung disease.

Class II

These drugs are the β-blockers and they decrease the effects of sympathetic stimulation and endogenous catecholamines such as NE and epinephrine. They are routinely used for controlling ventricular rate in supraventricular tachycardia and as chronic therapy when rate control is decided over a rhythm control strategy. Commonly used agents include propranolol (Inderal), esmolol (Brevibloc®), atenolol (Tenormin), and metoprolol tartrate (Lopressor).

Respiratory therapists should take note of the β-blocker a patient is receiving. As discussed in the Hypertension section of this chapter, recall that β-blockers can be β_1 (cardiac) selective and nonselective (block β_2 [pulmonary] receptors). Thus, when treating a patient who is receiving high doses of selective β_1-blockers (high doses may lose selectivity to the β_1-receptor) or nonselective β-blockers, and if the patient requires a bronchodilator, it is important to use an anticholinergic (i.e., ipratropium for a short-acting dilator or tiotropium for long-acting bronchodilation) or patients may require higher doses of inhaled β_2-agonists.

Class III

These agents are the potassium channel blockers and they represent one of the most commonly used antiarrhythmic classes. These agents prolong the action potential of the cardiac cell by inhibition of potassium channels. When this occurs, the refractory period is prolonged and an increase in the QT interval is observed. Similarly to the class Ia agents, this places the patient at an increased risk of developing torsades de pointes. These agents are used for ventricular arrhythmias and supraventricular arrhythmias; however,

some exceptions exist. Dronedarone (Multaq®) is only indicated for nonpermanent atrial fibrillation because of an increase in the rate of cardiovascular death, stroke, and HF in patients with permanent atrial fibrillation. Other drugs in this class (except dronedarone) may be used in patients who have preexisting HF. These agents are usually initiated in the hospital setting to monitor for proarrhythmic effects. Dofetilide should not be used in patients with severe renal impairment. Of importance for a respiratory care professional, amiodarone and less commonly dronedarone may cause irreversible pulmonary fibrosis or pneumonitis that may occur at high doses in patients receiving treatment for prolong periods of time and for some patients for unknown reasons. Examples of the class III antiarrhythmics include amiodarone (Cordarone®, Pacerone®), sotalol (Betapace®), ibutilide (Corvert®), dofetilide (Tikosyn®), and dronedarone (Multaq).

Class IV

The CCBs block the movement of calcium through “voltage-gated” L channels, resulting in negative chronotropic, dromotropic, and inotropic effects. When these drugs interfere with calcium influx, they decrease the rate of firing of the SA and AV nodes and thus slow the HR. The main use of these agents is treating AV nodal arrhythmias and other supraventricular tachycardias. Examples of the class IV agents include verapamil (Calan) and diltiazem (Cardizem).

Examples of Antiarrhythmic Drugs

Table 13-11 lists the various antiarrhythmic drugs according to class, number, mechanism of action, type of arrhythmia treated, and pertinent side effects. This table is general but emphasizes the variety of drugs available in treating various kinds of arrhythmias.

TABLE 13-11

Antiarrhythmic Drugs

Class and Drug	Mechanism of Action	Type of Arrhythmia	Side Effects
Class Ia			
Disopyramide	• Na^+ and K^+ channel blockers	Supraventricular and ventricular	• Anticholinergic (dry mouth, urinary hesitation, blurred vision) • Proarrhythmic
Quinidine			• Cinchonism (hearing and visual disturbances) • Hypotension • Proarrhythmic
Procainamide			• Hypotension • Lupus-like syndrome (extended use) • Low white blood cells (can be fatal) • Proarrhythmic
Class Ib			
Lidocaine	• Na^+ channel blockers	Ventricular	• Hypotension • Drowsiness • Seizures • Proarrhythmic
Mexiletine		Ventricular	• Diarrhea • Seizures • Blood dyscrasias • Liver failure • Proarrhythmic
Class Ic			
Flecainide	• Na^+ channel blockers • Propafenone also has weak β-blocking properties	Supraventricular and ventricular	• Dizziness • Blurred vision • Proarrhythmic • Do not use in structural heart disease
Propafenone			• Dizziness • Blurred vision • Bronchospasm • Proarrhythmic • Do not use in structural heart disease
Class II			
Propranolol	Beta-blockers	Ventricular and supraventricular	• Bradycardia • Hypotension • Fatigue • Depression • Bronchospasm (nonselective β-blockers and high-dose selective β-blockers)
Esmolol		Supraventricular	
Metoprolol		Supraventricular	
Atenolol		Ventricular and supraventricular	
Class III			
Amiodarone	• K^+ channel blocker • Sotalol is a nonselective β-blocker at low doses	Ventricular and supraventricular	• Corneal microdeposits • Skin (photosensitivity) • Thyroid (hypo- or hyperthyroidism) • Hepatotoxicity • Pulmonary fibrosis or pneumonitis • Proarrhythmic
Ibutilide		Supraventricular	• Proarrhythmic
Dronedarone		Supraventricular	• Diarrhea • Dermatitis • Pulmonary fibrosis or pneumonitis • Worsening heart failure • Proarrhythmic
Dofetilide		Supraventricular	• Chest pain • Proarrhythmic
Sotalol		Ventricular and supraventricular	• Bradycardia • Dyspnea

			• Proarrhythmic
Class IV			
Verapamil	Ca^{2+} channel blockers	Supraventricular	• Bradycardia • Hypotension • Edema • Constipation (verapamil)
Diltiazem		Supraventricular	

NEED TO KNOW

Amiodarone is a class III antiarrhythmic with many side effects, including pulmonary fibrosis and pneumonitis.

Coagulation Process

Coagulation is a normal function that occurs when trauma causes injury to a blood vessel. A clot forms to prevent further loss of blood from the injured area. This protective mechanism is called hemostasis and is important in maintaining the homeostatic balance in the body. Platelets first adhere to macromolecules in the subendothelial regions of the blood vessel. Then through a series of events, they aggregate to form a plug. This is accomplished by the release and activation of various proteins and receptors. P2Y1 and P2Y12 receptors on the platelet are activated by adenosine diphosphate (ADP) leading to activation of the fibrin-binding protein glycoprotein IIb/IIIa (GPIIb/IIIa) and cyclooxygenase-1 (COX-1) to promote platelet aggregation. COX-1 is then responsible for the formation of thromboxane A_2 (TXA_2) and additional platelet activation. The platelet plug then leads to local activation of plasma coagulation factors, leading to generation of a fibrin clot that reinforces the plug. Occasionally, the clotting mechanism (coagulation) becomes too active or, as a result of a narrowing of a blood vessel lumen, a clot is formed and a thrombus occurs. If the thrombus completely occludes or partially impairs the blood flow to the local tissue, it can lead to an infarct or necrosis. If the thrombus becomes dislodged, an embolus or clot is released into the bloodstream and can travel to various organs of the body, occluding other vessels. Tissues that are particularly prone to thrombus and embolism damage are the heart, lungs, and brain. Antiplatelets and anticoagulant drugs are administered to control the formation of thrombi or emboli by preventing clot formation.

In order to understand how anticoagulant drugs function, a brief review of the process of coagulation is presented. It is not necessary to memorize all the factors and pathways included in the clotting mechanism. In this text, the mechanism is reduced to three stages (**Figure 13-4**). At the end of each stage, three important substances are formed: factor Xa, thrombin, and fibrin. The anticoagulant drugs

work at various stages by affecting the formation of one of these three substances and thus prevent clotting.

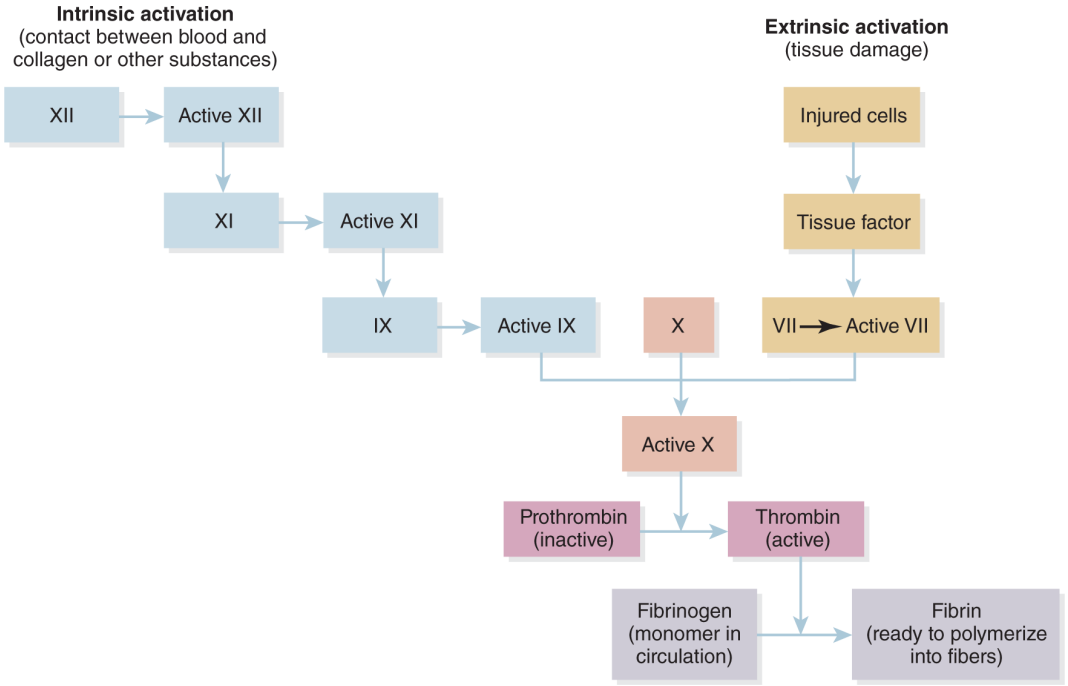


FIGURE 13-4 The clotting cascade.

Description

Anticoagulant Drugs

The most frequently used anticoagulant drugs are the oral anticoagulants and heparin. For many years, the most commonly used oral anticoagulant was warfarin (Coumadin®); however, a newer class of oral agents referred to as the direct-acting oral anticoagulants (DOACs) are becoming extremely popular in clinical practice because of their ease of administration and minimal monitoring. The main therapeutic effect of these drugs is to prevent the formation of a thrombosis. The diseases that result from thrombosis include stroke, deep vein thrombosis (DVT), pulmonary thrombosis, and MI. It is important for the respiratory care practitioner to recognize these drugs and their effects, particularly if a patient on anticoagulant therapy requires arterial blood gas sampling (extra precautions must be taken to avoid or minimize hematoma

formation at the site of an arterial puncture). These agents will lead to increased bleeding at the site of blood sampling and increased time to clot.

Unfractionated Heparin

Unfractionated heparin (UFH) is a naturally occurring substance found primarily in mast cells. It is administered via an injection, and it is used for the prevention and treatment of arterial and venous thrombosis. Heparin exerts its anticoagulant effect by binding to antithrombin and the subsequent inhibition of factors IXa, Xa, XIa, XIIa, and IIa. Because heparin is broken down in the stomach by hydrochloric acid, it is administered by injection (SC or IV). As a result, heparin almost always is administered in a hospital setting or an inpatient facility, where it can be monitored carefully. Monitoring parameters include activated partial thromboplastin time (aPTT), platelets, and bleeding. Adverse effects include bleeding. During the administration of heparin through the IV route, if drug levels become too high, it can cause bleeding in the mucosa (petechiae) and gastrointestinal bleeding. Other side effects include heparin-induced thrombocytopenia (HIT), which is an immune reaction that can lead to platelets clumping together and forming clots.

Low-Molecular-Weight Heparins

The low-molecular-weight heparins (LMWHs) have a similar anticoagulant effect as does UFH. Their therapeutic use is increasing over UFH owing to better SC absorption; a longer duration of action, allowing for less frequent dose administration, and a much lower risk of HIT. These agents are used for the prevention and treatment of DVT and pulmonary embolism (PE). These agents are administered by injection (SC) and, as a result, they may be utilized in both the inpatient and outpatient setting. Caution should be utilized when using these agents in patients who are obese, have poor renal function, and in pregnancy. Although the risk of HIT is low with these agents, platelets need to be monitored and these agents are contraindicated

in patients who have experienced HIT with heparin. Enoxaparin (Lovenox) and dalteparin (Fragmin) are LMWHs.

Factor Xa Inhibitors, Injectable

These agents are available as both injectable and oral formulations. The oral formulations will be discussed later in the chapter. These agents inhibit factor Xa in the coagulation cascade resulting in the prevention of a thrombus by decreasing thrombin formation. They are used for the prevention and treatment of DVTs and PE and they may be used in patients who have experienced HIT with UFH or LMWH. These agents are administered by injection (SC), and as a result, they can be utilized in the inpatient and outpatient setting. Similarly to the LMWH, renal function and weight must be assessed, because this will influence dosing strategies. Fondaparinux (Arixtra®) is an example of an injectable factor Xa inhibitor.

Direct Thrombin Inhibitors, Injectable

These agents are available as both injectable and oral formulations. The oral formulations will be discussed later in the chapter. The thrombin inhibitors reversibly inhibit coagulation by preventing thrombin-mediated effects, such as cleavage of fibrinogen to fibrin and thrombin-induced platelet aggregation. These agents are utilized in the inpatient setting as an anticoagulant for patients receiving percutaneous coronary intervention and they are first-line agents for management of HIT. These agents are administered by injection (IV). Monitoring parameters include aPTT, renal function, and hepatic function. Argatroban and bivalirudin (Angiomax®) are examples of injectable direct thrombin inhibitors.

Oral Anticoagulants, Coumadin

Warfarin (Coumadin) is one of the most widely used oral anticoagulants in medicine. It is primarily used to reduce the formation of clots; however, its use is complicated by a narrow therapeutic

index and several drug–drug and drug–dietary interactions. Warfarin exerts its effects by inhibiting the activation of the vitamin K-dependent clotting factors II, VII, IX, and X. Warfarin is given orally; however, because of the long half-lives of some of the coagulation factors, the full antithrombotic effect of warfarin is not achieved for several days. Because of this, it is a common practice to overlap warfarin with an injectable anticoagulant, such as UFH or LMWH, until warfarin is therapeutic. Once therapeutic, the injectable agent is discontinued and warfarin is continued. Monitoring includes the international normalized ratio (INR) and the goal for most indications is 2–3 and 2.5–3.5 for most mechanical cardiac valve replacements. The most common adverse effect is bleeding. Severe adverse effects include intracranial bleeding, purple toe syndrome, and skin necrosis. It is imperative to be vigilant and to assess drug–drug interactions when starting any agent in a patient receiving warfarin. Patients should also be counseled on dietary interactions, including maintaining a consistent diet of vitamin K–containing foods such as green leafy vegetables. Fluctuations in the consumption of these foods may increase or decrease the effectiveness of warfarin.

Oral Anticoagulants, DOACs

Warfarin has been the oral anticoagulant of choice for many years. The introduction of the DOACs as alternative to warfarin represents a major advancement in anticoagulation. In clinical trials, the DOACs have been found to be at least as effective as or more effective than warfarin, and in some cases, safer than warfarin for stroke prevention in atrial fibrillation and venous thromboembolism; however, these agents are not recommended for patients with mechanical heart valves. Several agents are available and their mechanisms have been discussed in earlier sections of the chapter. Dabigatran (Pradaxa®) is an oral direct thrombin inhibitor, and rivaroxaban (Xarelto®), apixaban (Eliquis®), and edoxaban (Savaysa®) are the oral factor Xa inhibitors. Refer to **Table 13-12** for a summary of the available DOACs. These agents confer great benefits over warfarin, including fixed dosing, minimal monitoring, fewer drug and dietary

interactions, and rapid onset and short half-lives, thus precluding the need for overlap with UFH and LMWH. Although efficacy monitoring is not required, weight and renal function must be assessed because this may impact dosing recommendations.

TABLE 13-12
Pharmacology of Direct-Acting Oral Anticoagulants (DOACs)

DOAC	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Savaysa®)
Mechanism of action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Indication	Not indicated for mechanical heart valves			
	• A Fib • VTE treatment/ prophylaxis • Prophylaxis after hip surgery	• A Fib • VTE treatment/prophylaxis • Prophylaxis after hip/knee surgery	• A Fib • VTE treatment/ prophylaxis • Prophylaxis after hip/knee surgery	• A Fib • VTE treatment
Dosing considerations	• Renal dosing	• Renal dosing • Doses >10 mg must be taken with food	• Renal dosing • Dose reduce if > 80 years of age, weight <60 kg, or SCr > 1.5	• Renal dosing
Adverse effects	• Bleeding • Dyspepsia	• Bleeding	• Bleeding	• Bleeding

Antiplatelet Drugs

Antiplatelet agents are a commonly used drug class for the prevention of cardiovascular events. These drugs are available as both oral and intravenous formulations, with aspirin being the most widely used. As previously discussed, platelets provide the initial hemostatic plug at sites of vascular injury and they participate in various pathologic thrombosis that lead to cardiovascular events such as MI and stroke. There are various antiplatelet drugs available today and they each have a unique mechanism in decreasing platelet adhesion and aggregation (**Figure 13-5**). Some of these agents are used alone or in combination for additive or synergistic effects. Aspirin is widely used for both primary (prevent a first MI or stroke) and secondary prevention (prevent another MI or stroke) of cardiovascular events. Other agents are used to prevent restenosis

and thrombosis during angioplasty and vascular stenting of lesions. Refer to **Table 13-13** for a review of the most commonly used antiplatelet agents.

TABLE 13-13
Pharmacology of Antiplatelet Agents

Drug	Mechanism of Action	Indication	Precautions/Side Effects
Aspirin: many trade names	Inhibits COX-1 and the synthesis of TXA_2, a potent mediator of platelet aggregation	• Pain and fever • Prevention and treatment of MI, stroke	• Hypersensitivity and bleeding • Do not use in children <12 years of age due to Reye's syndrome
Dipyridamole (Aggrenox®, contains aspirin)	Decreases platelet aggregation by increasing adenosine and cyclic adenosine monophosphate (cAMP)	• Used together with aspirin to reduce stroke risk	• Headache
Clopidogrel (Plavix®)	*Irreversibly* blocks ADP binding to P2Y12 on the platelet receptor and the subsequent activation of GPIIb/IIIa complex	• Various cardiovascular conditions (similar to aspirin) • Can be used in combination with aspirin • Good alternative for patients who cannot take aspirin because of hypersensitivity reactions	• Bleeding • Proton pump inhibitors (omeprazole) may decrease effectiveness
Prasugrel (Effient®)		• Reduction of stent thrombosis in patients managed with percutaneous coronary intervention	• Bleeding • Contraindicated in history of transient ischemic attack and patients >75 years of age (may be considered in high risk patients with diabetes or history of MI) • Dose reduce in patients weighing <60 kg
Ticagrelor (Brilinta®)	*Reversibly* blocks ADP binding to P2Y12 on the platelet receptor and the subsequent activation of GPIIb/IIIa complex	• Reduction of stent thrombosis in patients managed with percutaneous coronary intervention	• Bleeding • Dyspnea • Do not use with aspirin doses >100 mg/day
Abciximab (ReoPro®)	Inhibits platelet aggregation by blocking GPIIb/IIIa receptors	• Reduction of stent thrombosis during percutaneous coronary intervention (all agents intravenous only)	• Bleeding • Thrombocytopenia
Eptifibatide (Integrilin®)			
Tirofiban (Aggrastat®)			

ADP, adenosine diphosphate; MI, myocardial infarction.

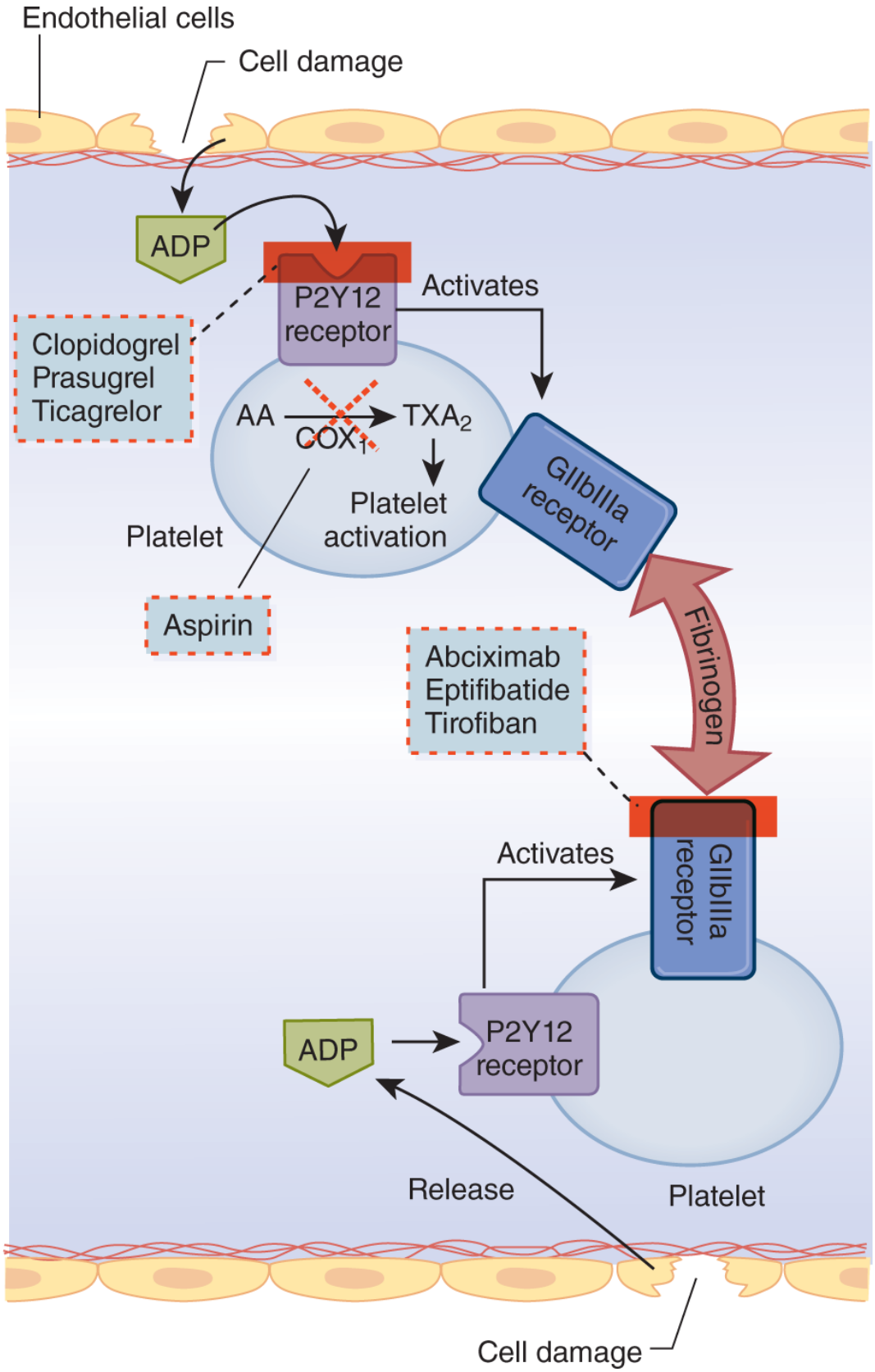


FIGURE 13-5 Mechanism of platelet aggregation and action of antiplatelet agents.

Description

NEED TO KNOW

Prasugrel is contraindicated in patients with a history of a transient ischemic attack.

Lipids

Even though a balanced diet requires proteins, carbohydrates, and lipids (fats), it has been well established that certain disease processes are clinically related to high lipid levels in the blood. Even though cholesterol is essential for the formation of cell membranes, nerve tissue, and lipoproteins, when they occur in sufficiently high levels they permit the formation of fatty deposits in the walls of arterial blood vessels. These plaques, called atherosclerosis, can lead to CAD, stroke, and hypertension. The different components that make up cholesterol will be briefly discussed but is beyond the scope of this chapter. Many drugs are used for lowering cholesterol, and these agents are commonly referred to as hypolipidemic agents. One of the most commonly used drug classes include the 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-Co-A) reductase inhibitor (statins) drugs. Their primary target is lowering **low-density lipoprotein (LDL)** cholesterol. Many randomized controlled trials have indicated a reduction in atherosclerotic cardiovascular disease (ASCVD) from statins in both primary and secondary prevention populations. Therefore, the statins represent the most commonly used hypolipidemic agent. LDL plays a significant role in the pathology of atherosclerosis and is the primary target of hypolipidemic agents. Approximately half of available LDL is taken up by peripheral cells or deposited in coronary arteries, where atherosclerosis can develop. Depending on a patient's past medical history and risk factors, they may be candidates for a "high-intensity" or "moderate-intensity" statin (refer to **Table 13-14,** for examples of moderate- and high-intensity statins). The intensity of the statin refers to the potency of the particular agent or the dose of drug. A high-intensity statin will decrease LDL by at least 50% and more and a moderate-intensity statin will decrease LDL by 30 to less than 50%.

TABLE 13-14

HMG-Co-A Reductase Inhibitor (Statin) Intensities and LDL Reduction		
High-Intensity Statin Therapy	**Moderate-Intensity Statin Therapy**	**Low-Intensity Statin Therapy**
Reduction in LDL by >50%	Reduction in LDL from 30% to <50%	Reduction in LDL <30%
• Atorvastatin, 40–80 mg • Rosuvastatin, 20–40 mg	• Atorvastatin, 10–20 mg • Rosuvastatin, 5–10 mg • Simvastatin, 20–40 mg • Pravastatin, 40–80 mg • Lovastatin, 40 mg • Fluvastatin, 40 mg BID • Pitavastatin, 2–4 mg	• Simvastatin, 10 mg • Pravastatin, 10–20 mg • Lovastatin, 20 mg • Fluvastatin, 20–40 mg • Pitavastatin, 1 mg

LDL, low-density lipoprotein.

In addition to drug therapy, lifestyle modification (i.e., adhering to a healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a health weight) should be emphasized for health promotion and ASCVD risk reduction.

TGs are another target for drug therapy. TGs are synthesized from very-low-density lipoproteins (VLDLs) in the liver. Elevated TGs are typically treated when they exceed 500 mg/dL as it places the patient at increased risk of developing pancreatitis.

Drugs Used in Treatment of Hyperlipidemia

There are currently many drugs available that lower blood lipids. There is a great amount of interest in this area of drug therapy, and many new drugs are continually being developed. It is not the intent of this text to present all these agents in great detail, but the following discussion lists some of the more commonly used hypolipidemic drugs, with a brief description of their mechanism of action and adverse effects.

Statins

Statins lower cholesterol levels by interfering with synthesis in the liver and also lower the lipoproteins, specifically LDLs (refer to Table 13-14 for LDL lowering effects of statins). Effectiveness of statin exceeds that of all the other agents. Adverse effects include severe liver toxicity and myositis (inflammation of the muscles) or rhabdomyolysis (muscle breakdown). The statins include atorvastatin (Lipitor®), simvastatin (Zocor®), pitavastatin (Livalo®), pravastatin (Pravachol®), rosuvastatin (Crestor®), fluvastatin (Lescol®), and lovastatin (Mevacor®).

Bile Acid Sequestrants

These agents work to bind with bile salts in the small intestine. The bile salts are products of cholesterol breakdown and normally are reabsorbed in order to synthesize new cholesterol. Primarily these agents decrease LDL but they may increase TGs. Cholestyramine is not absorbed into the bloodstream, and there are very few side effects beside minor nausea and vomiting. These drugs do produce significant drug interactions because of binding and they must be separated by other drugs 1–4 hours before or 4–6 hours. Bile acid sequestrants include cholestyramine (Questran®), colestipol (Colestid®), and colesevelam (Welchol®).

Niacin (Niaspan®)

Niacin in the form of nicotinic acid lowers the hepatic production of TGs and LDLs. It also increases high-density lipoprotein (HDL) levels more effectively than other anticholesterol drugs. The most common adverse effects include nausea, vomiting, diarrhea, pruritus, hepatotoxicity, and vasodilation. The vasodilation causes extreme flushing in the face and is caused by release of vasodilatory prostaglandins. Also, niacin can increase uric acid levels and glucose; therefore, caution should be exercised in patients with gout and diabetes.

Fibric Acid Derivatives

Fibric acid derivatives interfere with the synthesis of TGs and VLDLs in the liver and increase the level of HDL in the blood. Fibrates are used primarily to lower TGs. Common side effects include nausea, headaches, diarrhea, and skin rash; they also can alter liver function. Most of these agents should be avoided with statins because they can have additive effects and cause rhabdomyolysis. Examples include gemfibrozil (Lopid®), choline fenofibrate (Trilipix®), and fenofibrate (Tricor®).

Cholesterol Absorption Inhibitors

This class of drugs impair dietary and biliary cholesterol absorption at the brush border of the intestine, primarily resulting in a reduction in LDL. No real efficacy is seen with decreasing TGs or increasing HDL. Adverse effects include diarrhea and fatigue. Examples include ezetimibe (Zetia®).

Omega-3 Fatty Acids

The mechanism of omega-3 fatty acids is unclear, but it may be because of reduction in hepatic TG synthesis. The omega-3 fatty acids contain docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and these agents are primarily used for TG lowering; they do not provide LDL reduction. Adverse effects include dyspepsia, eructation, and diarrhea. Examples include EPA/DHA (Lovaza®) and icosapent ethyl (Vascepa®). **Table 13-15** summarizes the various hypolipidemic agents and their effects on cholesterol.

TABLE 13-15
Effects of Hypolipidemic Agents on Cholesterol

Drug Class	LDL	HDL	TG
Statins	↓	↑	↓
Bile acid sequestrants	↓	—	↑
Niacin	↓	↑	↓
Fibric acid derivatives	↓	↑	↓
Cholesterol absorption inhibitor	↑	Negligible	Negligible
Omega-3 fatty acids	↓only Lovaza®	Negligible	↓

HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.

Review Questions

1. Briefly describe the neurohormonal model in HFrEF.
2. Describe the mechanism of action of sacubitril/valsartan, and describe the roles of ACE inhibitors, ARBs, aldosterone antagonists, diuretics, and digoxin in the treatment of HFrEF.
3. Compare the difference between supraventricular arrhythmias and ventricular fibrillation.
   Supraventricular arrhythmias:
   Ventricular fibrillation:
4. Compare and contrast the mechanism and side effects of the agents found in each of the Vaughan William antiarrhythmic categories.

Classification	Example
a.	a.
b.	b.
c.	c.
d.	d.

5. List two antiarrhythmic agents that may cause pulmonary fibrosis or pneumonitis.
6. Describe the overall effects of antianginal drugs in terms of relieving pain and list the correct way for a patient to administer sublingual nitroglycerin.
7. List two categories of antianginal drugs other than the nitrates and an example of each category.

Category	Example
a.	a.
b.	b.

8. Why is it necessary to treat hypertension? Define hypertension and explain how antihypertensive drugs alter factors that determine BP?
9. List two first-line agents for the management of hypertension. Include class and drug, mechanism of action, and common

adverse effects.

Class	Example
a.	a.
b.	b.

10. List three nonselective β-blockers and explain how they can affect the bronchodilator therapy.
    a.
    b.
    c.
11. Explain the mechanism a kidney uses to ensure adequate blood flow. How does this mechanism affect hypertension?
12. List five classes of diuretics and explain the mechanism of action of each class. Also, give an example of a drug from each class.

Class	Mechanism of Action	Example
a.	a.	a.
b.	b.	b.
c.	c.	c.
d.	d.	d.
e.	e.	e.

13. List the four DOACs and their corresponding mechanism of action and list three indications for which these drugs are used.

Drug	Mechanism of Action
a.	a.
b.	b.
c.	c.

d.	d.

14. List the mechanism of action, INR goal for nonmechanical heart valve patients, and dietary interactions for warfarin.
    a. Mechanism of action:
    b. INR goal for nonmechanical heart valve:
    c. Dietary interactions:
15. List the statins and doses that are considered high-intensity statins on the basis of LDL reduction.

Posttest

For each of the following questions, try to select the *one* best answer from the choices given.

1. All of the following statements about digoxin are true, *except:*
   a. these drugs cause a decrease in intracellular calcium.
   b. these drugs cause an increase in force of contraction.
   c. these drugs cause an increase in SV and cardiac output.
   d. these drugs have a narrow therapeutic index and drug levels must be monitored.
2. An arrhythmia can cause symptoms ranging from mild palpitations to cardiac arrest. True or False?

3–6. The following statements describe the mechanism of action of various antiarrhythmic drugs. From the list of drugs on the right, match the appropriate drug with the appropriate mechanism of action.

3. Calcium channel blocker	a. quinidine
4. Beta-blocker	b. metoprolol tartrate (Lopressor®)
5. Potassium channel blocker	c. amiodarone
6. Sodium channel blocker	d. verapamil (Calan®)

7. Adverse effects of the nitrates include all of the following, *except*:
   a. severe headache.
   b. dizziness.
   c. hypertension.
   d. hypotension.
8. Stage II hypertension is classified as a BP greater than or equal to:
   a. 120/80 mm Hg.
   b. 140/90 mm Hg.
   c. 150/90 mm Hg.
   d. 160/100 mm Hg.
9. A respiratory therapist is caring for a patient with COPD and HFrEF. The patient's current BP is 145/98 mm Hg. The patient's HR is 102 beats/min, and breath sounds reveal moist crackles

bilaterally. Which of the following medications should be suggested?

a. Beta-agonist
b. Anticholinergic
c. Ipratropium and albuterol (Combivent®)
d. Diuretic

10. All of the following are drugs that are considered first-line agents for hypertension, *except*:
    a. lisinopril (Zestril®).
    b. amlodipine (Norvasc®).
    c. hydralazine (Apresoline®).
    d. chlorthalidone (Hygroton®).
11. Dabigatran (Pradaxa®) is an oral factor Xa inhibitor. True or False?
12. Which of the following antiarrhythmics may cause pulmonary fibrosis?
    a. Quinidine (Quinaglute®)
    b. Propafenone (Rythmol®)
    c. Amiodarone (Cordarone®)
    d. Dofetilide (Tykosyn®)
13. All of the following are adverse effects of valsartan, *except*:
    a. hyperkalemia.
    b. angioedema.
    c. elevated serum creatinine.
    d. cough.
14. All of the following anticoagulants can place a patient in an increased risk of developing HIT, *except*:
    a. enoxaparin (Lovenox®).
    b. dalteparin (Fragmin®).
    c. UFH.
    d. fondaparinux (Arixtra®).
15. All of the following statements regarding rivaroxaban (Xarelto®) are true, *except*:
    a. it is an oral factor Xa inhibitor.
    b. doses greater than 10 mg must be taken with food.
    c. it cannot be used in patients with mechanical heart valves.

d. patients must avoid foods high in vitamin K.

References/Recommended Readings

Braunwald E. Mechanism of action of calcium channel blocking agents. *N Engl J Med.* 1982;307:1618.

Broyles BE, Reiss BS. *Pharmacological Aspects of Nursing Care.* Clifton Park, NY: Delmar-Cengage Learning; 2013.

Brunton LL, Lazo JS, Parker KL, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 11th ed. New York, NY: McGraw-Hill Medical Publishing; 2006.

Deglin JH, Vallerand AH, *MedNotes*. Philadelphia, PA: F.A. Davis Company; 2004.

Rainforth Collins, S. *Mosby's Drug Reference for Health Professionals.* 6th ed. St. Louis, MO: Mosby-Elsevier; 2018

Hamer J. Antiarrhythmic drugs. In J Hamer (ed.), *Drugs for Heart Diseases.* 3rd ed. London: Chapman and Hall; 1987.

Hartupee J, Douglas M. Neurohormonal activation in heart failure with reduced ejection fraction. *Nat Rev Cardiol*. 2017;14(1):30–38.

Hitner H, Nagle BT. *Pharmacology: An Introduction.* 6th ed. San Jose, CA: Glencoe Publishing Co; 2011.

James PA, Oparil S, Carter BL, et al. 2014 evidence-based guidelines for the management of high blood pressure in adults. *JAMA.* 2014;311(5):507–520.

Mancano MA, Gallagher JC, eds. *Frequently Prescribed Medications*. 2nd ed. Burlington, MA: Jones and Bartlett; 2014.

Marder VJ, Sherry S. Thrombolytic therapy: Current status 1; Thrombolytic therapy: Current status 2. *N Engl J Med.* 1988;318:1512–1520; 1585–1595.

McCance KL, Huether, SE. *Pathophysiology: The Biologic Basis for Disease in Adults and Children.* 6th ed. St. Louis, MO: Mosby-Elsevier; 2010.

McMuirray, JJ. Systolic heart failure. *N Engl J Med.* 2010;362:228–238.

McMurray, JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371:993–1004.

Nordlander R. Use of nitrates in the treatment of unstable and variant angina. *Drugs.* 1987;33(suppl 4):131–139.

Smith TW. Digitalis, mechanisms of action and clinical use. *N Eng J Med.* 1988;307:1357–1362.

Spratto GR, Woods AL. *Nurse's Drug Handbook*. Clifton Park, NY: Delmar-Cengage Learning; 2013.

Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;129:S1–S45.

Taber's Cyclopedic Medical Dictionary. 21st ed. Philadelphia, PA: F.A. Davis, Co; 2009.

Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guidelines for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:1495–1539.

Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused updated of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College

of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of American. *Circulation*. 2017;136(6):e137–e161.

Zeind CS, Carvalho MG, eds. *Applied Therapeutics the Clinical Use of Drugs.* 11th ed. Philadelphia, PA: Wolters Kluwer; 2018.

CHAPTER

14

Pharmacology of the Central Nervous System

© Anna RubaK/ShutterStock, Inc.

OUTLINE

Introduction
General Anatomy of the CNS
  Cerebrum
  Diencephalon
  Brain Stem
  Cerebellum
Effects of Drugs on the CNS
Sedative Hypnotics and Antianxiety Drugs
  Barbiturates
  Benzodiazepines
  Alcohol (Ethanol)
Psychopharmacology and Treatment of Psychiatric Disorders
  Categories of Psychopharmacologic Drugs
  Antipsychotics
  Treatment of Depression
  Mood Stabilizers
  CNS Stimulants
Epilepsy
  Antiepileptic Drugs
Analgesics and Pain Management

Opioid Analgesics
Non-Opioid Analgesics
General Anesthetics
Properties of an Ideal General Anesthetic
Inhaled General Anesthetics
Preanesthetic Medications
Conscious Sedation

OBJECTIVES

After completion of this chapter and its learning activities, you will be able to:

1. Describe the general anatomy of the central nervous system and list the functions of each area.
2. Compare the uses, mechanisms of action, and adverse effects of barbiturates and benzodiazepines.
3. Identify factors that can enhance the effects of barbiturates and benzodiazepines.
4. Distinguish between the toxicities associated with the first-generation and second-generation antipsychotics and their place in therapy of each class.
5. Describe the mechanisms of action of selective serotonin reuptake inhibitors, tricyclic antidepressant, and monoamine oxidase inhibitor antidepressant drugs used in treating depression, and indicate the precautions and uses of each class.
6. Discuss the mechanisms of action of valproic acid and lithium in treating bipolar disorder and design a monitoring plan for each.
7. List the psychostimulant drugs used to treat attention-deficit hyperactivity disorder and the pros and cons of these drugs to treat this condition.
8. Explain the difference between focal and generalized seizures and discuss the toxicities associated with the antiseizure medications used to treat each.
9. List the commonly used opioid and non-opioid analgesics and their place in the treatment of pain.
10. Describe the mechanism of action of opioid analgesics and the physiologic effects on each organ system.
11. Recommend a drug therapy for the treatment of respiratory depression caused by an acute opioid overdose.
12. Evaluate the differences in mechanisms of action and adverse effects between aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs.
13. Define the term *general anesthesia* and list the properties of an ideal general anesthetic.
14. Support the use of other drug classes in conjunction with inhaled anesthetics and list examples of these agents.
15. List the inhaled general anesthetic agents currently used and classify them as volatile liquids or gases and determine appropriate uses and precautions of each.

KEY TERMS

Analgesia

Analgesic
Antidepressant
Antipsychotics
Antipyretic
Anxiolytic
Conscious sedation
Equianalgesic doses
Extrapyramidal symptoms (EPS)
General anesthetic
Hypnotic
Sedative
Stimulant
Tardive dyskinesia
Uricosuria

Introduction

The drugs discussed in this chapter are the most widely used group of drugs in patient care. Many of these drugs have the potential to be abused. They have a broad range of effects and a great deal of overlap regarding their therapeutic use. The therapeutic central nervous system (CNS) drugs discussed here include sedative hypnotics, psychopharmacologic drugs, antiepileptics, general anesthetics, and analgesics. This chapter reviews the anatomy of the CNS, discusses some general characteristics of CNS drugs, and discusses the more important groups of drugs that are therapeutically useful in the various categories of CNS pharmacology.

General Anatomy of the CNS

The general anatomy of the CNS is extremely complex, with many different nuclear centers and locations that interact with each other. In order to simplify the study of the CNS function, the brain is divided into four parts: the cerebrum, the diencephalon, the brain stem, and the cerebellum (**Figure 14-1**). These parts are described next, with a brief discussion of the functions of each area.

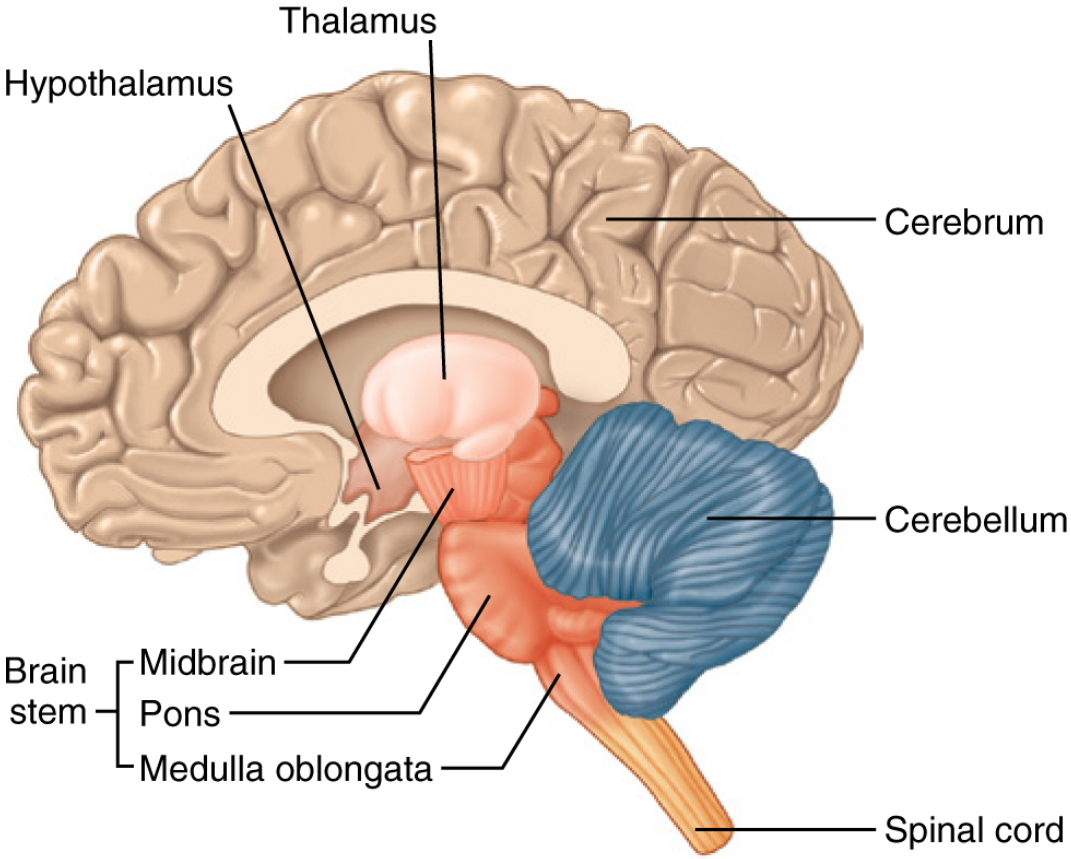


FIGURE 14-1 Structures of the brain.

Description

Cerebrum

The cerebrum is the largest area of brain tissue and occupies the superior part of the CNS. It comprises the left and right hemispheres. The cortex of each hemisphere contains billions of nerve cell bodies that directly or indirectly control most motor functions of the body. This area of the brain is also where interpretation, memory, feelings, and reasoning occur. The cerebral cortex is divided into lobes, and these lobes control both sensory and motor functions that involve involuntary and voluntary actions, the special senses, personality, and intelligence.

Diencephalon

This area is located immediately above the brain stem and comprises mainly of the thalamus and hypothalamus. The main function of the thalamus is to serve as a relay station for most sensory input and output from the cerebral cortex to the spinal cord. It functions as a center for interpretation of pain, touch, sound, and taste. The function of the hypothalamus is to control most body tissues and help maintain homeostasis. It controls temperature, water balance, sleep cycles, the autonomic nervous system, and certain emotions. The hypothalamus also controls release and production of many hormones.

Brain Stem

The brain stem extends from the base of the diencephalon to the spinal cord and consists of the midbrain, medulla oblongata, and the pons. It makes up the smallest portion of the brain, but it is involved in functions critical for human survival. The midbrain controls eye functions and auditory and visual processing. The function of the pons is to act as a sensory relay center and respiratory rhythmicity center. The medulla oblongata controls autonomic functions such as to control respiration, vascular tone, heart rate, and gastrointestinal (GI) function.

Cerebellum

This area is located inferior to the cerebrum and posterior to the brain stem. The main function of the cerebellum is coordination of motor skills (e.g., walking and riding a bike) and proprioception. Proprioception is the sense our brain sends to our body to know what position it is in (e.g., when you trip, it sends your body a signal to put your arms out to gain balance).

Effects of Drugs on the CNS

In general, drugs manifest their effects on the CNS in a fashion similar to their effects on the peripheral nervous system, but because of the complexity of the organization of the CNS, drug action there is much harder to predict and understand. For example, CNS drugs work at synapses just as they do in the peripheral nervous system, but in the CNS there are multiple neurotransmitters and multiple receptor sites. A few CNS drugs are quite selective, but most are nonspecific regarding their site of action, and many side effects can result from this lack of specificity. A major problem in studying CNS pharmacology is that there are 50–100 billion neurons interconnected by complex circuitry. Unlike the autonomic and somatic nervous system, where there are few neurotransmitters, the CNS contains multiple neurotransmitters, neuromodulators, and neurohumoral substances such as acetylcholine, norepinephrine, epinephrine, dopamine, serotonin (5-hydroxytryptamine [5-HT]), amino acids, and various neuropeptides. These neurotransmitters, along with multiple excitatory and inhibitory pathways, cause a variety of effects. As a result, it is often difficult to predict the effect of a particular drug on the CNS.

Some of the mechanisms of action of drugs on the CNS are similar to those on the peripheral nervous system, but because of the complexity of organization of the CNS, the possibilities of drug action at the synaptic site are greatly increased. CNS drugs can alter the effect of transmitters by enhancement, prolongation, antagonism, or various other mechanisms. Also, CNS drugs can alter the amount of neurotransmitters released by increasing or reducing the synthesis of these substances. Many mechanisms of drug action are not completely understood, and for some CNS drugs, the specific mechanisms of action, the receptor site, and the site of action are still unknown.

Sedative Hypnotics and Antianxiety Drugs

These drugs represent a diverse group of therapeutic agents that are widely used and also often abused by the patient. The original sedative **hypnotic** drugs were the barbiturates, but these drugs have been replaced by benzodiazepines because of their greater selectivity and improved safety. In order to better understand the **sedative** hypnotic and antianxiety drugs, the appropriate terminology used for clinical classifications follows:

- *Sedative*: produces a calming effect, decrease in CNS activity, and drowsiness
- *Hypnotic*: produces drowsiness and facilitates the onset of sleep
- *Antianxiety agent* (**anxiolytic**): reduces anxiousness

It should be noted that sedation and hypnosis are related to dose; that is, if the dose of a sedative drug is increased, it will lead to either hypnosis or sleep. Also, if a hypnotic drug is given at a less than therapeutic dose, it will create only sedation.

Barbiturates

Historically, the barbiturates have been the prototype agents used as sedative hypnotics, but with the introduction of the benzodiazepines and some recently developed drugs, they are rarely used as sedative hypnotics. They do, however, have a limited number of valid uses in other areas of medicine, and therefore a brief description of their pharmacology is presented.

As a group, the barbiturates are powerful CNS depressants, and the amount of CNS depression is dose-related. They can be used as sedatives or hypnotic drugs, but when used as sleeping agents, they do not produce a normal physiologic rapid eye movement (REM) sleep pattern. The use for sleep has fallen out of favor for safer

alternatives. Barbiturates are used for induction of anesthesia or in the treatment of seizures or refractory status epilepticus.

They depress all excitable tissues in the CNS by binding to the $GABA_A$ receptors, which lead to opening of the Cl^- channels (**Figure 14-2**). This can enhance the effect of gamma-amino butyric acid (GABA) or barbiturates that lead to channel opening in the absence of GABA. This class of drugs can also inhibit glutamate release. These various mechanisms contribute to the potency of these agents to cause a range of effects from sedation to coma, respiratory depression, and death. Because these agents have no **analgesic** properties, any type of surgical procedure that is performed using these agents should be done in combination with an analgesic. They are metabolized in the liver and produce a clinically significant induction of the hepatic microsomal enzyme system that affects the metabolism of other drugs when used chronically, in the case of seizure treatment. Their effects are enhanced and prolonged in the elderly or in patients with liver dysfunction. Barbiturates can depress the cardiovascular and respiratory system, and this effect is pronounced at high dosages or in the case of an overdose. They exhibit the phenomenon of redistribution, which means that following absorption, barbiturates often are redistributed or stored in fatty tissue throughout the body. This tends to create a secondary site for release of drug later, and thus many barbiturates tend to have a long-acting or hangover effect. Also, the barbiturates have a strong addiction liability, which can cause a life-threatening withdrawal scenario. **Table 14-1** provides a brief summary of a few of the commonly used barbiturates, with an approximate range of their duration of action and some main clinical uses.

TABLE 14-1
Classification of Barbiturates

Drug	Duration of Action	Clinical Use
Methohexital (Brevital®)	Ultrashort (<1 h)	Induction of surgical

		anesthesia
Pentobarbital (Nembutal®)	Intermediate (30 min–3 h)	Sedative/hypnotic, refractory status epilepticus
Phenobarbital (Luminal®)	Long-acting (6 h)	Anticonvulsant in treatment of chronic seizures or status epilepticus

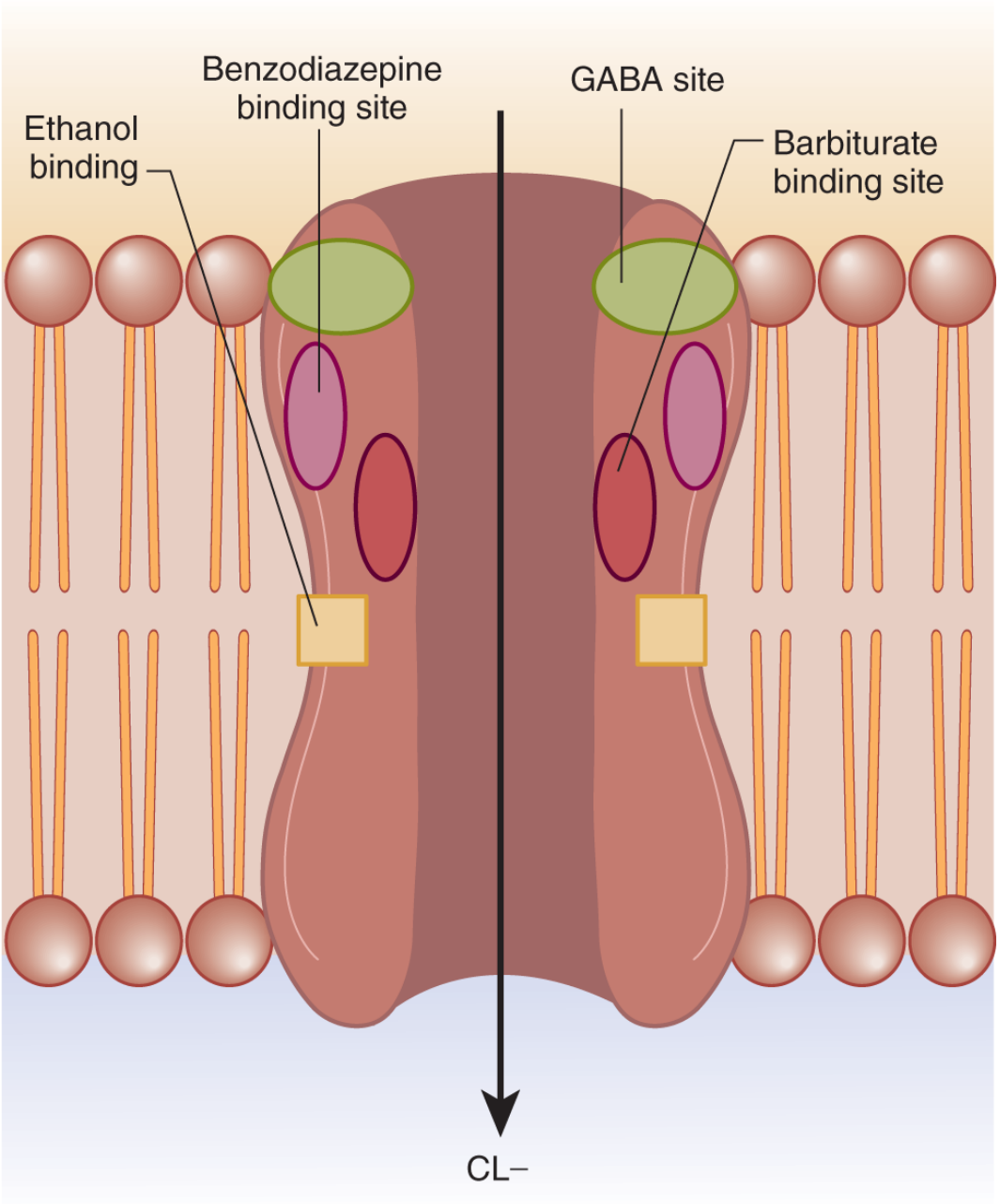


FIGURE 14-2 GABA receptors and mechanism of GABA agonist agents.

Description

NEED TO KNOW

Barbiturates, such as methohexital or phenobarbital, are CNS depressants and can cause respiratory depression at high doses.

Benzodiazepines

These drugs are the most widely used sedative hypnotic and antianxiety agents today and have replaced the barbiturates. The shift in usage toward these drugs has occurred because of their greater selectivity, fewer side effects, fewer drug interactions, and lower addiction potential. The benzodiazepines were first introduced in the 1950s with the development of the drug chlordiazepoxide (Librium®). Since that time numerous other drugs have been introduced, and basically all the agents have similar properties, with some being used for specific conditions.

On a worldwide scale, these drugs represent the most widely prescribed class of CNS drugs. The main clinical use of these drugs is as anxiolytics, with some patients experiencing mild sedation (see **Table 14-2** for commonly used agents and their therapeutic uses).

TABLE 14-2
Commonly Used Benzodiazepines

Drug	Duration of Action	Clinical Use
Diazepam (Valium®)	Long-acting	Anxiolytic
Chlordiazepoxide (Librium®)	Long-acting	Anxiolytic
Clonazepam (Klonopin)	Intermediate	Anxiolytic, muscle relaxant, anticonvulsant

Lorazepam (Ativan®)	Intermediate	Anxiolytic; may be useful as an adjunct to mechanical ventilation to improve patient–ventilator synchrony (Chapter 12)
Temazepam (Restoril)	Intermediate	Sedative for sleep
Alprazolam (Xanax®)	Short-acting	Anxiolytic, sedative for sleep
Triazolam (Halcion®)	Short-acting	Sedative for sleep
Midazolam (Versed®)	Short-acting	Amnesia; anxiolytic; commonly used for conscious sedation and may be useful as an adjunct to mechanical ventilation to improve patient–ventilator synchrony (Chapter 12)

In some cases the sedative effect may be desirable, but most patients become tolerant to the sedation without losing any therapeutic result. Benzodiazepines act by enhancing the effects of the inhibitory GABA neurotransmitters in the brain (Figure 14-2). They enhance GABA binding to the $GABA_A$ receptor and will bind at specific benzodiazepine receptor sites. All these agents can produce dose-related sedation and hypnosis, and most can decrease sleep latency (onset time). When used as sleep agents, discontinuation may lead to rebound effects, especially regarding REM sleep. Many of the drugs have additional effects such as muscle relaxant effects, anticonvulsant properties, and cause amnesia.

Benzodiazepines have relatively few adverse effects, and in contrast to the barbiturates are rarely fatal in overdose. In therapeutic doses, these agents do not significantly depress respiration and cardiovascular function; however, when combined with other CNS depressants, especially alcohol, additive effects can cause severe depression. All benzodiazepines, especially, longer-acting drugs, may produce prolonged sedative effects in patients with renal and liver dysfunction, as well as in pediatric and elderly patients. The

commonly seen effects are drowsiness, confusion, ataxia, and dizziness. When taken for sleep, they have what has been described as a hangover effect in the morning. Paradoxical excitation (e.g., nightmares, tachycardia, and anxiety) may be seen with use of these agents as well. Chronic use of benzodiazepines creates a risk of abuse and dependence. Withdrawal can be seen when chronically used or abused benzodiazepines are discontinued abruptly. Tremors, anxiety, hallucinations, and seizures can be seen in severe withdrawal. In the case of benzodiazepine overdoses, the drug flumazenil is a benzodiazepine receptor antagonist that can reverse the effects of benzodiazepines with a potential risk of inducing seizures in patients using benzodiazepines chronically. Additive or enhanced effects and respiratory depression can be seen when benzodiazepines are used with other CNS depressants (e.g., alcohol and barbiturates).

NEED TO KNOW

Benzodiazepines can cause excess sedation when used in patients with renal or liver impairment and in patients with extremes of age. Respiratory depression is not seen with benzodiazepines unless used with other CNS depressants.

Alcohol (Ethanol)

Although alcohol (e.g., ethyl alcohol) rarely is used as a therapeutic agent, it does have a number of pharmacologic actions that affect the whole body. It has an antiseptic/disinfection action on bacteria and will inhibit bacterial growth when used at 70–90% concentration. Also, because of its wide social use, it is appropriate that mention be made about its major actions on the body, adverse effects, and addiction liability.

After oral administration, ethyl alcohol is absorbed from the GI tract within 30 minutes and is metabolized in the liver. The most prominent effect of alcohol is its ability to depress the CNS, and, like many of the sedative hypnotic drugs, the amount of depression is

dose-related. Many individuals have the misconception that drinking alcohol provides a stimulatory effect. This apparent stimulation is actually caused by the fact that in small doses, the inhibitory areas of the brain are depressed first and the “stimulation” is manifested by lack of inhibition, lack of self-consciousness, and, in some cases, violent or obnoxious behavior. As the dose is increased, both the excitatory and inhibitory areas of the brain are depressed, and this gradually leads to sedation, hypnosis, and eventually coma. The mechanism of CNS depression is related to effects on GABA ion channels and its inhibition of excitatory neurotransmitters. These CNS depressant effects are enhanced when used with other agents that cause sedation such as benzodiazepines or opioids.

Short-term use of ethyl alcohol can cause headache, thirst, confusion, and nausea/vomiting. Chronic alcohol use can lead to esophageal reflux, dementia, and alcoholic hepatitis. The cardiovascular system, GI tract, and fetal development are also affected by alcohol. In the cardiovascular system, alcohol causes peripheral vasodilation that may create the feeling of warmth, but actually an increase in heat loss and potential hypothermia can occur. In moderate doses, alcohol does not appear to have any effect on coronary blood flow, but with chronic use, cardiomyopathy may occur. In the GI tract, alcohol can stimulate saliva flow and increase hydrochloric acid secretion in the stomach. With chronic use, this can lead to gastric and duodenal ulcer formation, which is similar to the irritation caused by heavy aspirin use. In regard to fetal development, alcohol consumption can lead to fetal alcohol syndrome, with the possibility of causing mental dysfunction in the child. It is well established that alcohol is highly addictive; the withdrawal symptoms associated with alcohol addiction can lead to anxiety, tremor, nervousness, delirium, hallucinations, and seizure. Symptoms of withdrawal can be treated with short-term use of benzodiazepines.

Case Study 14-1

A 76-year-old man is brought into the emergency department by ambulance. The patient's son found him minimally response when he went to check on him this morning and found an empty bottle of vodka on his nightstand. As the respiratory care practitioner (RCP), you are asked to put a non-rebreather mask and 12 L/min of oxygen and potentially be prepared for endotracheal intubation.

History: Insomnia, alcoholic cirrhosis, hypertension, and diabetes.

Vital signs: Heart rate, 118 beats/min; blood pressure (BP), 95/55 mm Hg; respiratory rate, 10 breaths/min; and O_2 saturation 93% on room air.

Home medications: Diazepam 20 mg HS for sleep (new prescription), propranolol 20 mg PO twice daily, and insulin glargine 20 units at bedtime.

Questions

1. Explain why or why not you believe diazepam is an appropriate benzodiazepine being used for sleep in this patient?
2. What were the factors that contributed to this patient's change in mental status and respiratory depression?
3. What drug can be used to reverse the effects of diazepam in this patient and what are the precautions for its use?

Psychopharmacology and Treatment of Psychiatric Disorders

Psychopharmacology involves the use of drugs to control or correct the chemical imbalances that may be associated with various mental disorders. Some of the psychological disorders that are treated pharmacologically include schizophrenia, bipolar affective disorder (manic-depressive psychosis), and major depression. Research regarding some of these conditions has linked underlying biochemical imbalance to the potential etiology of many psychological disorders; thus, many of the clinical conditions can be treated by attempting to correct chemical imbalances with the appropriate use of drugs.

The modern era of psychopharmacology began in the early 1950s, with the introduction of the drug chlorpromazine. This drug literally revolutionized the treatment of various mental disorders such as schizophrenia. Since the 1950s, there has been continual pharmacologic progress in the treatment of a variety of psychiatric conditions and behavioral disorders. Presently, the treatment approach to these disorders is pharmacologic rather than institutionalization. Psychiatrists today have a number of medications at their disposal that have greatly expanded their ability to treat mental illness. The knowledge of the biology of behavior is growing at a rapid rate, and with reasonable diagnostic skill and with knowledge of appropriate drugs, many physicians can treat cases of psychiatric disorders that are encountered in general medical practice.

Categories of Psychopharmacologic Drugs

The major categories of the psychopharmacologic drugs are listed in **Table 14-3**. Each of these categories is discussed in the following sections.

TABLE 14-3
Classes of Drugs Used to Treat Psychiatric Conditions

Category	Examples of Drugs	Related Psychiatric Disorders
Antipsychotics	*First-generation* Chlorpromazine (Thorazine®)	Psychosis
	Second-generation Olanzapine (Zyprexa)	
Antidepressants	*Tricyclic antidepressant* Imipramine (Tofranil®)	Various types of depression
	MAO inhibitors Isocarboxazid (Marplan®)	Various types of depression
	Selective serotonin reuptake inhibitors(SSRIs) Fluoxetine (Prozac®)	Various types of depression
	Trazodone (Desyrel®)	Various types of depression
	Bupropion (Wellbutrin®, Zyban®)	Various types of depression; also useful as an adjunct to quit smoking
Mood stabilizers	Lithium carbonate Carbamazepine (Tegretol®) Valproic acid (Depakote)	Bipolar disorder
Psychostimulants	Methylphenidate (Ritalin®) Other amphetamines	Hyperactivity
Anxiolytic/sedative agents	Alprazolam (Xanax) Clonazepam (Klonopin) Diazepam (Valium®) Lorazepam (Ativan®)	Anxiety

MAO, monoamine oxidase.

Antipsychotics

The **antipsychotics** are a group of agents that are used to treat various types of psychosis, and the prototype drugs are the phenothiazines. The older or first-generation antipsychotics (FGAs) are effective for treating psychosis but are associated with excess sedation and movement disorders or **extrapyramidal symptoms (EPS)**. The second-generation antipsychotics (SGAs) were designed to have fewer EPS compared with the older agents. Schizophrenia is the most common indication for using antipsychotics. Schizophrenics typically present with a variety of symptoms. The patients are known for having positive symptoms that consist of delusions and hallucinations. Antipsychotics are most effective in treating these symptoms. These patients also have negative symptoms (e.g., flat affect, inability to speak, inability to feel pleasure, or decreased motivation) and cognitive impairment associated with the disease and are associated with poor social function and less responsive to medication therapy. SGAs are more effective than FGAs at treating negative and cognitive symptoms but still cannot improve symptoms completely in all patients.

First-Generation Antipsychotics

FGAs, such as chlorpromazine, haloperidol, fluphenazine, and thioridazine (**Table 14-4**), are thought to work by acting as a dopamine-2 (D_2) antagonist and to a lesser extent as a serotonin-2 receptor (5-HT_{2A}) antagonist. EPSs and sedation are the most bothersome side effects associated with FGAs. EPS is an umbrella term for a variety of symptoms that are caused by dopamine blockade. These effects include dystonia (i.e., severe acute muscle spasm), akathisia (i.e., inability to sit still), and pseudoparkinsonism, which all may be treated with benzodiazepines or diphenhydramine and resolve within hours to days. **Tardive dyskinesia** is an irreversible disorder that causes abnormal involuntary movements that usually affect the tongue, jaw, and limbs resulting from long-term use of FGAs. Inhibition of dopamine by FGAs also leads to elevated

prolactin levels. Hyperprolactinemia leads to gynecomastia, menstrual irregularities, decreased libido, and sexual dysfunction.

TABLE 14-4
Commonly Used Antipsychotics

Drugs	Distinct Characteristics
First-Generation Antipsychotics (FGAs)	
Thioridazine (Mellaril®)	Associated with significant QTc prolongation, sedation, and anticholinergic effects
Chlorpromazine (Thorazine®)	Most weight gain among FGAs, sedation, and anticholinergic effects
Fluphenazine (Prolixin®)	Associated with significant EPS, hyperprolactinemia, and available in long-acting injection
Haloperidol (Haldol)	Used for treatment of acute delirium/psychosis, associated with significant EPS, hyperprolactinemia, and available in long-acting injection
Loxapine (Loxitane, Adasuve)	Anticholinergic effects. Available as an oral inhalation, can cause bronchospasm and respiratory distress, and contraindicated in patients with lung disease
Second-Generation Antipsychotics (SGAs)	
Aripiprazole (Abilify)	Associated with low rates of adverse effects
Clozapine (Clozaril)	Associated with agranulocytosis and WBC count should be monitored monthly, most weight gain, development of diabetes, sedation, anticholinergic effects, and most effective but used in patients nonresponsive to multiple therapies
Olanzapine (Zyprexa)	Associated with most metabolic effects (weight gain, diabetes, hyperlipidemia) and sedation
Quetiapine (Seroquel)	Causes orthostatic hypotension and sedation

Risperidone (Risperdal)	Causes orthostatic hypotension and hyperprolactinemia
Ziprasidone (Geodon)	Associated with low rates of adverse effects

EPS, extrapyramidal symptoms; WBC, white blood cell.

Second-Generation Antipsychotics

The SGAs (Table 14-4) have a moderate-to-high D_2 antagonism and have a higher affinity to 5-HT_{2A} receptors. The changes in mechanism compared with FGAs lead to lower risk of movement disorders. Glucose intolerance leading to the development of diabetes, hyperlipidemia, and weight gain has been associated with many of the SGAs. Weight gain and glucose intolerance is associated most with olanzapine but can occur with other agents as well. Fatal arrhythmias have also been associated with FGAs and SGAs, especially when used at high doses and in conjunction with other medications that cause arrhythmias.

Nonadherence with medication therapy is a common problem with schizophrenia patients. Cognitive behavioral therapy, counseling, and adjusting medication to minimize adverse effects can improve adherence to this condition. Orally disintegrating tablets, extended-release formulation, long-acting injections, and inhaler formulations of medications are available to improve treatment in these patients.

NEED TO KNOW

FGAs have a higher likelihood of developing movement disorders such as EPS and tardive dyskinesia because of the higher antagonism of D_2 compared with the SGAs.

Treatment of Depression

Depression or major depression is a serious medical condition that causes feelings of sadness, loss of interest or pleasure, and feelings of worthlessness that can cause impairment in social functioning.

Adults in the United States have a 20% lifetime risk of developing major depression. The odds of developing depression are more in women than men, in whites than other ethnicities, and are most common in ages 18–29 years. The goals of treatment are to resolve current symptoms and prevent future symptoms from reoccurring. Symptoms of depression reflect changes in norepinephrine, serotonin, and dopamine levels. There are various other types of short-term depressions that occur throughout life, incited by such events as a death in the family, divorce, or financial losses. These short-term depressions can be treated with medication, but their response to drug therapy is unpredictable and not well-documented. However, these mood changes should not be ignored; probably these patients should be referred to a psychiatrist or psychologist for evaluation. The main treatment modality of moderate-to-severe major depressive disorders is the use of **antidepressant** agents as well as psychotherapy. There are three main classes of antidepressant medication therapy: monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs) (**Table 14-5**). There is no evidence that one class is more effective than another, but specific treatment is determined based on what therapies have historically worked, concurrent medical conditions, symptoms, risks of adverse effects, and potential drug–drug or drug–food interactions. The onset of response will be seen in 3 weeks, but usually a maximal response is not seen until 6 weeks of therapy. Table 14-5 lists the categories of drugs used in treating various types of depressive disorders as well as their other clinical uses.

TABLE 14-5
Classes of Antidepressants and Common Clinical Uses

Drug Category	Examples	Clinical Use
Tricyclic antidepressants (TCAs)	Imipramine (Tofranil®)	Depression, neuropathic pain, and migraines

	Amitriptyline (Elavil®)	
Monoamine oxidase inhibitors (MAOIs)	Isocarboxazid (Marplan®)	Depression
	Phenelzine (Nardil®)	
	Tranylcypromine (Parnate®)	
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram (Celexa)	Depression, general anxiety disorder (GAD), eating disorders, and posttraumatic stress disorder
	Escitalopram (Lexapro)	
	Fluoxetine (Prozac®)	
	Paroxetine (Paxil)	
	Sertraline (Zoloft)	
Norepinephrine and dopamine reuptake inhibitor	Bupropion (Wellbutrin®)	Depression and smoking cessation
Serotonin–norepinephrine reuptake inhibitors (SNRIs)	Duloxetine (Cymbalta)	Depression, fibromyalgia, GAD, and neuropathic and chronic musculoskeletal pain
	Desvenlafaxine (Pristiq)	Depression
	Venlafaxine (Effexor)	Depression, GAD, and panic disorder
Mixed serotonergic effects	Trazodone (Desyrel®)	Depression and sleep

SSRIs, Serotonin–Norepinephrine Reuptake Inhibitors, and Norepinephrine and Dopamine Reuptake Inhibitors

SSRIs are usually chosen as the first-line treatment for major depression. They are effective when compared with placebo with few adverse effects and less risk for fatal overdose compared with TCAs

and MAOIs. SSRIs block the reuptake of serotonin (5-HT), serotonin–norepinephrine reuptake inhibitors (SNRIs) block the reuptake of serotonin and norepinephrine, and bupropion blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron. The drugs in the class of SNRIs block serotonin and norepinephrine at varying levels and differ between agents. All drugs in these classes are safer than older agents. The most common adverse effects of any drugs that modulate serotonin are nausea, vomiting, and sexual dysfunction. A withdrawal syndrome may occur with abrupt discontinuation and therefore should be slowly tapered. Venlafaxine may cause a dose-related increase in BP and should be monitored during therapy. Bupropion may additionally cause insomnia, tremor, dry mouth, agitation, and risk for seizures. It is associated with less sexual dysfunction than other antidepressants.

TCAs and MAOIs

TCAs and the MAOIs are less commonly used than the newer SSRIs and SNRIs. The TCAs are used more often because the MAOIs have a greater potential for toxicity and interaction with certain foods and drugs. The TCAs and the MAOIs increase the levels of norepinephrine and/or serotonin in brain tissue. The TCAs increase the levels of norepinephrine and serotonin by blocking the reuptake of each of these neurotransmitters into the nerve ending. The TCAs also act on other receptor systems including cholinergic, histamine, and alpha-adrenergic, which contribute to the common side effects. The MAOIs inactivate the enzyme monoamine oxidase in the nerve ending and, thus increase the levels of norepinephrine and serotonin being secreted by the nerve ending. For reasons that are not understood, both drug groups have a latency of onset of about 2–3 weeks, which can be frustrating for a patient suffering from severe depression.

The TCAs exhibit an anticholinergic property that produces sedation, blurred vision, dry mouth, constipation, impotence, and urinary retention. In therapeutic doses, some of the TCAs can cause orthostatic hypotension, tachycardia, and arrhythmias, and this can also occur with use of MAOIs. Other adverse effects that commonly

occur with MAOIs include weight gain and sexual dysfunction. Hypertensive crisis (severely high BP causing organ failure) can occur with MAOIs as a result of eating foods that contain the amino acid, tyramine, or in combination with other medication therapy. Tyramine precedes the release of norepinephrine and epinephrine, and patients who are taking long-term doses of MAOIs should be carefully monitored and instructed to avoid foods containing tyramine. Tyramine is found in chesses, especially aged cheeses, canned fish, meat, and wine. In a patient taking MAOIs, the levels of norepinephrine are already elevated, and with the addition of tyramine in the diet, more norepinephrine is released. Thus, the norepinephrine levels increase to a point at which increased vasoconstriction can occur, causing a severe hypertensive crisis.

Mood Stabilizers

Mood stabilizers are traditional drugs used to treat bipolar disorder or manic-depressive episodes. Some therapies are more effective for manic episodes and some are more effective for depressive symptoms. Lithium, valproic acid, and carbamazepine are traditional mood stabilizers used for bipolar, but many of the SGAs are used to treat bipolar disease as well. These agents may be used alone or in combination. Mania is a condition wherein the patient is in an extremely high level of excitation; in manic-depressive psychosis, the patient alternates between high activity and a depressed state. Lithium is considered the drug of choice in the treatment of bipolar disorder. It reduces the frequency of manic-depressive cycles and in higher doses can control the manic phase of the disorder. The mechanism of action of lithium is to exert its effect as a cation similar to sodium and potassium. It increases the reuptake of norepinephrine and serotonin and thus decreases the levels of these excitatory neurotransmitters in the synaptic cleft. It may also enhance glutamate clearance. Its onset of effect can be as long as 8 weeks. The anticonvulsant drugs, carbamazepine (Tegretol®) or valproic acid (Depakote), have been proven to be effective when given in

combination with lithium or in patients unresponsive or intolerant to lithium. Valproic acid is most effective to treat acute mania and works by enhancing the effects or actions of GABA. Carbamazepine is a drug that is related to the TCAs and is used not only as an anticonvulsant but also in treating nerve pain. It is usually used as a second-line agent for bipolar after treatment failure with lithium or valproic acid.

Adverse effects of lithium are seldom seen when the dosage is maintained at normal therapeutic levels, but individuals who are taking higher levels of these drugs can experience some of the following side effects: nausea, vomiting, and diarrhea; in the CNS, sedation, tremor, confusion, and, in some cases of overdose, coma; and in the cardiovascular system, it may cause reversible heart block and bradycardia. Lithium may also cause weight gain and increased thirst and urine output. It also should be noted that in some individuals, long-term doses of lithium can lead to hypothyroidism along with altered renal function.

CNS Stimulants

Stimulant drugs may be used for narcolepsy, treatment of obesity, and in managing attention-deficit/hyperactivity disorder (ADHD). This group of drugs usually includes the amphetamines, mixed amphetamine salts, and methylphenidate (**Table 14-6**). Methylphenidate and amphetamines increase the levels of norepinephrine in the brain tissue, and this is brought about by several mechanisms: direct stimulation of adrenergic receptors, release of norepinephrine and dopamine from storage sites, and prevention of norepinephrine reuptake. Norepinephrine and dopamine systems are thought to be abnormal in people with binge eating disorders. Because norepinephrine and dopamine are involved in the reward pathway, stimulants, specifically lisdexamfetamine is thought to work by causing increased release of norepinephrine and dopamine.

TABLE 14-6
Stimulant Drugs Used in ADHD and Other Clinical Uses

Drug	Trade Name	Use
Dextroamphetamine	Dexedrine, ProCentra, Zenzedi	ADHD and narcolepsy
Dextroamphetamine/amphetamine	Adderall, Mydayis	ADHD and narcolepsy
Dexmethylphenidate	Focalin, Focalin XR	ADHD
Lisdexamfetamine	Vyvanse	ADHD and binge eating disorder
Methylphenidate	Ritalin, Concerta (many)	ADHD and narcolepsy

ADHD, attention-deficit/hyperactivity disorder.

The main clinical use of stimulants is in the treatment of ADHD in children. Because these drugs increase mental and physical activity, it is paradoxical that they are the drug of choice in treating hyperactive individuals. The exact mechanism by which these stimulant drugs work in hyperactivity is not fully understood. When these drugs are used therapeutically in treating hyperactive children, they improve attention span and ability to concentrate and cause a decrease in diffuse hyperactivity. There are many preparations and formulations of stimulants available. Immediate-release products must be administered multiple times per day but may cause less insomnia. Extended-release or controlled-release formulations are more commonly used to avoid drug administration in the middle of the school day and enhances medication adherence. The longer-acting formulations provide a more stable blood concentration of active drug and provide less abuse potential. Administration with food may delay the onset of action or decrease absorption of these agents.

The most common adverse effects include weight loss or reduced appetite, stomach fullness, insomnia, headache, and irritability or jitteriness. Rare but serious adverse effects may include psychosis,

mood disturbances, panic attacks, tics or abnormal movements, priapism, hypertension, and hallucinations. Stimulants may also affect growth in children but the effects are minimal. Abrupt withdrawal of the drug may lead to withdrawal feeling of anxiety, fatigue, and depression. These drugs should not be combined with other stimulants or antidepressants that modulate serotonin.

Epilepsy

Epilepsy is a common CNS disorder in which a person is predisposed to develop seizures. There are multiple types of epilepsy that vary in severity, causes, seizure type, and frequency. The frequency and severity of episodes are dependent on the portion of the CNS involved. There are many etiologic factors associated with the various forms of epilepsy; these may include trauma, infection, stroke, alcohol, various drugs, and genetic predisposition. There are also types that are of unknown origin.

The types of seizures may vary and manifest in various ways and occur in different parts of the brain. Treatment may vary or be exacerbated depending on the classification of seizure. The classification of seizure activity is complex, and because of the introductory level of this text, only the following broad categories are described:

1. Focal onset: begins in one hemisphere of the brain
   a. Aware: relatively localized discharge in the brain without loss of consciousness
   b. Impaired awareness: loss of consciousness or impaired consciousness
2. Generalized onset seizures: begins in both hemispheres of the brain
   a. Nonmotor (absence): characterized by rapid onset, impaired awareness, and staring behavior or upward rotation of the eyes
   b. Motor—
      1. Tonic-clonic/tonic/clonic/myoclonic/atonic: can range from brief muscle contractions or jerks that can affect one or multiple body parts, they can be bilateral or have stiffening of the limbs or loss of muscle tone
      2. Other motor: tonic-clonic or epileptic spasms

The diagnosis of epilepsy is primarily on the basis of patient reported symptoms, types and frequency of seizures, and medical signs. An electroencephalography or brain imaging, such as computerized tomographic scanning and magnetic resonance imaging (MRI), may also be used to assist in the diagnosis. Once the diagnosis has been established, the overall management of epilepsy is dependent on the selection of appropriate drug therapy. The treatment goal should be to improve symptoms and eliminate seizures with as few adverse effects as possible. Many patients fail to become seizure-free on drug therapy but limiting the frequency of seizures if a reasonable, achievable goal.

Antiepileptic Drugs

Antiseizure drug therapy is the foundation of epilepsy management. There are currently over 20 antiseizure medication therapies available in the United States. Once a diagnosis is made, the choice of antiseizure therapy will depend on epilepsy classification, seizure type, frequency, age, and other comorbid conditions of the patient. Monotherapy with one antiseizure agent should be initiated initially. Management of the patient with only one medication offers many advantages, such as better control of toxicity, improved patient compliance, avoidance of unpredictable drug interactions, and better control of unusual side effects. When monotherapy has failed to achieve the treatment goal, a second agent can be added to the regimen. It is important to note that medications used in the treatment of epilepsy only prevent seizures and do not modify or cure the actual disease. When medication therapy is started, it should be initiated at the lowest dose and titrated slowly to the lowest effective dose. Treatment for epilepsy should not be abruptly discontinued and should be slowly tapered off with close monitoring from a clinician. Although there are many drugs and drug combinations that can be used, this chapter discusses only the most commonly used antiseizure drugs. Phenytoin, carbamazepine, valproic acid, phenobarbital,

ethosuximide, topiramate, lacosamide, and levetiracetam will be discussed in more detail.

Phenytoin (Dilantin®)

Phenytoin has been one of the first-line drugs in treating generalized tonic-clonic and focal seizures, but newer agents with less long-term side effects are starting to replace it in therapy. It works by preventing the spread of seizure in the brain by blocking sodium channels. Phenytoin blood concentrations should be monitored regularly and doses should be adjusted slowly to avoid toxicity. Drug interactions should be carefully monitored with phenytoin, affecting both phenytoin and phenytoin affecting other agents. CNS side effects are the most common, affecting cognition, coordination, and dyskinesia. Long-term use can cause gingival hyperplasia and peripheral neuropathy. Unpredictable and serious side effects include bone marrow suppression, life-threatening rash, and hepatitis.

Carbamazepine (Tegretol®)

Carbamazepine is one of the first-choice drugs to treat many types of seizures. It is primarily used to treat patients with focal and generalized tonic-clonic seizures. It may worsen absence seizures and generalized tonic-clonic seizures in patients with multiple seizure types. It acts by enhancing fact inactivation of voltage-gated Na+ channels. It is dosed based on drug blood concentrations, and dosing may need to be adjusted based on this. Carbamazepine may induce its own metabolism or clears itself from the body faster, which makes dosing complicated and causes interactions with multiple medications including other antiseizure therapy. The most common and serious side effects include life-threatening rash (Stevens-Johnson syndrome or toxic epidermal necrolysis), nausea, low sodium levels (which can also cause seizures), leukopenia, vertigo, and lethargy. It causes low degree of cognitive impairment compared with other first-generation antiseizure drugs. It is teratogenic and not a preferred agent in pregnancy.

Valproic Acid (Depakote, Depakene®)

Valproic acid is useful for the treatment of all types of focal and generalized seizures. It can be used as monotherapy or as adjunct to other drugs. As discussed, it is also commonly used to treat bipolar disorder and migraines. This agent prevents spread of seizure activity by enhancing the inhibitory GABA pathways, but increases availability of GABA or mimics its action on postsynaptic receptor sites. GI problems (e.g., nausea, vomiting, and anorexia) and weight gain are the most common side effects. Hair loss, tremor, pancreatitis, and in some individuals, hepatic failure and thrombocytopenia at high doses can be associated with valproic acid. It is available in multiple dosage formulations, including a once daily tablet formulation. Blood concentrations should be monitored periodically, especially if interacting drugs are started or stopped, side effects are suspected, or seizures are failing to cease. This agent is a known teratogen and should not be used in pregnancy.

Lacosamide (Vimpat)

Lacosamide is an agent approved for focal seizures. It may be more expensive than older agents but is being used more frequently because of its lack of drug interactions and minimal adverse effects. It works by stabilizing hyperexcitable neuronal membranes and decreases repeat neuron firing by enhancing slow inactivation of sodium channels. It can cause dizziness, nausea, headache, double or blurred vision, and ataxia. Higher doses are associated with increased risk of side effects.

Levetiracetam (Keppra)

Levetiracetam can be used as monotherapy or adjunct to treat focal and generalized seizures. The exact mechanism is unknown but is thought to inhibit calcium channels, facilitate GABA activity, and modulating other neurotransmitter release. It is eliminated by the kidney and has no drug interactions, except it may enhance sedation when used with other CNS depressants. Adverse effects include

sedation, fatigue, depression, hostility, aggressive behavior, and muscle weakness. This agent is becoming more commonly used because of its low incidence of serious adverse effects and lack of drug interactions.

Ethosuximide (Zarontin®)

Ethosuximide is a first-choice drug in the treatment of absence seizures. It works by raising the seizure threshold by reducing calcium current and inhibiting calcium channels. Nausea and vomiting are common but can be minimized by using smaller dose more frequently.

Topiramate (Topamax)

Topiramate is used as monotherapy in focal and generalized tonic-clonic seizures. It is also commonly used to prevent migraines. It works by affecting Na+ and calcium channels as well as on the GABA receptor. CNS effects are the most problematic with this agent. It can cause word-finding difficulty, cognitive impairment, kidney stones, and metabolic acidosis. The lowest effective dose should be used to lessen cognitive and memory-related side effects.

Phenobarbital

Phenobarbital is a first-generation, older antiseizure agent that is associated with multiple adverse effects. It is now rarely used as a first-line treatment. It enhances inhibitory GABA pathways and blocks repetitive firing but inhibiting glutamate release. It interacts with many medications, and other medications specifically antiseizure drugs can affect serum concentrations. Phenobarbital use is limited by adverse effects such as sedation, depression, changes in sleep patterns, cognitive impairment, rash, anemia, and liver toxicity.

Analgesics and Pain Management

Pain is defined as “an unpleasant sensory or emotional experience associated with tissue or potential tissue damage.” Analgesics are classes of drugs that are used to treat or reduce the sensation of pain. Pain involves interactions between the peripheral and CNS in response to painful stimuli. When one comes into contact with painful stimuli (e.g., touching a hot surface), the nerve receptors nociceptors are stimulated. When these receptors are stimulated, there is a release of chemicals that activate the receptors. The chemicals involved in the activation of the nociceptors include serotonin, bradykinin, histamine, prostaglandins, and substance P. These signals are transmitted to the spinal cord. The spinal cord releases excitatory neurotransmitters, glutamate, and substance P. Pain signals are then transmitted to the brain. Pain signals can be decreased by endogenous opioids (e.g., enkephalins and endorphins), GABA, and norepinephrine. Serotonin is also released to stimulate more enkephalin release. Several different receptor sites have been located in the thalamus and other areas of the CNS where enkephalins/endorphins can combine. It is currently believed that the combination of these endogenous peptides released at these receptor sites is similar to that seen following administration of morphine and other opioid analgesics. Thus, these receptor sites are often referred to as “opioid-like receptors.” It should be noted that many different receptors and subreceptor groups have been identified, but in this book they will be collectively called “opioid receptors.”

There are other types of pain that are different from nociceptive pain and not caused from actual tissue damage or from a direct injury. This type of pain is as a result of damage or malfunctioning of nerve tissue. One type of pain can be as a result of nerve injury and other types of pain can result from dysfunction in processing pain within the CNS.

The narcotic or opioid analgesics are the main group of drugs used to treat moderate to severe pain. The non-opioid, nonsteroidal anti-inflammatory drugs (NSAIDs), including salicylates, and acetaminophen are also used for pain. Drugs found in each of these classes will be discussed in further detail in this chapter. Today, most narcotic agents are termed opioids, although morphine and codeine are the only naturally occurring substances that can be obtained from the poppy plant (natural source of opium). In this chapter, the term opioid will be used to include all naturally occurring and synthetic congeners of opium derivatives (e.g., morphine and codeine). Thus, the terms narcotic and opioid will be used interchangeably. Non-opioids (e.g., NSAIDs) are recommended for the treatment of mild-to-moderate pain, and opioids are usually reserved for patients with severe pain or if patients have a contraindication to a non-opioid agent.

Pain should be assessed in order to determine the etiology and to obtain an accurate description in order to determine the best treatment course. Patients should assess their pain on a scale from 0 to 10, 0 meaning no pain and 10 meaning the worst or most severe/unbearable pain. Patients should be asked what makes pain better, worse, describe the feeling (tingling, burning, stabbing, dull, etc.) and location of pain, and if it changes over time. Understanding these patient-specific factors can help determine the best course of treatment for each patient.

NEED TO KNOW

Opioids analgesics are primarily reserved to treat severe acute pain or used when non-opioids are contraindicated.

Opioid Analgesics

Morphine is the oldest naturally occurring opioid analgesic; it is the best understood, and therefore the standard against which all other analgesics are compared. Opioids are used in the treatment of

severe acute pain and cancer pain. This class may also be used for chronic pain but should be used cautiously in these cases because of the risk of abuse, as well as the lack of long-term efficacy. Opioids exert their analgesic effects by acting on the mu, opioid receptors. The mu receptor is the main site of opioid activity, which is found throughout the peripheral and CNSs. They act by decreasing or minimizing the sensation of pain and not always able to eliminate pain. They allow the pain to be tolerable for patients. Opioids are classified into three major subgroups according to the activity at the various opioid or mu receptors: (1) agonist (stimulates receptors), (2) agonist–antagonist (stimulates some receptors or blocks some receptors) or also called partial agonists, and (3) antagonist (blocks receptors) (**Table 14-7**). The opioid agonists stimulate the opioid receptors and thus mimic the effects of the endorphin substances. Methadone, another opioid agonist, has an additional mechanism of action. It acts at the mu receptors as well as antagonizes the *N*-methyl-D-aspartate receptors and blocks serotonin and norepinephrine reuptake. The agonist–antagonists (partial agonists), such as buprenorphine, pentazocine, and nalbuphine, are competitive mu receptor antagonists and exert weak analgesic effects from activity on kappa receptors (another class of opioid receptors). These agents were designed to produce **analgesia** with a low risk of respiratory depression, but use of these agents has been very limited. The antagonists (e.g., naloxone) bind to the receptors throughout the body but fail to activate them.

TABLE 14-7
Characteristics of Available Opioid Agonists and Partial Agonists–Antagonists

Classification (Derivatives)	Equianalgesic Doses (Oral)	Generic Name (Brand)	Uses and Unique Properties
Agonist			
Morphine-like agonists Naturally occurring	30 mg	Morphine (many)	Causes histamine-related rash, pruritus, hypotension, and nausea/vomiting
	130 mg	Codeine (many)	Similar to morphine but used for mild-to-moderate pain and used in combination with APAP
Semisynthetic morphine derivatives	6 mg	Hydromorphone (Dilaudid)	More potent than morphine and less pruritus
	10 mg	Oxymorphone (Opana, Opana ER)	No advantage over other agents
	4 mg	Levorphanol	Long duration of action, and no advantage over other agents
	30 mg	Hydrocodone (Hysingla ER, Zohydro, Lortab, Vicodin)	Commonly prescribed and available in extended-release form and in combo with non-opioids
	20 mg	Oxycodone (Percodan®, Percocet®, Roxicodone, OxyContin, Oxaydo)	Available in combo with APAP and available in extended-release and in immediate-release form
Synthetic derivatives	300 mg	Meperidine (Demerol®)	*Not recommended for use and increased CNS effects, anxiety, tremors, and seizures Elderly, patients with renal impairment, and chronic use at higher risk of side effects
	10 mg*	Methadone (Dolophine®)	Cheap, long duration of action, can be used for chronic pain, nerve pain, opioid-dependence disorder, and can cause cardiac arrhythmias
	See package labeling guidelines	Fentanyl (Sublimaze®, Actiq, Duragesic, Fentora, Ionsys)	Fast-acting, used in anesthesia, in intensive care units, and for chronic pain, available in many dosage forms (IV, transdermal, sublingual, transmucosal, intranasal), and causes dose-dependent muscle rigidity
	N/A	Remifentanil (Ultiva)	Fast-acting, short duration of action, used in anesthesia and in ICU, and causes dose-dependent muscle rigidity
	N/A	Sufentanil (Sufenta®)	Fast-acting, short duration of action used in anesthesia, and causes dose-dependent muscle rigidity
Agonist–antagonist	N/A	Buprenorphine (Buprenex®, Belbuca)	Used for chronic pain, opioid withdrawal, and opioid-dependence disorder Analgesic ceiling effect seen
	N/A	Butorphanol (Stadol)	Weak analgesic, causes dysphoria, heart rate/BP, less respiratory depression, and can precipitate opioid withdrawal if given to chronic opioid users
	N/A	Nalbuphine (Nubain)	
	N/A	Pentazocine	
Antagonists	—	Naloxone (Narcan®)	Used for opioid-dependence disorder and treat acute overdose
	—	Naltrexone (Vivitrol)	Used for opioid-dependence disorder

*Equianalgesic doses of methadone may be lower in converting from other chronically used agents—a pain specialist should be involved in conversion of other opioids to methadone to avoid potentially fatal overdose.

APAP, acetaminophen; CNS, central nervous system; N/A, not available.

Opioid agents are available in multiple dosage forms such as tablets, liquid, intravenous, transdermal, and intranasal. All opioid agonists are equally effective when used at **equianalgesic doses** or equally effective doses. Opioids share common adverse effects on multiple organ system of the body, but the CNS and GI system are most commonly affected. Following are the adverse effects of opioids described by organ system.

1. Central Nervous System
   Opioids can produce sedation or drowsiness and inability to concentrate in many individuals. Severe sedation is a precursor to overdose and respiratory depression. Opioids also cause euphoria (or a sense of well-being); however, there are a number of individuals who experience a dysphoric response. Patients also report a disruption in normal sleep patterns with use of these agents. Miosis or pupillary constriction can also be seen in patients taking opioids and is more prominent in an overdose.
2. GI System
   Opioids stimulate the chemoreceptor trigger zone in the medulla and activate the emesis (vomiting) center in the brain, causing severe nausea and vomiting. Opioids also decreases GI motility. This can lead to severe constipation, which can become a serious problem with long-term opioid use. Laxatives should be used in patients taking opioids to prevent constipation.
3. Respiratory System
   Opioids are a powerful respiratory depressant and can directly affect the medullary center, causing a decrease in respiratory rate and tidal volume that in turn increases CO_2. Respiratory arrest is a common cause of death with overdose of opioids. Individuals who are elderly or pediatric and are on other CNS depressants, have chronic lung disease (chronic obstructive pulmonary disease, sleep apnea), have abnormal organ function, and are receiving high doses are at a higher risk of developing respiratory depression.

NEED TO KNOW

Older or young individuals and patients on other CNS depressants having chronic lung disease and who are receiving high doses of opioid analgesics are at the highest risk of developing respiratory depression.

4. Cardiovascular System
   Morphine, codeine, and meperidine can induce a histamine-mediated vasodilation. This may cause orthostatic hypotension in patients who are ambulatory or can cause hypotension in other critically ill patients. Other opioids (e.g., fentanyl and hydromorphone) that do not stimulate histamine release cause little to no hemodynamic instability.
5. Skin
   Morphine occasionally causes urticaria and mild dermatitis. This is the result of histamine release, which also causes some vasodilation, leading to redness of the skin and eyes, as well as pruritus (itching). Morphine, codeine, and meperidine are the agents associated with the most histamine release.
6. Genitourinary System
   Morphine causes spasm of smooth muscles of the urinary bladder, leading to decreased urinary retention. This can become clinically significant with long-term doses. Opioids can also decrease sexual activity, causing a decrease in libido with long-term use.
7. Tolerance and Dependence
   Tolerance is the decline of drug effect over time where increased doses are needed to obtain the same clinical effect. This occurs with all opioids to varying degrees. Physical dependence occurs when uncomfortable symptoms of withdrawal ensue upon abrupt discontinuation of the medication. When narcotic agents are administered over long periods of time, tolerance and physical dependence are more likely to occur.

NEED TO KNOW

Sedation, miosis, and respiratory depression are symptoms of using high doses or in an overdose of opioid analgesics.

NEED TO KNOW

Constipation, drowsiness, and rash are common adverse effects experienced by individuals using opioids for the treatment of pain. Histamine release caused by morphine, codeine, or meperidine more commonly cause rash, urticaria, or dermatitis than other opioids.

Narcotic Antagonists

Naloxone (Narcan®) and naltrexone (Vivitrol) are opioid antagonists that block the activity of opioids on the mu receptor. They pose no agonist or analgesic activity. Naloxone is used for the treatment of opioid overdose and can also be used to treat opioid-dependence disorder. Naltrexone is used to treat opioid-dependence disorder. Care should be taken when giving these drugs to individuals who are physically dependent on opioids and are not having overdose symptoms because they can precipitate a withdrawal syndrome. The main antagonist is naloxone (Narcan). It should be noted that the reversal of the overdose effect may be temporary and the patient should be observed closely for possible relapse into respiratory depression. Naloxone is available in an injectable and intranasal formulation for quick reversal in an opioid overdose.

Non-Opioid Analgesics

The non-opioid analgesics are not related chemically or structurally to the opioid agents. They relieve mild-to-moderate pain without the loss of consciousness. In addition, these agents produce analgesia through a peripheral as well as a central mechanism of action and do not produce tolerance or physical dependence with long-term use. Also, most of the nonnarcotic agents produce an **antipyretic** effect to reduce fever, and some produce an anti-inflammatory effect. The

salicylates, NSAIDs, and acetaminophen are the most commonly used non-opioid drug classes. These agents do not produce tolerance or dependence like opioids.

Nonsteroidal Anti-Inflammatory Drugs

There are multiple clinically significant drugs that fall into the class of NSAIDs (**Table 14-8**). Aspirin is the prototype of the salicylates and other NSAIDs. Salicylates are considered NSAIDs owing to the similar mechanism of action but they differ in the frequently used indications from other NSAIDs. Prostaglandins are mediators of inflammation and are released from pain nerves when one perceives pain. Prostaglandins can also stimulate the hypothalamus to elevate body temperature. Cyclooxygenase enzymes (e.g., COX-1 and COX-2) convert arachidonic acid into prostaglandins. NSAIDs exert their effects by inhibiting these enzymes and decrease the synthesis of prostaglandins in both the periphery and the hypothalamus. This mechanism of action leads to the analgesic, anti-inflammatory, and antipyretic effects of NSAIDs. NSAIDs inhibit thromboxane A_2, thus inhibiting platelet aggregation as well. Aspirin irreversibly inhibits cyclooxygenase and other NSAIDs only reversibly inhibit the enzyme. The irreversible action of aspirin leads to a longer antiplatelet activity, thus preventing platelet aggregation beneficial in the prevention or treatment of thrombosis leading to myocardial infarction (MI) and stroke.

TABLE 14-8
Commonly Used NSAIDs

Drug	Therapeutic Use	Adverse Effects
Aspirin (acetylsalicylic acid)	Antiplatelet in prevention or treatment of MI or stroke, analgesic, anti-inflammatory, and antipyretic	GI irritation, GI bleeding, bruising, renal failure, aspirin-induced asthma, hypersensitivity, edema, tinnitus, anemia, and elevated liver enzymes

Methyl salicylate (Bengay, Salonpas, Icy Hot)	Topical treatment for temporary relief of minor aches/pains associated with joints, arthritis, backaches, and sprains/strains	Skin irritation, blistering, and second- or third-degree burns
Ibuprofen (Advil®, Motrin®)	Analgesic, antipyretic, and anti-inflammatory	GI irritation, GI bleeding, bruising, renal failure, hypersensitivity, rash, edema, hypertension, MI, stroke, anemia, and elevated liver enzymes
Naproxen (Naprosyn®)	Same as ibuprofen	Same as ibuprofen, lower to no cardiovascular risk, and longer half-life leads to less frequent dosing
Indomethacin (Indocin®)	Anti-inflammatory and gout	Same as ibuprofen, anemia, thrombocytopenia, and agranulocytosis
Ketorolac	Analgesic	IV formulation, increased risk of GI ulceration, and renal dysfunction (limit use to 3–5 days)
Piroxicam (Feldene®)	Anti-inflammatory	Same as ibuprofen
Meclofenamate (Meclomen®)	Anti-inflammatory	Same as ibuprofen
Diclofenac (Voltaren®)	Analgesic and anti-inflammatory	Same as ibuprofen, lower risk of GI ulcer, higher risk of MI/stroke at high doses, and hepatotoxicity
Celecoxib (Celebrex)	Analgesic and anti-inflammatory	Same as ibuprofen, lower risk of GI ulcer, increased risk of MI, and stroke

GI, gastrointestinal; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs.

NSAIDs are primarily used for the treatment of pain caused by headache, muscle pain, osteoarthritis, rheumatoid arthritis, and gout. They are also used as an antipyretic to lower body temperature

(when elevated). In high doses, these drugs can cause **uricosuria** and increase the excretion of uric acid to facilitate the management of gout. The most common use of aspirin is for its antiplatelet activity in the prevention or treatment of cardiovascular disease.

The adverse effects reported with NSAIDs may limit their use in some patient populations. The lowest effective dose administered for the shortest time may limit the side effects with these agents. About 0.2–0.9% of the population experiences a hypersensitivity reaction resembling a true allergic phenomenon. These hypersensitivity reactions include bronchospasm, urticaria, edema, and hypotension. Some patients develop an asthma-like reaction associated with aspirin use. Other NSAIDs should not be used in these patients for risk of cross-sensitivity. The most common adverse effects with NSAIDs are GI discomfort, dyspepsia, nausea, vomiting, and diarrhea, and when used in high doses or for long periods of time can cause a GI ulceration and bleeding. The antiplatelet activity of aspirin may be beneficial in some patients when administered at low doses but may still increase the risk of bleeding. NSAIDs may also cause bruising and bleeding, which is increased when used with other antiplatelet drugs and anticoagulants. Although aspirin can be beneficial in patients with cardiovascular disease, NSAIDs that more selectively inhibit the COX-2 enzyme (e.g., celecoxib and diclofenac) have been associated with an increased risk of developing a MI, heart failure, and stroke. Another known adverse effect of all NSAIDs is the development of renal dysfunction and hypertension with chronic use. This is usually only seen in patients at risk of renal dysfunction, such as with concomitant dehydration, hypovolemia, heart failure, and in chronic liver or kidney disease.

NEED TO KNOW

Aspirin can cause a worsening of asthma and hypersensitivity reaction in some patients. There is a risk of cross-sensitivity with other NSAIDs and should not be used in patients that develop this reaction to aspirin.

In the case of an overdose, both aspirin and most NSAIDs can present with a metabolic acidosis, nausea, vomiting, tinnitus (ringing in the ear), CNS changes, and renal dysfunction. Salicylates initially cause hyperventilation, resulting in a respiratory alkalosis, then develops into a metabolic acidosis. Supportive care, intravenous sodium bicarbonate, and hemodialysis are treatment strategies for these overdoses.

Acetaminophen

Other non-salicylate drugs that are commonly used today are substances that are classified as para-aminophenols. Acetaminophen (Tylenol®) is the only drug available in this class. Acetaminophen is commonly used and relatively safe. Its most frequent uses are as an analgesic and antipyretic in adults and children. It is frequently used in combination with opioids in the treatment of pain. It weakly inhibits cyclooxygenases and has insignificant anti-inflammatory activity. Acetaminophen's mechanism of action is not fully clear, but it acts as a noncompetitive, weak inhibitor of cyclooxygenase.

Acetaminophen is much better tolerated than aspirin and other NSAIDs. It causes minimal gastric upset and has no effect on platelets, cardiovascular, and renal function. However, in high doses, it can cause severe hepatic necrosis and death. It should be noted that, in cases of acetaminophen overdose, treatment often includes the use of a respiratory mucolytic agent, acetylcysteine, administered orally or intravenously. The use of this drug is discussed in Chapter 8.

NEED TO KNOW

Aspirin, NSAIDs, and acetaminophen have antipyretic and analgesic effects, but only NSAIDs and aspirin have anti-inflammatory and uricosuric properties.

General Anesthetics

A **general anesthetic** can be defined as a drug that induces the absence of all sensation. General anesthetics are a diverse group of drugs that include gases, volatile liquids, and intravenous agents (**Table 14-9**). Analgesia is the absence of pain and some anesthetics also have analgesic properties. Anesthesia is used to facilitate surgical procedures. Inhaled anesthetics and volatile liquids are commonly used with induction agents, opioids, and muscle relaxants. Lower and safer doses can be used when multiple agents are used together. There are many theories as to the mechanism of action of general anesthetics. They represent a clinically diverse group of drugs. Many agents work by enabling GABA activity at the GABA receptors. Although there are probably several different types of mechanisms operating, the current theory is that general anesthetics inhibit excitatory presynaptic activity and potentiate postsynaptic channel inhibitory activity by influencing synaptic nerve transmission. When general anesthetic agents are administered, they cause direct depression of the CNS so that various surgical procedures can be performed without regard to patient discomfort. However, there are other effects that occur, such as cardiovascular depression caused by a direct effect on the myocardium and vascular smooth muscle.

TABLE 14-9
General Anesthetics

Inhalation
Gases: nitrous oxide
Volatile liquids: desflurane, enflurane, halothane, isoflurane, methoxyflurane, and sevoflurane
Intravenous agents: methohexital, fentanyl, ketamine, propofol, remifentanil, and etomidate (discussed in Chapter 12 or in another section of this chapter)

With the introduction of ether as a general anesthetic agent in the mid-1800s, various clinical stages of anesthesia were observed and documented. The stages of anesthesia start as a decreased awareness to pain and can fluctuate to severe respiratory/cardiac depression leading to death. They were particularly important in the early days of general anesthetic administration in order to determine the approximate level of CNS depression. With the development of newer anesthetic drugs and sophisticated monitoring devices, the observation of the various stages of anesthesia is not quite as important. However, a well-qualified anesthesiologist must be able to observe the clinical signs of these stages along with the use of monitoring devices. The goal in surgical anesthesia is to render the patient unconscious without pain reflexes and maintain BP and respiration.

Properties of an Ideal General Anesthetic

There is no single agent available today that combines all the qualities that are desirable for an ideal general anesthetic. **Table 14-10** lists all the properties deemed necessary for safe and effective anesthesia. An anesthesiologist uses a combination of agents in an attempt to achieve as many of the desirable characteristics as possible.

TABLE 14-10
Characteristics of an Ideal General Anesthetic

1. High margin of safety at all levels
2. Capable of producing surgical anesthesia
3. Rapid and pleasant induction and recovery
4. Easily controlled and regulated at all levels
5. Low risk of cardiac and respiratory depression
6. Nonflammable and nonexplosive
7. Potent analgesic
8. Causes muscle relaxation
9. Low cost

Inhaled General Anesthetics

Since the demonstration of anesthesia with the gas nitrous oxide (N_2O) by Wells in 1844 and the volatile liquid diethyl ether (C_2H_5–O–C_2H_5) by Morton in 1846, the inhalation anesthetics have been the mainstay of general anesthesia. The main inhaled gas used in clinical practice for anesthesia is nitric oxide as well as three volatile liquid anesthetics, isoflurane, desflurane, and sevoflurane. The other volatile liquids in Table 14-10 are either no longer available or not used in clinical practice. The volatile liquids are combined with either oxygen or nitric oxide, vaporized and inhaled and absorbed from the alveoli into systemic circulation and into the brain. **Table 14-11** summarizes the various inhalation agents available along with some advantages and disadvantages.

TABLE 14-11
Inhaled General Anesthetics

Name	Advantages	Limitations
Nitric oxide	Rapid induction, analgesic, and minimal effect on BP	Low potency, causes vomiting, and cannot be used as sole anesthetic
Desflurane (Suprane)	Very rapid recovery (ideal in obese, neurology, and outpatients) and causes skeletal muscle relaxation	Airway irritant (cannot be used for induction) and hypotension
Isoflurane (Forane)	Rapid recovery, causes bronchodilation, and some muscle relaxation	Airway irritant (cannot be used for induction), cheaper than desflurane and sevoflurane, and dose-dependent hypotension
Sevoflurane (Ultane)	Can be used for induction, rapid recovery, potent bronchodilator, and causes muscle relaxation	Expensive, possible renal toxicity, risk of causing spontaneous fire, and decreased BP and cardiac output

BP, blood pressure.

Preanesthetic Medications

Before a surgical or endoscopic procedure, patients may be apprehensive, frightened, and extremely anxious. This extreme anxiety can increase the overall level of excitability of the CNS, which in some cases can necessitate administering higher levels of general anesthetics to obtain the proper level of surgical anesthesia. In order to control these levels of excitability and anxiety, various drugs can be administered before the procedure that has the following effects: analgesia, antianxiety, sedation, hypnosis, and decrease in secretions. Used in various combinations and administered according to specific need, these agents can relieve preoperative and postoperative pain, decrease the amount of general anesthetic agent needed, and decrease adverse side effects. Opioids, benzodiazepines, and dexmedetomidine can be used to relieve pain and decrease anxiety or act as adjuncts to other inhaled or intravenous anesthetics. Atropine or glycopyrrolate are commonly used anticholinergics to decrease secretions. These categories of drugs are used as preanesthetic, pre-procedure, or conscious sedation agents.

Conscious Sedation

Conscious sedation is a procedure in which a patient who is undergoing an invasive procedure, such as a bronchoscopy, colonoscopy, or cardiac catheterization, is given medications to reduce the pain and anxiety of such procedures while allowing the patient to follow verbal commands and maintain his or her own airway. Respiratory therapists are often included in the healthcare professionals trained to administer conscious sedation because they also provide a knowledge and skill base to assist in resuscitation, airway management, and patient care.

Standards for providing conscious sedation have been developed by the Joint Commission on Accreditation of Healthcare Organizations. These standards do not specify which health professionals should be credentialed to provide conscious sedation

(RCP, registered nurse, radiographic technologist, certified registered nurse anesthetist, etc.), but they provide specific guidelines for patient safety. Guidelines include requiring the presence of at least two qualified providers during conscious sedation and they address minimum monitoring requirements. All patients receiving conscious sedation should have an IV established and should be continuously monitored by pulse oximetry. BP should be monitored at least every 15 minutes during sedation, and if the patient becomes more deeply sedated, the monitoring should include end-tidal CO_2 measurement and more frequent BP measurements (i.e., every 5 minutes). Electrocardiogram monitoring should also be available and should always be initiated if the patient has a history of cardiac dysrhythmias or becomes more deeply sedated.

When conscious sedation is required before a patient undergoing diagnostic imaging via MRI, the drug of choice is midazolam (Versed®). Although lorazepam (Ativan®) may adequately sedate the patient before the procedure, patients sedated with lorazepam do not tolerate the noise and vibration associated with MRI.

Review Questions

1. Which part of the brain maintains respiratory function?
2. Describe the mechanisms of action of barbiturates and benzodiazepines and, assessing their adverse effects, explain why barbiturates have fallen out of favor as sedative hypnotics.
3. List three examples of SSRIs and explain why they are used as first-line agents in the treatment of depression compared with MAOIs and TCA drugs.
4. List the three mood-stabilizing drugs used to treat bipolar disorder and the monitoring parameters associated with the use of each to assess effectiveness and prevent toxicity.
5. List the common uses of psychostimulant drugs and describe how these agents improve focus and cons associated with use.
6. Define the term epilepsy and explain the difference between a focal and generalized seizure disorder.
7. Summarize the mechanisms of action of phenytoin, valproic acid, carbamazepine, and levetiracetam and the effects that should be monitored to assure efficacy and toxicities associated with long-term use.
8. Compare the mechanisms of action of FGAs and SGAs and explain the differences in effectiveness and toxicities in the treatment of schizophrenia.
9. Discuss the differences in mechanism of action between opioid and non-opioid analgesics.
10. Describe the adverse effects of opioids on the respiratory, CNS, and GI systems.
11. Describe the important clinical use of naloxone and its mechanism of action.
12. Compare and contrast the clinical uses and adverse effects of aspirin, other NSAIDs, and acetaminophen.
13. Define the term *general anesthesia* and list five properties of an ideal general anesthetic.

14. List four commonly used inhaled anesthetic gases or volatile liquids.
15. Discuss the rationale for the administration of preanesthetic agents and other drugs with inhaled anesthetics.

Posttest

For each of the following questions, try to select the *one* best answer from the choices given.

1. A respiratory therapist is about to initiate incentive spirometry for a post-op patient. When reviewing the patient's chart and current medications, which of the following medications might cause the therapist to have concerns regarding the patient's ability to follow directions and cooperate with the treatment?
   a. Theophylline
   b. Naloxone (Narcan®)
   c. Beclomethasone (QVAR®)
   d. Phenobarbital
2. Generally, a sedative drug can become a hypnotic by increasing the dose. True or False?
3. All of the following statements about benzodiazepines are true, *except*:
   a. These agents have relatively few side effects in comparison to barbiturates.
   b. The main clinical use of these drugs is the treatment of anxiety.
   c. The overall mechanism of action is to block the inhibitory effect of GABA neurotransmitters.
   d. They can create additive effects when administered with alcohol and other CNS depressants.
4. A respiratory therapist is caring for a patient with a flail chest who is intubated and receiving mechanical ventilation with positive end-expiratory pressure. Which of the following medications is the most appropriate recommendation to provide analgesia for this patient's severe pain?
   a. Midazolam
   b. Desflurane
   c. Morphine
   d. Haloperidol

5. All of the following general anesthetics agents are volatile liquids, *except*:
   a. sevoflurane.
   b. nitrous oxide.
   c. methoxyflurane.
   d. flurothane.
6. Which of the following side effects of morphine would a respiratory therapist be required to monitor?
   1) Hypotension
   2) Bradycardia
   3) Respiratory depression
   4) Tachypnea
   5) Pupillary dilation
      a. 1 and 3 only
      b. 2, 4, and 5 only
      c. 1 and 5 only
      d. 3 and 5 only
7. Which of the following are reasons for administering preanesthetic medications before inducing general anesthesia?
   1) Decrease anxiety
   2) Decrease amount of general anesthetic agent needed
   3) Reduce secretions
   4) Avoid the need for skeletal muscle relaxants
      a. 1 and 3 only
      b. 1, 2, and 3 only
      c. 2, 3, and 4 only
      d. 1, 2, 3, and 4
8. All of the following are known effects of acetylsalicylic acid (aspirin), *except*:
   a. sedation.
   b. antiplatelet.
   c. anti-inflammatory action.
   d. antipyresis.
9. An RCP is providing incentive spirometry for a post-op patient and notes that the patient is febrile. What is the most appropriate

medication the therapist should recommend to treat this patient's fever?

a. Albuterol
b. Thorazine
c. Lorazepam
d. Acetaminophen

10. Which of the following agents can be used in the treatment of bipolar disorder and for epilepsy?
    a. Lithium
    b. Phenytoin
    c. Lorazepam
    d. Valproic acid

References/Recommended Readings

American Association for Respiratory Care. *Position Statement: Administration of Sedative and Analgesic Medications by Respiratory Care Practitioners*. Irving, TX: AARC; 1998.

American Psychiatric Association. Practice Guideline for the Treatment of Major Depressive Disorder. 3rd ed. Arlington, VA: American Psychiatric Association; 2010.

Barr J, Fraser G, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation and delirium in adult patients in the intensive care unit: special article. *Crit Care Med.* 2013;41(1):263–306.

Bennett S, Hurford W. When should sedation or neuromuscular blockade be used during mechanical ventilation? *Respir Care.* 2011;56(2):168–180.

Beumont A, Hughes J. Biology of opioid peptides. *Annu Rev Pharmacol*. 1979;19:203–244.

Blackwell B. Newer antidepressant drugs. In: Meltzer HY, ed. *Psychopharmacology: The Third Generation of Progress.* New York, NY: Raven Press; 1987:1041–1049.

Broyles BE, Reiss BS, *Pharmacological Aspects of Nursing Care.* Clifton Park, NY: Delmar Cengage Learning; 2013.

Brunton LL, Lazo JS, Parker KL, eds. *Goodman and Gilman's the Pharmacological Basis of Therapeutics*. 11th ed. New York, NY: McGraw-Hill Medical Publishing; 2006.

Buoli M, Kahn RS, Serati M, et al. Haloperidol versus second-generation antipsychotics in the long-term treatment of schizophrenia. *Hum Psychopharmacol*. 2016;31:325–331.

Cavaliere F, Antonelli M, Arcangeli A, et al. A low-dose remifentanil infusion is well-tolerated for sedation in mechanically ventilated, critically-ill patients. *Can J Anaesth*. 2002;49(10):1088–1094.

Clavenna A, Bonati M. Safety of medicines used for ADHD in children. *Arch Dis Child*. 2014;99:866–872.

Conti G, Arcangeli A, Antonelli M, et al. Sedation with sufentanil in patients receiving pressure support ventilation has no effects on respiration: a pilot study. *Can J Anaesth*. 2004;51(5):494–499.

Coxib and Traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet.* 2013;382(9894):769–779.

Dawsom J, Jones M. The principles of anaesthesia. *Surgery.* 2016;34:74–78.

Dopheide JA, Pliszka SR. Attention deficit hyperactivity disorder: an update. *Pharmacotherapy.* 2009;29:656–679.

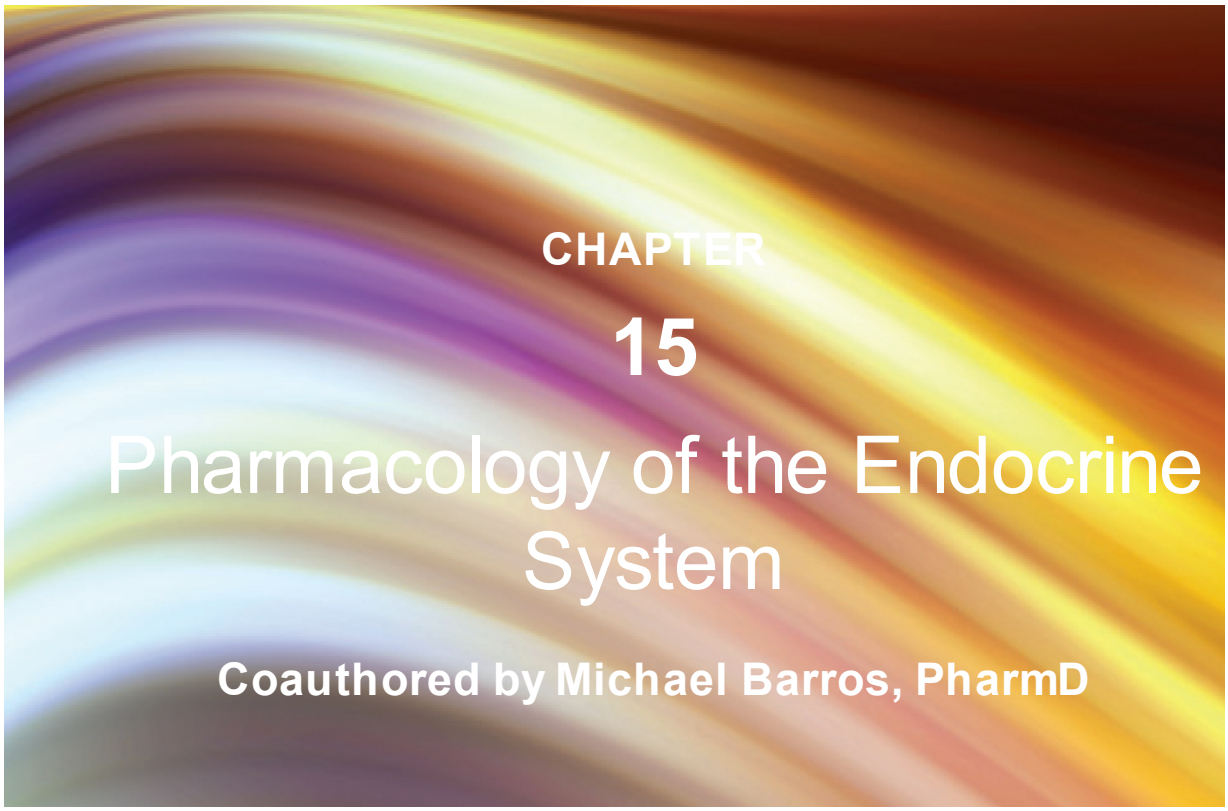
Dopheide JA, Pliszka SR. Attention deficit/hyperactivity disorder. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach.* 10th ed. New York, NY: McGraw-Hill Education; 2017:945–958.

Durbin CG. Respiratory therapists and conscious sedation. *Respir Care.* 1999;44:909.

Food and Drug Administration (FDA). Drug Safety Communication: rare cases of serious burns with the use of over-the-counter topical muscle and joint pain relievers, 2012. http://www.fda.gov/Drugs/DrugSafety/ucm318858.htm. Accessed August 2, 2018.

Hilal-Dandan R, Brunton LL. General anesthetics and therapeutic gases. In: Hilal-Dandan R, Brunton LL, Hilal-Dandan R, Knollmann BC. eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 13th ed*. New York, NY: McGraw-Hill; 2018.

Giuseppe N, Di Maio A, Rosano A, et al. Remifentanil improves breathing pattern and reduces inspiratory workload in tachypneic patients. *Respir Care.* 2011;56(6):827–833.
Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILEA evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*. 2013;54:551–563.
Hasin D, Sarvet A, Meyers J. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry*. 2018;75:336–346.
Hitner H, Nagle BT. *Basic Pharmacology: An Introduction.* 6th ed. San Jose, CA: Glencoe Publishing Co; 2011.
International Association for the Study of Pain. Classification of Chronic Pain, Second Edition (Revised). 2012. http://www.iasp-pain.org/PublicationsNews/Content.aspx?ItemNumber=1673&navItemNumber=677. Accessed September 2, 2018.
Komossa K, Rummel-Kluge C, Hunger H, et al. Olanzapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010;3:CD006654.
McElroy SL, Hudson JI, Mitchell JE, et al. Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry*. 2015;72:235–246.
Rainforth Collins, S. *Mosby's Drug Reference for Health Professionals.* 6th ed. St. Louis, MO: Mosby-Elsevier; 2018
Muellejans B, Lopez A, Cross, MH, et al. Remifentanil versus fentanyl for analgesia based sedation to provide patient comfort in the intensive care unit: a randomised, double-blind controlled trial. *Crit Care.* 2004;9(3):R200–R210.
Natalini G, Di Maio A, Rosano A, et al. Remifentanil improves breathing pattern and reduces inspiratory workload in tachypneic patients. *Respir Care* 2011;56(6):827–833.
Rizzo DC. *Fundamentals of Anatomy and Physiology.* Clifton Park, NY: Delmar Cengage Learning; 2010.
Sakai EM, Connolly LA, Klauck JA. Inhalation anesthesiology and volatile liquid anesthetics: focus on isoflurane, desflurane and sevoflurane. *Pharmacotherapy.* 2005;25:1773–1788.
Scheffer IE, Berkovic S, Capovilla G. ILAE classification of the epilepsies: position paper of the ILEA commission for classification and terminology. *Epilepsia*. 2017;58:512–521.
Scheffler RM, Brown TT, Fulton BD, et al. Positive association between attention deficit/hyperactivity disorder medication use and academic achievement during elementary school. *Pediatrics* 2009;123:1273–1279.
Shankar V, Churchwell KB, Deshpande JK. Isoflurane therapy for severe refractory status asthmaticus in children. *Intensive Care Med.* 2006;32(6):927–933.
Skolnick P, Paul SM. The mechanism of action of benzodiazepines. *Med Res Rev.* 1982;306:401.
Spratto GR, Woods, AL, *Nurse's Drug Handbook*. Clifton Park, NY: Delmar Cengage Learning; 2013.
Turner DA, Heitz D, Cooper MK, et al. Isoflurane for life-threatening bronchospasm: a 15-year single-center experience. *Respir Care.* 2012;57(11):1857–1864.
Wang GJ, Geliebter A, Volkow ND, et al. Enhanced striatal dopamine release during food stimulation in binge eating disorder. *Obesity.* 2011;19:1601–1608.
Wilkins RL, Stoller JK, Kacmarek RM. *Egan's Fundamentals of Respiratory Care.* 9th ed. St. Louis, MO: Mosby-Elsevier; 2009.



© Anna RubaK/ShutterStock, Inc.

OUTLINE

Introduction
Pituitary Gland and Hypothalamus
Control of Hormone Release
Corticosteroids
  Glucocorticoids
  Mineralocorticoids
Function of the Thyroid Gland
  Treatment of Hypothyroidism
  Treatment of Hyperthyroidism
Function of the Pancreas
  Cystic Fibrosis
  Diabetes Mellitus
  Treatment of Type 1 Diabetes
  Treatment of Type 2 Diabetes
Antigen–Antibody Reactions
  Effects of Histamine
  Histamine Receptors
  Antihistamines and Antiallergic Agent Definitions

OBJECTIVES

After completion of this chapter and its learning activities, you will be able to:

1. Explain the relationship between the pituitary gland and the hypothalamus as the regulatory mechanism of hormones.
2. Describe negative feedback as an example of an endogenous control mechanism of hormones, using thyroxin as an example.
3. Summarize the overall effects, therapeutic uses, and side effects of the glucocorticoids; also list some of the synthetic glucocorticoids.
4. Compare and contrast hyperthyroidism and hypothyroid symptoms and list the drugs and mechanism to treat each.
5. Describe the overall function of the pancreas and explain the functions of insulin and glucagon.
6. List the pancreatic enzymes found in pancreatic enzyme replacement therapy for cystic fibrosis and explain the rationale for use.
7. Compare the pathogenesis of the two types of diabetes mellitus (DM).
8. Choose appropriate drug therapy for the treatment of type 1 and type 2 DM and describe the general mechanism of action and side effects of each drug class.
9. Describe the relationship between antigen–antibody reactions, mast cells, and histamine.
10. Identify the overall effects of histamine and list the locations and types of histamine receptors.
11. Distinguish between the common uses and the adverse effects of first- and second-generation antihistamines.

KEY TERMS

Antibody
Antigen
Corticosteroids
Cystic fibrosis
Diabetes mellitus
Glucocorticoids
Gluconeogenesis
Histamine
Homeostasis
Hormones
Negative feedback
Releasing hormones
Tropic hormones

Introduction

Like the nervous system, the endocrine system regulates various functions of the body. This is accomplished by the release of chemicals (**hormones**) directly into the bloodstream from various endocrine glands located throughout the body. In contrast to nervous control of the body's functions, hormones have a slower onset and a longer duration of action. Hormones are regulatory and are an intricate part of the body's control mechanisms. They differ from drugs in the following ways:

1. In general, hormones have a higher therapeutic index, meaning that the effective dose or concentration is much lower than a dose or concentration that can give you toxic effects.
2. Unlike most drugs, many have an endogenous control mechanism called feedback control that can shut off or turn on activity.
3. Many hormones have effects on various organ systems.
4. The effects of one hormone can be additive, nonreactive, or antagonistic with those of a second hormone.

Hormones and related compounds are used therapeutically and have the following uses:

1. Replacement therapy
2. To reduce endogenous hormone synthesis
3. To reduce the effects of endogenous hormones
4. In the diagnosis of endocrine pathophysiology

This chapter discusses a select group of hormones that are commonly used therapeutically along with some disease states that are treated by these hormones. The hormones included are adrenocorticosteroids, thyroid and parathyroid hormones, insulin, and glucagon. Because many drug classes used in the treatment of diabetes regulate insulin by different mechanisms, the treatment of this common and important disease state is discussed in this chapter.

The antihistamines are also discussed in this chapter because histamine is an endogenous substance that is released into the bloodstream by mast cells and, like hormones, have a broad effect throughout the body.

Pituitary Gland and Hypothalamus

The pituitary gland is often referred to as the “master endocrine” gland of the body. It is a pea-sized gland, located in the brain attached to an inferior portion of the brain called the hypothalamus (**Figure 15-1**), which is located behind the bridge of the nose.

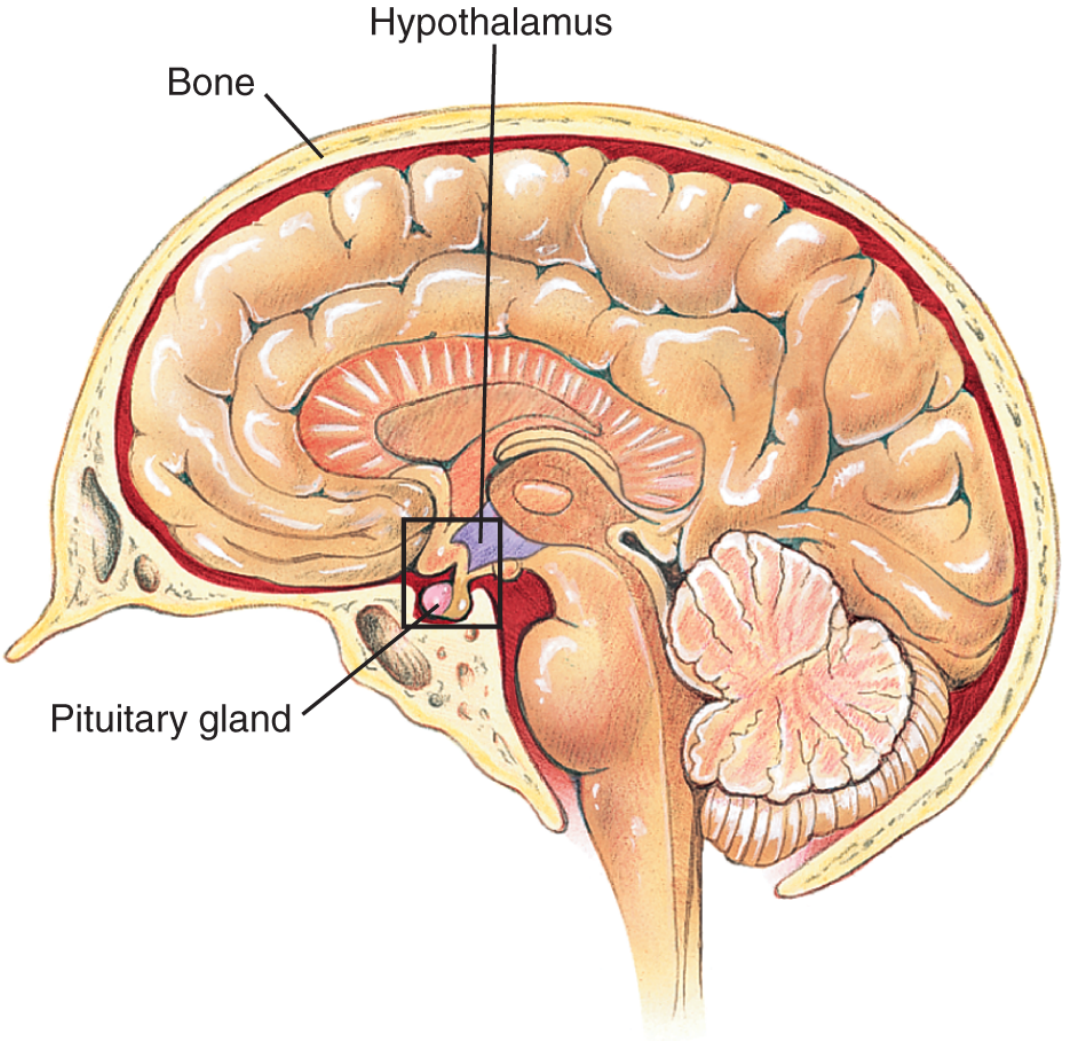


FIGURE 15-1 Relationship between pituitary gland and hypothalamus.

The hypothalamus is the part of the central nervous system (CNS) that controls the autonomic nervous system as well as the pituitary gland. It is the close association between the hypothalamus and the

pituitary gland that establishes a direct anatomical relationship between the two systems of the body responsible for involuntary control of **homeostasis** between the autonomic nervous system and the endocrine system. The autonomic nervous system was reviewed in Chapter 3; this chapter discusses how the hypothalamus controls the pituitary gland. Whereas the autonomic nervous system controls functions of the body by direct innervation through parasympathetic and sympathetic nerves, the endocrine system controls body functions by secreting hormones directly into the bloodstream.

The pituitary gland comprises two lobes: the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis). Each of these lobes contains different hormones that can be released into the systemic circulation. Each lobe is controlled by the hypothalamus by two different mechanisms. The hormones of the adenohypophysis (anterior lobe) are controlled by **releasing hormones** produced by the hypothalamus. The hormones of the adenohypophysis include growth hormone, human chorionic gonadotropin, adrenocorticotropic hormone (also referred to as corticotropin), follicle-stimulating hormone, prolactin, luteinizing hormone, thyroid-stimulating hormone (TSH, also referred to as thyrotropin), and melanocyte-stimulating hormone. Most of the hormones in the anterior lobe have an effect on other endocrine glands located throughout the body. Hormones that affect other endocrine glands are called **tropic hormones**.

The hormones of the posterior pituitary gland, also known as the neurohypophysis, are synthesized in the hypothalamus and travel through the nerve axons of neurosecretory cells to the posterior lobe, where they are stored until release. The hormones secreted by the neurohypophysis include antidiuretic hormone and oxytocin. In summary, there are actually three types of hormones that function in the endocrine system: the releasing hormones produced in the hypothalamus, the tropic hormones released from the anterior lobe that affect other endocrine glands, and the hormones released from each of the individual endocrine glands. **Figure 15-2** represents the structure of the pituitary gland and the hormones that are released from both lobes.

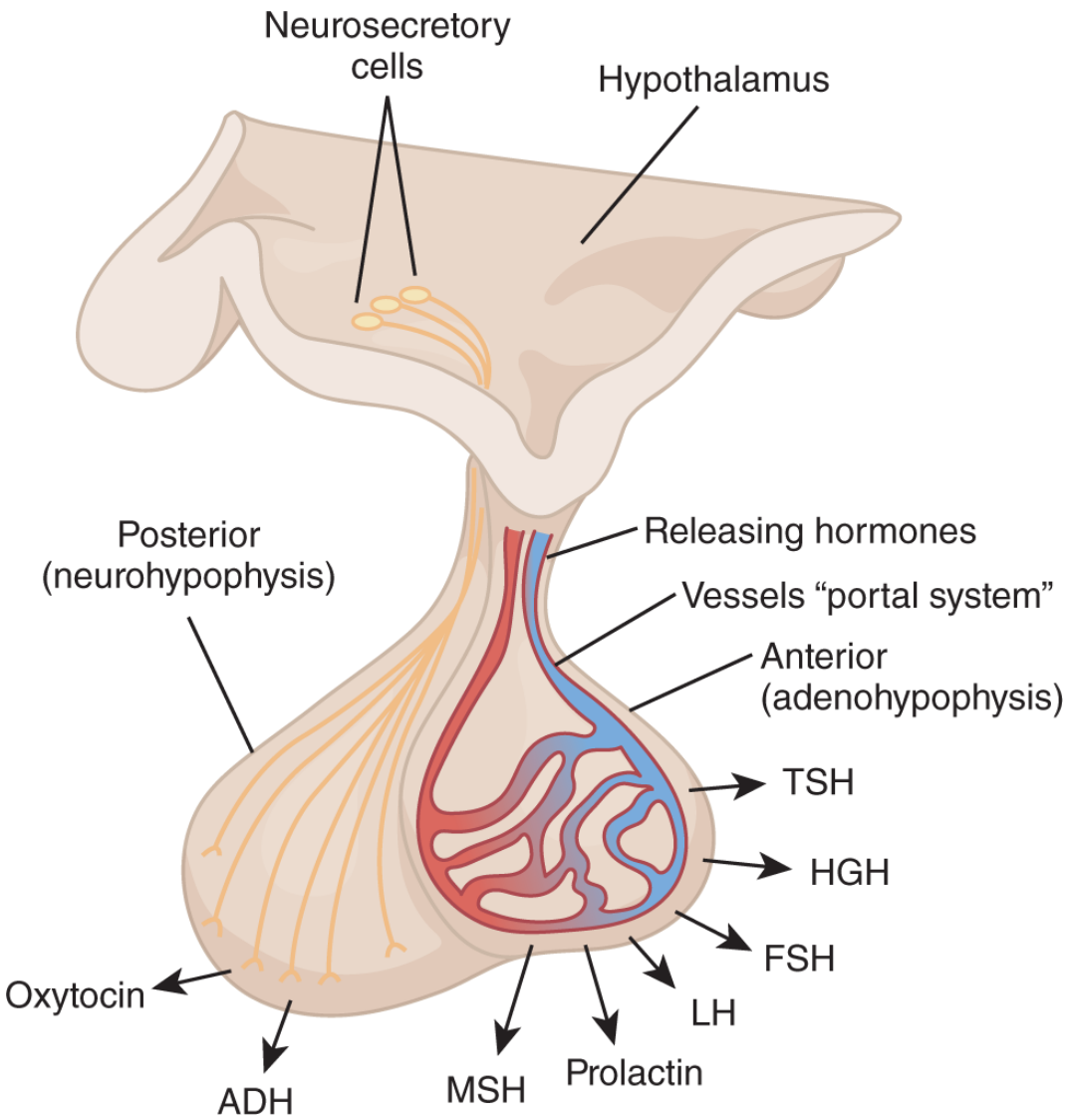


FIGURE 15-2 Hormones of the pituitary gland.

Description

Control of Hormone Release

With the release of the various hormones throughout the body, there is need for some type of control mechanism. Although several different mechanisms exist, the main type of control mechanism is known as **negative feedback**. The term negative feedback does not mean that the feedback is in some way harmful, but that, once a hormone is released and reaches a certain blood level, this appropriate blood level inhibits or prevents any further release by negative feedback. **Figure 15-3** shows an example of this negative feedback with the control of thyroxin release.

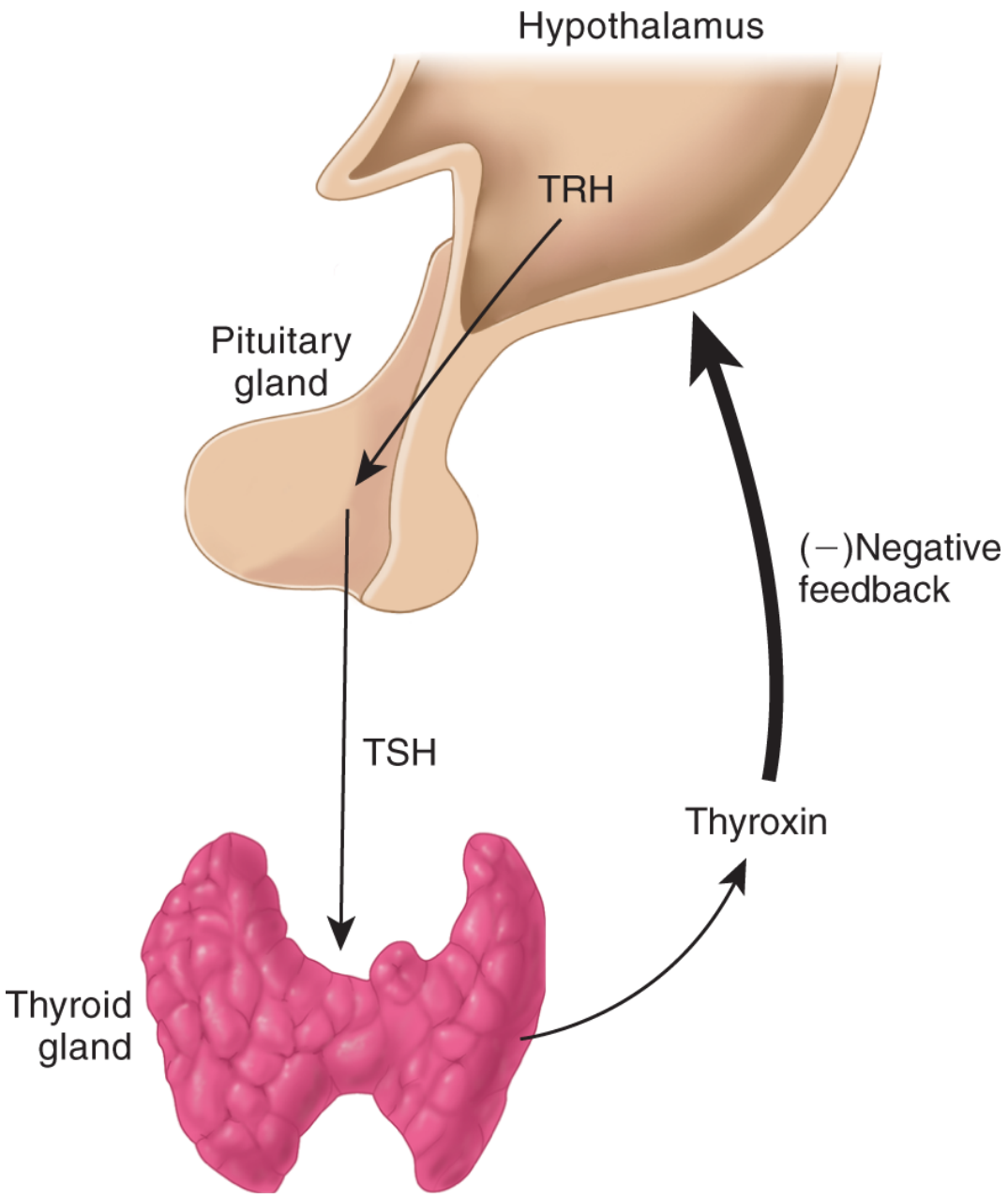


FIGURE 15-3 Negative feedback control of thyroxin.

Description

As seen in Figure 15-3, when thyroxin levels are low or there is a physiologic need to increase these levels, the hypothalamus releases thyrotropin-releasing hormone (TRH). This hormone travels through the portal system to the adenohypophysis and causes the release of TSH. TSH then travels to the thyroid gland through the systemic circulation and causes the thyroid gland to release thyroxin. When

thyroxin reaches normal levels, the elevated hormone concentration feeds back to the hypothalamus and shuts off the release of TRH. Thus, the increased level of the hormone feeds back and decreases its own release.

Corticosteroids

The adrenal (suprarenal) glands are located on the superior surface of each kidney. Each gland comprises an outer cortex and an inner medulla (**Figure 15-4**). The medulla is responsible for the secretion of catecholamines, which include epinephrine (also referred to as adrenaline) and norepinephrine (also referred to as noradrenaline). This is innervated by the sympathetic nervous system. When the body is in a "fight or flight" condition, catecholamines are secreted into the blood by the adrenal medulla. The adrenal cortex is divided into three zones, each of which produces a different hormone. These hormones are the **glucocorticoids**, the mineralocorticoids, and the gonadocorticoids, collectively known as **corticosteroids**. All the corticosteroids have specific functions and effects on the body. Glucocorticoids and mineralocorticoids are clinically more prevalent. Therefore, this chapter will only mention the general function of the glucocorticoids and mineralocorticoids. **Table 15-1** summarizes the overall effects of corticosteroids.

TABLE 15-1
Function of Corticosteroids

Corticosteroids	Overall Function
Glucocorticoids	Regulate metabolism of carbohydrates and proteins by gluconeogenesis and protein catabolism; have a potent anti-inflammatory effect; plays an important role in the body's response to stress
Mineralocorticoids	Sodium and potassium balance: controlled by reabsorption of sodium in the kidneys
Gonadocorticoids	Converted to testosterone and estrogen

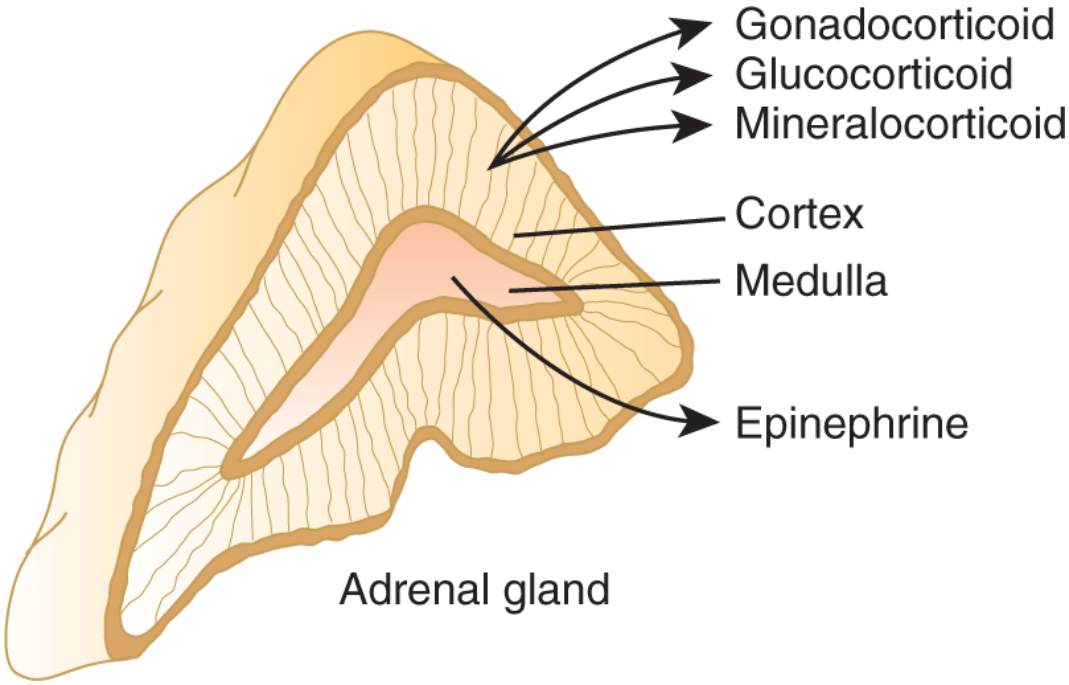


FIGURE 15-4 Hormone production of the adrenal gland.

Glucocorticoids

Glucocorticoids exert effects on almost every organ system and their effects are numerous. These agents are utilized at physiologic doses for replacement therapy when endogenous production is impaired. In addition, they possess anti-inflammatory properties and they are used in a variety of inflammatory and autoimmune disease states. The glucocorticoids are responsible for carbohydrate and protein metabolism, particularly during periods of stress. When the body is stressed, there is a need for glucose, particularly in glucose-dependent tissues such as the brain and heart. This is accomplished by replenishing the body stores of glucose through **gluconeogenesis** and protein catabolism. Other therapeutic uses of glucocorticoids include replacement therapy for adrenal gland insufficiency, as seen in Addison's disease, and the glucocorticoids often are used clinically as potent anti-inflammatory and immunosuppressive agents because of altering the immune response of lymphocytes. As such, these agents are widely used in conditions such as gout, allergic urticaria, and organ transplant. Inhaled glucocorticoids have become the first-

line control agents for chronic asthma and are discussed in more detail in Chapter 7. Systemic and oral steroid use may be needed in clinical situations such as an asthma or chronic obstructive pulmonary disease (COPD) exacerbation or when aerosolized steroids have been ineffective in controlling or reducing symptoms.

NEED TO KNOW

Systemic glucocorticoids may be used in emergency situations such as an asthma exacerbation when aerosolized bronchodilators and other measures have been unable to effectively reduce the patient airway obstruction.

Usually inflammation is a normal reaction of the healing process, but there are many pathologic conditions wherein inflammation itself becomes the disease process. Some of these are rheumatoid arthritis, asthma, systemic lupus erythematosus, and various chronic allergies. Clinically, the naturally occurring glucocorticoids were used as therapeutic agents, but today, newer synthetic agents are administered because of their longer duration of action and generally fewer side effects. **Table 15-2** lists the glucocorticoids, along with their comparative anti-inflammatory potency and doses.

TABLE 15-2
Anti-Inflammatory Activity of Corticosteroids

Drug	Anti-Inflammatory Potency	Mineralocorticoid Activity	General Anti-Inflammatory Equivalent Doses (mg)
Glucocorticoids			
Hydrocortisone	1	2	20
Cortisone	0.8	2	25
Prednisone	4	1	5
Prednisolone	4	1	5
Methylprednisolone	5	0	4
Triamcinolone	5	0	4
Betamethasone	25	0	0.75
Dexamethasone	25	0	0.75
Mineralocorticoids			
Fludrocortisone	10	125	N/A

A major problem with the clinical use of glucocorticoids arises from both abrupt withdrawal and prolonged use at high doses. A frequent problem with withdrawing steroids may include a flare-up of the underlying disease for which the steroids are being used. Also, acute adrenal insufficiency may occur from rapid withdrawal of the agent after prolonged therapy because of hypothalamic–pituitary–adrenal axis suppression. Therefore, it is recommended that steroids not be stopped suddenly but tapered slowly. Recommendations regarding when and how to taper a steroid, such as prednisone, remain controversial, but generally a taper is not needed if patients are taking less than 20 mg/day of prednisone for less than 2–3 weeks. This is the usually the case when using short-burst steroids for asthma or COPD. **Table 15-3** lists some of the adverse side effects that can occur with long-term glucocorticoid use.

TABLE 15-3
Adverse Effects of Glucocorticoids

Drug Effect	Symptoms
Increased gluconeogenesis	Obesity and diabetes mellitus

Increased protein catabolism	Muscle weakness, osteoporosis, decreased growth in children, poor wound healing, increase in infection, peptic ulcer formation, and Cushing's syndrome (edema, moon face, buffalo hump, etc.)
Miscellaneous effects	Glaucoma, cataract formation, euphoria, anxiety, and depression

Mineralocorticoids

The mineralocorticoids are responsible for maintaining a balance between sodium and potassium and help maintain fluid–electrolyte balance. The mineralocorticoid, aldosterone, is the main substance that controls sodium reabsorption. This occurs in the distal convoluted tubal of the nephron in exchange for potassium. Because of the reabsorption of sodium, water is also reabsorbed and thus normal sodium and water balance is maintained.

The mineralocorticoids are used clinically only when there is some type of adrenal failure, causing hyposecretion of aldosterone. This occurs when the adrenal gland is removed or as the result of some type of tumor. Also, the mineralocorticoids are used as replacement therapy in Addison's disease; however, a more potent mineralocorticoid, such as fludrocortisone (Table 15-2), is used because it will help in preventing sodium loss, hyperkalemia, and intravascular volume depletion. The main adverse effects that occur with mineralocorticoid use are sodium and water retention and loss of potassium. The symptoms associated with high levels of mineralocorticoids include edema, hypertension, and muscle weakness from the potassium loss.

Function of the Thyroid Gland

The thyroid gland is located anterior to the trachea just below the larynx. It produces three hormones that are responsible for growth and development of body tissue: triiodothyronine (T_3), thyroxine (T_4), and calcitonin. The designations T_3 and T_4 represent the number of iodine atoms attached to the central molecule. Iodine is absolutely essential in the synthesis of these two hormones, and this is one of the reasons that iodine is added to the normal source of salt (iodized salt) to ensure adequate amounts in the normal diet.

The secretion of T_3 and T_4 is under the control of TSH from the anterior pituitary gland. The secretion of calcitonin is controlled by calcium levels in the blood and is discussed in the section covering the parathyroid gland. When T_3 and T_4 are released into the bloodstream, they are responsible for stimulation of protein synthesis, increase in levels of blood glucose, increase in circulation of fatty acids, and decrease in serum cholesterol. All these substances are necessary and essential for cell repair and energy. Also, when there is an increase in T_3 and T_4, cellular metabolism increases and results in an elevation of the basal metabolic rate. Thus, these hormones are important in the generation of heat.

There are two disease entities or conditions of the thyroid gland that are treated by drugs: hyposecretion of T_3 and T_4, leading to hypothyroidism, and hypersecretion, leading to hyperthyroidism. Hyposecretion can be caused by excessive exposure to radiation, autoimmune thyroiditis (Hashimoto disease), lack or excess of iodine, lack of secretion of TSH from the pituitary, surgical removal of a thyroid gland, and drug-induced (e.g., amiodarone and lithium). Hypersecretion can be caused by tumors, drug-induced (e.g., amiodarone and lithium) or autoimmune disease (e.g., Graves' disease).

Treatment of Hypothyroidism

When hypothyroidism occurs, it is manifested differently in children and adults. In children and infants, hyposecretion can lead to mental and physical retardation and dwarfism. In adults, hyposecretion can cause symptoms including lethargy, low blood pressure, cold intolerance, depression, weight gain, menstrual disturbances, dry skin, and arthralgias.

Hypothyroidism is treated by hormone replacement, and these hormones are extracted from various animal sources or are produced synthetically. Levothyroxine, a synthetic form of T_4, is preferred for the treatment of hypothyroidism because this agent mimics the natural physiology of the thyroid gland and produces a more predictable dose–response. Although the various preparations are effective, they must be given on a gradual basis and carefully monitored to meet the patient's needs. Both liotrix and desiccated thyroid contain T_3 and T_4. The American Thyroid Association taskforce does not recommend the combination T_3 and T_4 formulations owing to a risk of thyrotoxicosis because of high T_3 concentrations in these formulations. **Table 15-4** lists several of the currently used preparations, along with their trade names.

TABLE 15-4
Thyroid Preparations

Drug	Trade Name
Levothyroxine sodium	Levothroid®, Synthroid®, Unithroid®
Liothyronine sodium	Cytomel®
Liotrix	Thyrolar®
Thyroid hormone (desiccated)	Armour Thyroid®

Adverse effects that are associated with overdose of thyroid hormones can include symptoms similar to hyperthyroidism, such as psychic disorders, diarrhea, increased blood pressure, weight loss, menstrual irregularities, and sweating. Also, elevated levels of these hormones can have a profound effect on the cardiovascular system, causing angina, hypertension, and cardiac arrhythmias. Patients should be instructed to take their dose in the morning on an empty stomach, at least 30–60 minutes before food. Also, thyroid supplementation should not be administered within 4 hours of calcium- or iron-containing products because efficacy may diminish.

NEED TO KNOW

Levothyroxine is the preferred synthetic hormone used for the treatment of hypothyroidism because it more closely resembles the natural physiology of the thyroid gland and produces a more predictable dose–response.

Treatment of Hyperthyroidism

When hyperthyroidism occurs, it is the result of increased secretion or release of T_3 and T_4. This excessive secretion usually is caused by a glandular tumor of the thyroid or pituitary gland or a malignancy of the hypothalamus. In addition, an autoimmune disease (e.g., Graves' disease) produces effects similar to chronic thyroid stimulation. The overall effects of excessive thyroid secretion cause symptoms that resemble excessive stimulation of the sympathetic nervous system. The hypersecretion may cause a condition of exophthalmic goiter, hypertension, weight loss, and thyroid storm. Thyroid storm is an acute life-threatening condition that can lead to dangerously high blood pressure, heart rate, and body temperature. This condition must be treated immediately when recognized.

The treatment of hyperthyroidism is accomplished by three approaches: use of antithyroid drugs, radiation, or surgical removal. Often a combination of these three methods is used in the treatment of this disease. The drugs used in the treatment of hyperthyroidism

have a very complex mechanism of action and basically interfere with various methods of absorbing iodine. This chapter will not go into details of the mechanism of action but will only summarize the main mechanisms that are pertinent to the various drugs mentioned. **Table 15-5** lists some of the commonly used antithyroid drugs with a brief description of mechanism of action.

TABLE 15-5
Antithyroid Drugs

Drug	Mechanism of Action
Potassium iodide and sodium iodide (Lugol's solution*)	• Excessive iodine doses inhibit the incorporation of iodine into the gland • Iodine also temporarily inhibits thyroid hormone synthesis and secretion into the circulation
Radioactive iodine (Iodotope I-131®)	• Emits radioactive particles to the glandular cell and destroys the gland
Methimazole (Tapazole®)	• Interferes with synthesis of T_3 and T_4
Propylthiouracil	• Interferes with synthesis of T_3 and T_4

The adverse effects of the antithyroid drugs include rash, fever, myalgia, jaundice, nausea, and bone marrow suppression. Methimazole is considered first-line agent over propylthiouracil. Propylthiouracil specifically has a "black box warning" for severe liver injury and acute liver failure. The goal of patients using radioactive iodine is to give a dose to induce hypothyroidism and then use replacement therapy throughout life. Also, high doses of iodine (high doses inhibit the thyroid gland from incorporating iodine) should be used only for short-term treatment because eventually the gland overcomes the suppression and there is an immediate surge in T_3 and T_4, causing a hyperthyroid crisis. Methimazole may cause birth

defects in the first trimester of pregnancy. Therefore, propylthiouracil is recommended in pregnant patients with hyperthyroidism during the first trimester, and then switched to methimazole after the first trimester to avoid potential liver toxicity.

Function of the Pancreas

The overall function of the pancreas is to produce important digestive enzymes plus two hormones, insulin and glucagon. Therefore, the pancreas functions as both an exocrine gland for digestion and an endocrine gland for the control of blood glucose levels. This chapter will not mention the digestive functions but will discuss the endocrine function of the two hormones.

Located throughout the body of the pancreas are islands of cells (islets of Langerhans) that secrete the two hormones. A type of cell called an α-cell secretes glucagon and another cell called a β-cell secretes insulin. Insulin levels are controlled in response to blood glucose levels. When the blood glucose level increases, insulin is released that has the following functions:

1. Increases glucose absorption into tissues that cannot absorb glucose without a special mechanism (i.e., skeletal muscle, cardiac tissue, and fat)
2. Stimulates the storage of glycogen
3. Stimulates the storage and synthesis of fat and protein

Glucagon is released in response to a drop in blood glucose levels and has the following functions: (1) stimulates breakdown of glycogen to glucose (glycogenolysis) and (2) stimulates the breakdown of protein through the conversion of amino acids to glucose (gluconeogenesis). Thus, insulin and glucagon maintain a homeostatic balance of blood glucose.

Cystic Fibrosis

Cystic fibrosis (CF) is a genetic disorder in which there is a deficiency of pancreatic digestive enzymes (usually leading to malabsorption of nutrients from the diet) and a mutation of a gene associated with the movement of chloride ions through cell membranes, which also affects sodium. The irregularity of sodium

movement results in changes in the consistency of secretions, and pulmonary secretions become copious, very thick, and tenacious (they are sticky and patients have difficulty clearing secretions by coughing). The excessive and tenacious secretions provide a rich environment for bacterial growth, thus CF patients are susceptible to developing recurrent pulmonary infections. Because the pulmonary complications of CF are the leading cause of death in these patients, respiratory therapists are often involved with CF care. Improving and maintaining clearance of secretions is discussed in Chapter 8 (Mucokinesis and Mucolysis). Administering aerosolized antibiotics to treat pulmonary infections is discussed in Chapter 10 (Aerosolized Antimicrobial Therapy). Symptoms of pancreatic insufficiency include steatorrhea (fatty/greasy stools) and failure to thrive, resulting in malnutrition and decreased weight or growth. In CF patients with pancreatic insufficiency, pancreatic enzyme replacement therapy (PERT) is used to improve fat absorption.

Pancreatic Enzyme Replacement Therapy

PERT is effective in CF patients with pancreatic insufficiency and inability to maintain an adequate weight. Pancreatic enzymes break down fats from food. Lipase, amylase, and protease are the pancreatic enzymes available in PERT replacement products. PERT consists of capsules or tablets that contain varying amounts of all three of these enzymes, but dosing is on the basis of lipase component. Guidelines have recommended a dose of 500–2500 units/kg/meal up to 10,000 units/kg/day or 4000 units/g of fat per day. The dose can be adjusted based on fat-containing meals, symptoms, and stool fat content. The majority of these preparations are capsules containing enteric-coated beads that are needed to prevent the enzymes becoming inactivated in the acidic environment in the stomach. Patients requiring lipase doses more than 6000 units/kg/meal are at risk for developing a complication called fibrosing colonopathy, which can lead to colonic strictures. The capsules or tablets should not be chewed because the enzymes can cause mouth sores or irritation.

Diabetes Mellitus

Diabetes mellitus (DM) is a common disease of endocrine cell dysfunction affecting an estimated 29.1 million people in the United States. This chronic metabolic disorder is characterized by hyperglycemia that may result in long-term complications such as microvascular (e.g., retinopathy, neuropathy, and nephropathy) and macrovascular (e.g., coronary artery disease, stroke, and coronary artery disease) complications if not treated appropriately. Diabetes may be characterized as having complete lack of insulin production, a relative lack of insulin production, or insulin resistance. Without the body's proper utilization of insulin, glucose cannot be utilized for energy and thus hyperglycemia occurs. Many classifications for diabetes exist; however, this chapter will focus on type 1 and type 2 diabetes. Type 1 diabetes is typically because of autoimmune β-cell destruction, leading to absolute insulin deficiency. This type of diabetes usually has an early onset in life and also is called juvenile onset. However, adults may present with type 1 diabetes and this late presentation is often referred to as latent autoimmune diabetes in adults. Type 2 diabetes represents approximately 90% of all diagnosed cases of diabetes and is because of a progressive loss of β-cell insulin secretion and insulin resistance. Insulin resistance is the primary factor in differentiating type 2 diabetes from other forms. This type of diabetes is referred to as adult-onset diabetes; however, type 2 diabetes is now being seen to occur in children as well as adults because of poor lifestyle choices. In type 2 diabetes, aging, obesity, and improper diet control, along with a corresponding genetic background, are factors involved in the development of this disease.

Although insulin deficiency and insulin resistance are the principle pathophysiologic issues encountered in diabetes, other known mediating pathways of hyperglycemia have been proposed. Many of these contribute to β-cell dysfunction and include the liver, muscle, adipose tissue, brain, colon, stomach, kidney, and immune inflammation. The mechanism of hyperglycemia behind these pathways is beyond the scope of this chapter; however, many new

drugs developed for diabetes now target these mediating pathways of elevating glucose.

Some of the classic characteristics of lack of glucose absorption in tissues and cells of the body are hyperglycemia, glucosuria, ketosis, polyphagia, polydipsia, polyuria, and dry mouth. **Table 15-6** summarizes some of the symptoms of DM.

TABLE 15-6
Symptoms of Diabetes Mellitus

Symptom	Cause
Hyperglycemia	Elevated glucose levels caused by lack of insulin to transport glucose into the tissues
Glucosuria	Glucose is increased in the urine because so much glucose is in the blood and the kidneys cannot reabsorb it.
Ketosis*	Because the cells cannot access glucose, the body breaks down protein and fats as source of energy, causing ketone bodies and ketone acidosis in the urine (ketonuria) and metabolic acidosis (ketosis).
Polyphagia	A desire to eat or “hunger” because the cells are starving thus causing a desire for increased food intake
Polydipsia	Extreme thirst because the glucose molecules in the kidney act as an osmotic diuretic, causing an increase in urine volume (dehydration)
Polyuria	Same as for polydipsia
Dry mouth	Caused by loss of excess amounts of water from the body and dehydration
Delayed healing of wounds	May be caused by vascular changes resulting in reduced circulation; elevated blood sugar may also contribute to bacterial growth

*It should be noted that ketosis is more common with type 1 diabetes than with type 2.

Depending on whether a patient has type 1 or type 2 diabetes, therapy generally is aimed at regulating glucose levels through diet control and/or drug administration. In terms of diet control, carbohydrate intake is limited so that a constant challenge for insulin release is decreased. In addition, it is important to maintain an adequate exercise program to burn excess glucose and thus decrease hyperglycemia. The American Diabetes Association recommends certain glycemic targets. These targets are used by both patients and medical providers in assessing overall glycemic control. Patients will be required to test their glucose at home with a glucometer, and these self-monitoring of blood glucose (SMBG) readings remain the standard method for routinely checking glucose readings. In addition to SMBG readings, providers will also obtain hemoglobin A1c (HbA1c). Glucose interacts with hemoglobin to form glycated derivatives and it provides for a 3-month average of glycemic control. The goal HbA1c is 7% and fasting blood glucose is 80–130 mg/dL. The goal glucose 1–2 hours postprandial (after eating) is 180 mg/dL. Less stringent glycemic goals may be appropriate for individual patients.

Treatment of Type 1 Diabetes

Insulin is the mainstay of therapy for individuals with type 1 diabetes. Exogenous insulin is used to mimic the endogenous loss of insulin. Patients are started on basal–bolus insulin, and this approach mimics normal insulin physiology (**Figure 15-5**). The basal insulin response will be replicated by using an intermediate- or long-acting insulin product, and a short- or rapid-acting insulin will be used to replicate the release of insulin during meals. In addition to proper control of dosage of insulin at proper intervals, the patient must continually watch for carbohydrate intake, maintain a healthy lifestyle, and maintain a good exercise program. Insulin is given parenterally; however, subcutaneous administration is the most common delivery in the outpatient setting. Common locations for subcutaneous injections of insulin include the abdomen, upper arms, thighs, and buttock. Many

patients taking insulin may experience various injection site reactions such as lipoatrophy and or lipohypertrophy and patients should be instructed to rotate the injection site. The most severe effect is when the insulin dose is too high, causing a sudden drop of blood glucose referred to as hypoglycemia. Hypoglycemia occurs with a blood glucose level of less than 70 mg. If the patient is conscious, they should take 15–20 g of glucose or any other form of carbohydrate that contains glucose. Glucagon injection is recommended for patients at increased risk of clinical significant hypoglycemia defined as a blood glucose level of less than 54 mg/dL. If the patient is unconscious and in a coma, IV glucose or some type of IV dextrose solution should be administered.

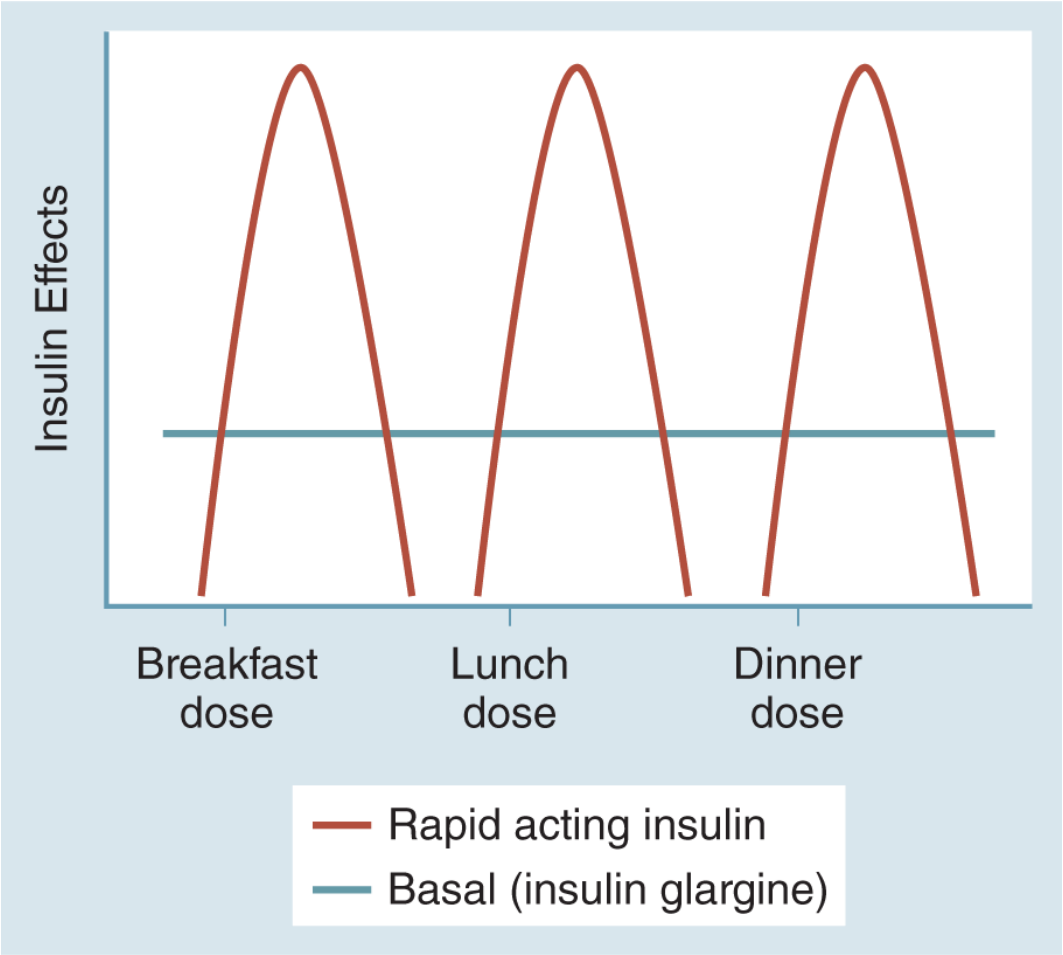


FIGURE 15-5 Effects of basal and bolus insulin in the treatment of diabetes.

Description

Insulin

Insulin is available in many different forms with various onsets of action. Synthetic human insulin, developed utilizing recombinant DNA technology, has become the only type of insulin available in the United States. Some patients were better able to manage their diabetes with animal insulin (i.e., pork or beef) and are allowed to import such drugs by the Food and Drug Administration (FDA) policy implemented in 1998. **Table 15-7** lists a few of the commonly available insulin preparations, which are listed according to the drug name and duration of action.

TABLE 15-7
Available Insulin Products

Insulin Product	Strength	Onset (min)	Peak (h)	Duration (h)
Bolus/Meal Time Insulin				
Rapid-acting • Aspart (NovoLog®) • Glulisine (Apidra®) • Lispro (Humalog)	U-100	10–30	1–2	3–5
Short-Acting • Regular (Humulin®, Novolin®)	U-100, U-500	30–60	1–5	4–12
Basal Insulin				
Intermediate-Acting • Neutral protamine Hagedorn (Humulin, Novolin)	U-100	1–4 h	4–6	14–24
Long-Acting • Glargine (Lantus®) • Glargine (Toujeo®) • Glargine (Basaglar®) • Detemir (Levemir) • Degludec (Tresiba)	 U-100 U-300 U-100 U-100 U-100, U-200	 3–4 h 6 h 3–4 h 3–4 h 1 h	Flat	 22–24 24–36 22–24 6–23 ~42

Treatment of Type 2 Diabetes

Type 2 diabetes can be treated with diet control, exercise, insulin, non-insulin injectables, and a group of drugs called oral hypoglycemic agents. A number of new drugs have been developed over the past decade for the management of type 2 diabetes; however, lifestyle modifications, including proper diet and exercise, remain an essential

part in achieving treatment success. Many treatment algorithms exist, and although the majority of treatment recommendations are similar, some differences exist. Many patient-related factors come into play when deciding which agent to select, and considerations should be made addressing a drug's risk for hypoglycemia, cost, metabolic effects (weight gain), and therapeutic efficacy. Therefore, a patient-centered approach is the best method for selecting a particular agent. The selection of an appropriate agent for the management of type 2 diabetes is beyond the scope of this chapter, but an understanding of the most commonly used agents is important and this will be discussed further. **Table 15-8** lists the most commonly used drug classes along with their corresponding mechanism of action.

TABLE 15-8
Glucose-Lowering Agents in Type 2 Diabetes

Class	Drug	Mechanism of Action
Biguanides	• Metformin (Glucophage®)	• Decrease hepatic glucose production • Increases peripheral glucose uptake and utilization
Sulfonylureas (second generation)	• Glyburide (Glynase®) • Glipizide (Glucotrol®) • Glimepiride (Amaryl®)	• Stimulates insulin release from the β-cells of the pancreas
Thiazolidinediones	• Pioglitazone (Actos®) • Rosiglitazone (Avandia®)	• Increase insulin sensitivity by stimulating peroxisome proliferator-activated receptor gamma
DPP-4 inhibitors	• Sitagliptin (Januvia®) • Saxagliptin (Onglyza®)	• Increase insulin secretion and decreases glucagon secretion by inhibiting the enzyme DPP-4

	• Linagliptin (Tradjenta®) • Alogliptin (Nesina®)	
Meglitinides	• Repaglinide (Prandin®) • Nateglinide (Starlix®)	• Stimulate insulin release from the β-cells of the pancreas
α-Glucosidase inhibitors	• Acarbose (Precose®) • Miglitol (Glyset®)	• Delay intestinal carbohydrate digestion/absorption by inhibiting α-glucosidase
SGLT2 inhibitors	• Canagliflozin (Invokana®) • Dapagliflozin (Farxiga®) • Empagliflozin (Jardiance®)	• Block glucose reabsorption in the kidney by inhibiting SGLT2
GLP-1 receptor agonists (injectable non-insulins)	• Exenatide (Byetta®) • Exenatide long-acting form (Bydureon®) • Liraglutide (Victoza®) • Albiglutide (Tanzeum®) • Dulaglutide (Trulicity®) • Lixisenatide (Adlyxin®) • Semaglutide (Ozempic®)	• Increase insulin secretion, decrease glucagon secretion, slow gastric emptying, and increase satiety by activating GLP-1 receptors

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose cotransporter-2.

Biguanides

The drug metformin (Glucophage®) is one of the first biguanides developed for blood glucose control and the only biguanide approved by the FDA in the United States. It is considered a first-line agent for type 2 DM. It is used as monotherapy or in combination with other oral and injectable agents, including insulin. Metformin works by decreasing hepatic glucose production and increasing insulin sensitivity. Metformin is effective, inexpensive, and relatively safe. Metformin can lower HbA1c by 1.5–2% and has favorable effects on weight (neutral/weight loss). Metformin does not affect insulin release from the pancreas so hypoglycemia, especially when using it as monotherapy, is not commonly seen. Major side effects include gastrointestinal (GI) side effects such as diarrhea. Patients should be instructed to take the dose with food or switch to a longer-acting formulation in order to avoid GI upset. Other side effects include vitamin B_{12} deficiency and lactic acidosis, which is rare. Use of metformin is based on renal function and the agent should not be started in patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2 and should be discontinued if the eGFR decreases to less than 30 mL/min/1.73 m^2.

Sulfonylureas

Sulfonylureas are another commonly used drug class; however, their use has declined owing to the advent of newer and safer agents. Sulfonylureas work by increasing insulin secretion from pancreatic β-cells in a non-glucose–dependent manner. The most commonly used agents are the second-generation sulfonylureas because of their more favorable side effect profile. Sulfonylureas have been shown to decrease HbA1c by 1.5–2%; however, many issues with this drug class exist. Sulfonylureas may exhaust pancreatic function with prolonged use and their effectiveness is reduced in patients with β-cell destruction. Dosing is also based on renal function and caution should be exercised in patients with compromised renal function and in the elderly because of the increased risk for hypoglycemia. Other side effects include hypoglycemia and weight gain, and caution should be exercised in patients with a sulfa allergy. Examples of

sulfonylureas include glyburide (Glynase®), glipizide (Glucotrol®), and glimepiride (Amaryl®).

NEED TO KNOW

Over time, sulfonylureas may decrease pancreatic β-cell function. These drugs also have a high incidence of causing hypoglycemia.

Meglitinides

These agents are similar to the sulfonylureas but have a much shorter onset and duration of action. These agents decrease HbA1c by 0.8–1% and are primarily dosed before meals to reduce postprandial glucose levels. Dosing is based on renal function and the most common side effect is hypoglycemia. Examples of meglitinides include repaglinide (Prandin) and nateglinide (Starlix).

Thiazolidinediones

These agents have a complex mechanism of action, but they essentially increase insulin sensitivity by stimulating peroxisome proliferator-activated receptor gamma. These agents do not cause hypoglycemia and they decrease HbA1c by approximately 1.5%. Use of these agents is based on hepatic function, and liver function tests need to be monitored. Side effects include heart failure exacerbation and they are not recommended in patients with NYHA (New York Heart Association) class III–IV. Other side effects include fluid retention, weight gain, risk of bone fractures, bladder cancer (pioglitazone), and elevated low-density lipoprotein (rosiglitazone). These agents have fallen out of favor because of their side effect profile. Examples of the thiazolidinediones include pioglitazone (Actos®) and rosiglitazone (Avandia ®).

Alpha-Glucosidase Inhibitors

These agents primarily work by inhibiting intestinal α-glucosidase, an enzyme responsible for breaking down complex carbohydrates. The result is a decrease in intestinal carbohydrate absorption. These agents decrease HbA1c by 0.3–1% and they are not associated with hypoglycemia. These drugs are best used to reduce postprandial glucose readings and they are dosed before meals. These agents are dosed based on renal function, and major side effects include abdominal discomfort and diarrhea. Examples of α-glucosidase inhibitors include acarbose (Precose®) and miglitol (Glyset®).

Dipeptidyl Peptidase-4 Inhibitors

The dipeptidyl peptidase-4 (DPP-4) inhibitors represent a commonly used drug class in managing diabetes. These agents lower blood glucose concentrations by inhibiting the DPP-4 enzyme responsible for inactivating incretin concentrations such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide. These agents cause an increase in glucose-dependent insulin release and a reduction in glucagon secretion (**Figure 15-6**). Owing to their glucose-dependent nature, these agents do not cause hypoglycemia. These agents decrease HbA1c by 0.7–1% and they primarily target postprandial glucose. Depending on the agent selected, renal function needs to be assessed in order to appropriately utilize the drug. Side effects include potential heart failure exacerbation (saxagliptin, alogliptin), pancreatitis, and joint pain. Examples of the DPP-4 inhibitors include sitagliptin (Januvia®), saxagliptin (Onglyza®), linagliptin (Tradjenta®), and alogliptin (Nesina®).

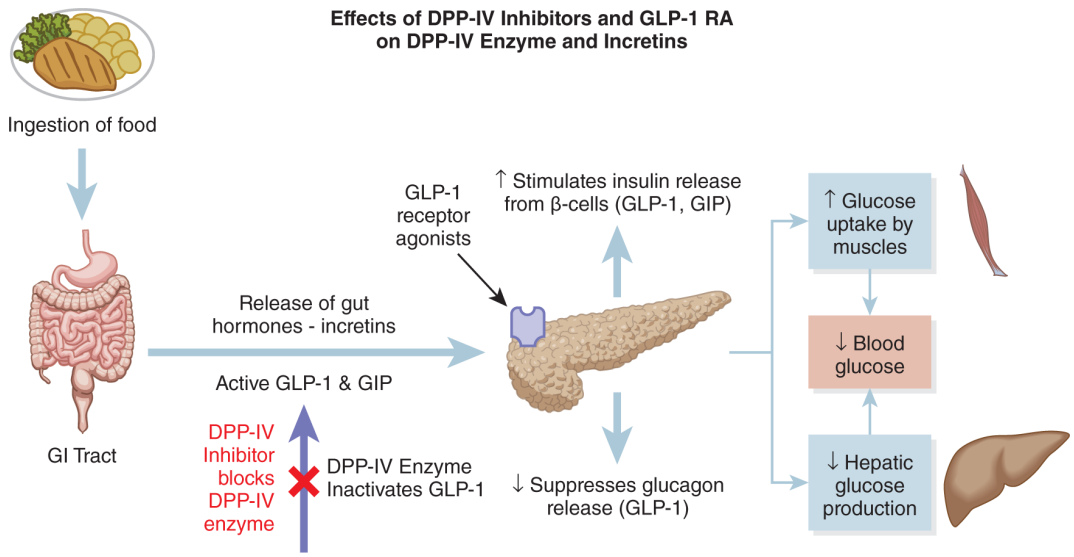


FIGURE 15-6 Effects of DPP-IV inhibitors and GLP-1 RA on DPP-IV enzyme and incretins.

Description

Sodium Glucose Cotransporter-2 Inhibitors

These agents, most commonly referred to as the sodium glucose cotransporter-2 (SGLT2) inhibitors, work by inhibiting the SGLT2 receptor in the proximal nephron. The SGLT2 receptor is responsible for 90% of glucose reabsorption in the proximal tubule. By blocking this receptor, they block the reabsorption of filtered glucose in proximal tubule, resulting in increased urinary glucose excretion. These agents decrease HbA1c by 0.7–1.3% and they do not cause hypoglycemia when used as monotherapy. Other benefits include weight loss because of caloric elimination, beneficial cardiovascular outcomes (depending on the agent selected), reduction in kidney disease progression, and a reduction in blood pressure. These agents are dosed based on renal function, and side effects include dehydration, hypotension, hyperkalemia, bone fractures, and genitourinary infections. Examples of the SGLT2 inhibitors include canagliflozin (Invokana®), dapagliflozin (Farxiga®), and empagliflozin (Jardiance®).

Glucagon-like Peptide-1 Receptor Agonists

These are non-insulin injectable agents, commonly referred to as the glucagon-like peptide-1 receptor agonists (GLP-1 RA), target multiple mediating pathways associated with hyperglycemia. These agents target GLP-1 receptors and have multiple positive effects of increased glucose-mediated insulin release, decreased glucose-mediated glucagon release, enhanced β-cell function, and delayed gastric emptying and satiety (Figure 15-6). These agents decrease HbA1c by 0.9–1.6% depending on the agent selected. These agents are not associated with hypoglycemia when used as monotherapy and other benefits include weight loss and beneficial cardiovascular outcomes (depending on the agent selected). These agents can be used in combination with other oral hypoglycemic agents and with basal insulin. Because of their positive glycemic effects, guidelines now recommend that these agents be considered as second line in addition to metformin if glucose is still elevated, and in addition to basal insulin before considering bolus/meal time insulin. These agents are administered subcutaneously, and depending on the agent selected, frequency of dosing ranges from twice daily to once weekly. The most commonly observed side effect is nausea and vomiting owing to the reduction in gastric emptying. Caution should be observed in patients with reduced renal function because dehydration caused by the nausea and vomiting can worsen renal function. Patients should be counseled that these GI issues tend to improve over time. Other concerns include injection site reactions, acute pancreatitis, and a black box warning exists about thyroid-c-cell tumors. These agents should not be used in patients with a family history or personal history of medullary thyroid cancer and multiple endocrine tumors. Examples of the GLP-1 RA include exenatide (Byetta®), exenatide extended-release (Bydureon®), liraglutide (Victoza®), dulaglutide (Trulicity®), albiglutide (Tanzeum®), lixisenatide (Adlyxin®), and semaglutide (Ozempic®).

Insulin

Most patients with type 2 DM eventually require insulin therapy because of the progressive nature of the disease. Unlike in type 1

diabetes, where a basal-bolus regimen is required, patients with type 2 diabetes are generally started on basal insulin. This is typically combined with metformin and other non-insulin agents. Because of the advent of longer-acting basal insulins, the use of intermediate-acting, neutral protamine Hagedorn (NPH) has declined. Newer basal insulins are typically dosed once daily, have less hypoglycemia, and supply a relatively stable concentration of insulin for over 24 hours.

Antigen–Antibody Reactions

Allergic reactions in the body are manifested by various symptoms, such as nasal congestion, sneezing, runny eyes, and itching. If a severe reaction occurs (antigen–**antibody**), more serious complications can result, such as severe drop in blood pressure, bronchoconstriction, and cardiovascular collapse. This type of reaction is termed *anaphylactic shock.* The substance that triggers an allergic or anaphylactic reaction is called an **antigen**. Antigens are usually protein in structure but can include a number of substances, such as animal products, mold, dust, and drugs.

When antigens enter the body, they stimulate the formation of *antibodies* in both the blood and tissues. When the body has become sensitized and an antigen is introduced or reintroduced, an antigen–antibody reaction occurs that can lead to severe allergic symptoms. Allergic reactions that occur in asthmatics can be very serious and greatly affect their ability to breathe. When an antigen–antibody reaction occurs, certain cells (mast cells) release a number of active substances into the blood. **Histamine** is an important substance that is released and is responsible for most of the symptoms of an allergic reaction.

Effects of Histamine

In order to understand the effects and mechanism of action of antihistamines, it is necessary to know the overall physiologic effects of histamine. Histamine is produced by mast cells and certain white cells (basophils) throughout the body. The largest concentrations of mast cells are in those areas that serve as a place of entry for an antigen and they include the respiratory epithelium, GI tract, and skin. When histamine is released into the bloodstream, it produces a number of physiologic effects, particularly in the vascular and nonvascular smooth muscle and the heart. These effects are summarized in **Table 15-9**.

TABLE 15-9
Effects of Histamine

System/Tissue	Effect	Sign/Symptom
Blood pressure	Decreased	Hypotension
Heart rate	Increased	Tachycardia
Bronchial	Constriction	Wheezing
Small vessels and capillaries	Dilation	Increased secretions and mucosal edema

Vascular Effects

The main effect of histamine on the vascular tissue is on the smooth muscles of blood vessels and capillaries. The smooth muscle relaxation causes vasodilation that also, in the presence of large amounts of histamine, can cause a profound drop in blood pressure and cardiovascular collapse. When the vasodilation occurs in the skin, it causes erythema (redness). When the vasodilation occurs in the brain, it causes a headache (histamine headache). In addition to the vasodilation, the capillary membranes become “leaky” and fluids diffuse into the extravascular space, causing congestion in the nasal and upper airway mucosa and edema and/or hives on the skin. Also, histamine stimulates small nerve endings, causing extreme itching and in some cases pain. In summary, the vascular effects of histamine cause the symptoms commonly associated with allergic reactions: swelling, itching, headaches, redness, and a drop in blood pressure.

Nonvascular Smooth Muscle

There are two main areas of nonvascular smooth muscle that are affected by histamine: the smooth muscle of the GI tract and the smooth muscle of the bronchial tree. In the GI tract, histamine causes smooth muscle contraction and the release of hydrochloric acid. In

the bronchial tree, histamine causes bronchial smooth muscle constriction, which can severely impair respiratory function. In humans, the bronchial smooth muscle effect of histamine is much stronger than the GI effect, and people with chronic respiratory disease (asthma) are unusually sensitive to it.

Heart Effects

Histamine usually causes an increase in heart rate and, when larger amounts are present, arrhythmias and cardiac collapse can occur.

NEED TO KNOW

Effects of histamine include tachycardia, increased secretions, mucosal edema, and bronchospasm.

Histamine Receptors

In order for histamine to create its physiologic action, it combines with two different types of receptors. These receptors are known as the H_1 and H_2 receptors. The most important receptors, as far as allergic reactions are concerned, are the H_1 receptors, which are located in the blood vessels, bronchioles, and smooth muscle. When these receptors are stimulated, the clinical effects of allergic reactions are seen. The H_2 receptors are primarily located in the GI tract.

Antihistamines and Antiallergic Agent Definitions

Antihistamines are substances that block the action of histamine in various tissues throughout the body. They are called antagonists, meaning they occupy the histamine receptor without causing any drug effect. Antihistamines are used to treat allergies and allergic symptoms.

Antiallergic drugs are substances that block the release of histamine from mast cells or interfere with the progression of the

inflammatory response. These agents (mast-cell stabilizers and leukotriene blockers/antagonists) are discussed in Chapter 7. Antihistamines have many uses other than treating allergies. Many antihistamines have side effects that, in some instances, are used therapeutically. Because of their sedative action, they are often used as main ingredients in over-the-counter sleep aids. Many of the antihistamines are also used in cold medications to decrease secretions. Another common use of antihistamines is in the control of vertigo and motion sickness. Drugs that are most commonly used for motion sickness are dimenhydrinate (Dramamine®) and meclizine (Antivert®).

Finally, antihistamines potentially can cause interaction with other drugs. The most important interaction occurs when they are combined with CNS depressants, such as alcohol, barbiturates, phenothiazines, and tranquilizers. With any of these drugs, antihistamines can potentiate or increase CNS depression.

Antihistamine Drugs

The main clinical effect of currently used antihistamines is to counteract the effect of histamine on the H_1 receptor sites. They are most effective when administered prophylactically as antagonists against histamine that have already been released. They are of little value in a rapidly developing or acute antigen–antibody reactions such as anaphylaxis. Most are administered orally and therefore some time (30 minutes to 1 hour) must elapse before clinical effects can be observed. All of the various antihistamines have similar properties but differ in onset of action and intensity of side effects. Also, many antihistamines that are effective in one individual may not be effective in another, thus requiring a change of medication in order to find an appropriate, effective antihistamine. Antihistamines are divided into two groups: first generation and second generation. The first-generation antihistamines cross the blood–brain barrier and in turn can cause sedation. The second-generation antihistamines, also referred to as nonsedating antihistamines, are largely excluded from the brain because they do not cross the blood–brain barrier. As such,

these agents do not typically cause sedation at therapeutic doses. **Table 15-10** lists some of the more commonly used antihistamines, along with their degree of sedation.

TABLE 15-10
Available Antihistamines

Drug	Degree of Sedation
First-Generation Antihistamines	
Diphenhydramine (Benadryl®)	High
Chlorpheniramine (Chlor-Trimeton®)	Intermediate
Meclizine HCL (Antivert®)	Intermediate
Promethazine (Phenergan®)	High
Dimenhydrinate (Dramamine®)	High
Hydroxyzine pamoate, HCL (Atarax®, Vistaril®)	High
Second-Generation Antihistamines	
Cetirizine (Zyrtec®)	None to very low
Desloratadine (Clarinex®)	None to very low
Loratadine (Claritin®)	None to very low
Fexofenadine (Allegra®)	None to very low

The main side effects of all antihistamines are similar but differ in intensity. The clinically important side effects include sedation and drying of secretions in the nasal lining and mouth (xerostomia). In recent years, several new antihistamines have been developed that

have very little sedative effects. These include fexofenadine (Allegra®), loratadine (Claritin®), desloratadine (Clarinex®), and cetirizine (Zyrtec®).

Review Questions

1. Explain how the hypothalamus controls the secretion of hormones from the adenohypophysis and neurohypophysis.
2. Define the term *negative feedback.*
3. List three categories of corticosteroids secreted by the adrenal cortex.
4. Describe the main therapeutic use of the glucocorticoids (corticosteroids) and eight long-term side effects?
5. Compare hypothyroidism to hyperthyroidism and list the first-line drugs used to treat each.
6. Compare the effects of glucagon and insulin on blood glucose levels.
7. Describe the pathophysiologic differences between type 1 and type 2 DM.
8. Which drugs are more commonly used in the treatment of type 1 diabetes and which drugs are more commonly used in the treatment of type 2 diabetes?
9. Describe the overall physiologic effects of histamine. Compare the location of H_1 and H_2 receptor sites in the body.
   a. vascular:
   b. nonvascular:
   c. heart effects:
10. Describe why antihistamines are not effective in treating an acute anaphylactic allergic reaction.
11. List two first- and two second-generation antihistamine drugs and the most common side effects.

Posttest

For each of the following questions, try to select the *one* best answer from the choices given.

1. In addition to an anatomical relationship between the hypothalamus and the pituitary gland, the hypothalamus controls homeostasis through the autonomic nervous system and the pituitary gland controls homeostasis through the release of hormones. True or False?
2. Which of the following adrenocortical hormones can alter potassium levels?
   a. Mineralocorticoids
   b. Glucocorticoids
   c. Gonadocorticoids
   d. None of these is correct.
3. Which of the following symptoms are *not* associated with long-term glucocorticoid use?
   a. Poor wound healing
   b. Edema
   c. Weight loss
   d. Cushing syndrome
4. Which of the following agents used to treat hyperthyroidism can cause liver failure?
   a. Methimazole
   b. Propylthiouracil
   c. Iodine
   d. Levothyroxine
5. Which of the following agents is used in the management of type 1 diabetes?
   a. Lantus®
   b. Metformin
   c. Glucotrol®
   d. All of these are correct.

6. All of the following are side effects of dulaglutide (Trulicity®), *except*:
   a. nausea.
   b. vomiting.
   c. hypoglycemia.
   d. pancreatitis.
7. Which of the following drugs works by decreasing reabsorption of glucose at the proximal tubule of the nephron?
   a. Metformin
   b. Empagliflozin
   c. Exenatide
   d. Januvia
8. Which of the following is the most common side effect seen with injectable insulin therapy?
   a. Weight loss
   b. Hypoglycemia
   c. Fungal infections
   d. Renal dysfunction
9. When an antigen–antibody reaction occurs in the body, histamine is released by:
   a. plasma cells.
   b. white blood cells.
   c. erythrocytes.
   d. mast cells.
10. Antihistamines are excellent drugs in treating acute anaphylactic reactions. True or False?
11. Which of the following statement regarding drugs used for the management of hypothyroidism is correct?
    a. Cytomel is the preferred thyroid replacement product.
    b. Doses should be adjusted every 1–2 weeks.
    c. Levothyroxine should be taken on an empty stomach at least 30 minutes before eating.
    d. Toxic effects of thyroid hormone include low blood pressure and weight gain.
12. Which of the following is a likely explanation for why a CF patient on PERT would develop fibrosing colonopathy?

a. A pancreatic enzyme capsule was chewed.
b. An allergic reaction has developed.
c. The dose of lipase is too high.
d. It is a sign the enzyme is ineffective.

References/Recommended Readings

American Diabetes Association. Standards of Medical Care in Diabetes—2018. *Diabet Care*. 2018;41(suppl 1):S1–S159.

Aroda VA. A review of GLP-1 receptor agonists: evolution and advancement, through the lens of randomized controlled trials. *Diabetes Obes Metab*. 2018;20(suppl 1):22–33.

Asmal AC, Marble A. Oral hypoglycemic agents: update. *Drugs*. 1984;28:62–78.

Bahn RS, Burch HB, Cooper DS, et al; American Thyroid Association; American Association of Clinical Endocrinologists. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract*. 2011;17(3):456–520.

Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;2014(133):1270–1277.

Bilezikian JP, Khan A, Potts JT, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target organ involvement, treatment and changes for future research. *J Bone Miner Res*. 2011;26(10):2317–2337. doi:10.1002/jbmr.483.

Borowitz D, Robinson KA, Rosenfeld M, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr*. 2009;155(6 suppl):S73–S93.

Broyles EB, Reiss BS, Evans ME. *Pharmacological Aspects of Nursing Care.* Clifton Park, NY: Delmar Cengage Learning; 2013.

Brunton L, Knollmann B, Hilal-Dandan R. *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*. 13th ed. New York, NY: McGraw-Hill.

Brunton LL, Lazo JS, Parker KL, eds. *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*. 11th ed. New York, NY: McGraw-Hill Medical Publishing; 2006.

Chisholm-Burns MA, Schwinghammer TL, Wells BG, et al. *Pharmacotherapy Principles and Practice*. 4th ed. New York, NY; McGraw-Hill; 2016.

Clinical Resource, *Corticosteroids: Selection, Tapering, and More. Pharmacist's Letter/Prescriber's Letter*. March 2018.

Rainforth Collins, S. *Mosby's Drug Reference for Health Professionals.* 6th ed. St. Louis, MO: Mosby-Elsevier; 2018

Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1-receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368:1696–1705.

Fainer AS, Dale DC, Balow JE. Glucocorticoid therapy: mechanisms of action and clinical considerations. *Ann Intern Med*. 1976;84:304–315.

Garber J, Cobin R, Gharib H, et al. Clinical Practice Guidelines for Hypothyroidism in Adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract*. 2012;18(6):988–1028.

Gomez-Peralta F, Abreau C, Lecube A, et al. Practical approach to initiating SGLT2 inhibitors in Type 2 diabetes. *Diabet Ther*. 2017;8(5):953–962. doi:10.1007/s13300-017-0277-0.

Hitner H, Nagle BT. *Pharmacology: An Introduction*. 6th ed. San Jose, CA: Glencoe Publishing Co.; 2011.

International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabet Care*. 2009;32(7):1327–1334.

Krystal-Whittemore M, Dillepan KN, Wood JG. Mast cell: a multi-functional master cell. *Front Immunol*. 2015;6:620. doi: 10.3389/fimmu.2015.00620.

Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol*. 2013;9:30. doi:10.1186/1710-1492-9-30.

McCance KL, Huether SE. *Pathophysiology: The Biologic Basis for Diseases in Adults and Children*. 6th ed. St. Louis, MO: Mosby-Elsevier; 2010.

Rizzo DC. *Fundamentals of Anatomy and Physiology*. 3rd ed. Clifton Park, NY: Delmar Cengage Learning; 2010.

Schimmer BP, Funder W. Adrenocorticotropic hormone, adrenal steroids, and the adrenal cortex. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. 13th ed. New York, NY: McGraw-Hill. http://accesspharmacy.mhmedical.com.libproxy.temple.edu/content.aspx?bookid=2189&sectionid=172482605. Accessed October 7, 2018.

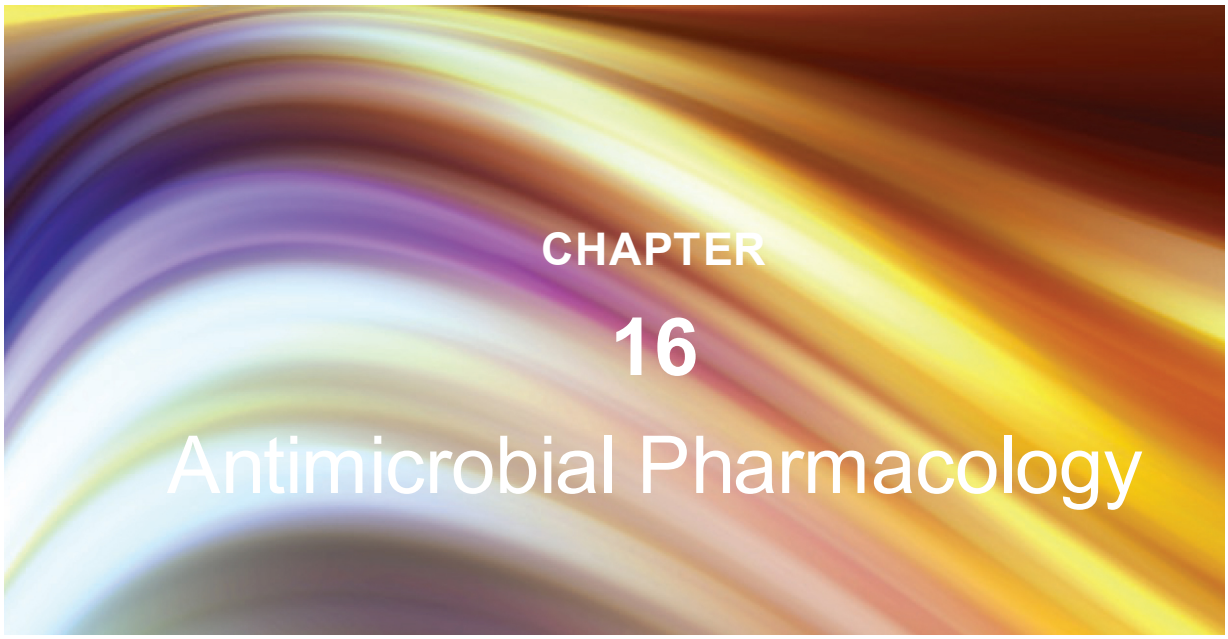
Schwartz S, Epstein S, Corkey BE, et al. The time is right for a new classification system for diabetes: rationale and implications of the beta-cell-centric classification schema. *Diabet Care*. 2016;39:179–186.

Seltzer HS. Efficacy and safety of oral hypoglycemic agents. *Ann Rev Med*. 1980;31:261–272.

Simons FE. Advances in H1-antihistamines. *N Engl J Med*. 2004;351:2203–2217.

Spratto GR, Woods R. *Nurse's Drug Handbook*. Clifton Park, NY: Delmar Cengage Learning; 2013.

Trujilio J, Nuffer W, Ellis SL. GLP-1 receptor agonists: a review of head-to-head clinical studies. *Ther Adv Endocrinol*. 2015;6(1):19–28.



© Winui/Shutterstock

OUTLINE

Introduction
Antimicrobial Agents and Definitions
  Principles in the Appropriate Use of Antibiotics
  Causes of Failure in Antibacterial Therapy
Categories of Antibiotic Drugs
  Beta-Lactam Antibiotics
  Quinolones
  Macrolides
  Sulfonamides
  Tetracyclines and Glycylcyclines
  Aminoglycosides (Amikacin, Gentamicin, Plazomicin, Streptomycin, and Tobramycin)
  Glycopeptides
  Oxazolidinones
  Cyclic Lipopeptides (Daptomycin)
  Agents for Anaerobic Infections
Tuberculosis
  Drugs Used in the Treatment of TB
Antifungal Drugs
  Antifungals Used in Systemic Fungal Infections
Antiviral Agents
  Antiviral Drugs

OBJECTIVES

After completion of this chapter and its learning activities, you will be able to:

1. Define the terms antibacterial, antimicrobial, antiviral, antifungal, bacteriostatic, and bactericidal.
2. Summarize the principles of appropriate use of antibiotics with regard to empiric and definitive therapy.
3. Identify the microorganisms that cause upper and lower respiratory tract infections and determine appropriate drug therapy to treat these infections.
4. Describe the mechanism of action of the β-lactam antibiotics and list the categories of penicillins and other β-lactams, including spectrum of activity and adverse effects.
5. Explain the differences and similarities in spectrum of activity of each of the five generations of cephalosporins and be able to recognize drugs in each class.
6. Compare and contrast the mechanisms of action, common uses, and adverse effects of fluoroquinolones, macrolides, and tetracyclines.
7. Choose the most appropriate gram-positive drug and recommend the adverse effects to be monitored, given a patient case study.
8. Identify the three categories of antifungal drugs, along with examples and adverse effects.
9. Describe the overall approach to the treatment of viral infections and list examples of antiviral drugs, along with therapeutic uses and adverse effects.
10. Recommend a four-drug treatment regimen for the management of tuberculosis and common side effects of each drug.

KEY TERMS

Acid-fast bacillus (AFB)
Antibiotic
Antimicrobial
Antiviral
Bacteriostatic
Bactericidal
Broad-spectrum
Cultures and sensitivities (C & S)
Definitive therapy
Empiric
Gram-negative
Gram-positive
Tuberculosis (TB)

Introduction

Infections accounted for significant morbidity and mortality until penicillin became widely available in the 1940s. There have been numerous classes of drugs used for the treatment of bacterial, viral, and fungal infections development since the 1940s and this has improved morbidity and death from infections worldwide. This chapter covers general definitions and basic principles in the use of antimicrobial drugs but is not intended to be a comprehensive review. The most common classes of antimicrobials, focusing on agents used to treat pulmonary infections, are reviewed in this chapter. Specific antimicrobials that are commonly administered by aerosol are described in Chapter 10.

Antimicrobial Agents and Definitions

Antimicrobial agents cause an effect on various microscopic organisms by being selectively toxic to them. Microorganisms are normally found on the skin, in mucus, and other body systems. They usually act to prevent harm (i.e., preventing overgrowth of harmful organisms) or cause no harm or benefit. In situations where humans are susceptible, these microorganisms may become pathogenic and cause active infection. In order to know which organisms are responsible for causing infections, you should be familiar with organisms that are normally found in different parts of the human body (**Figure 16-1**). This is accomplished by interfering with or preventing the growth of an organism or by permanently killing it. Most clinically effective agents are selectively toxic to organisms without causing damage to host cells or tissues. The degree of selectivity determines the ultimate usefulness of the drug in terms of side effects.

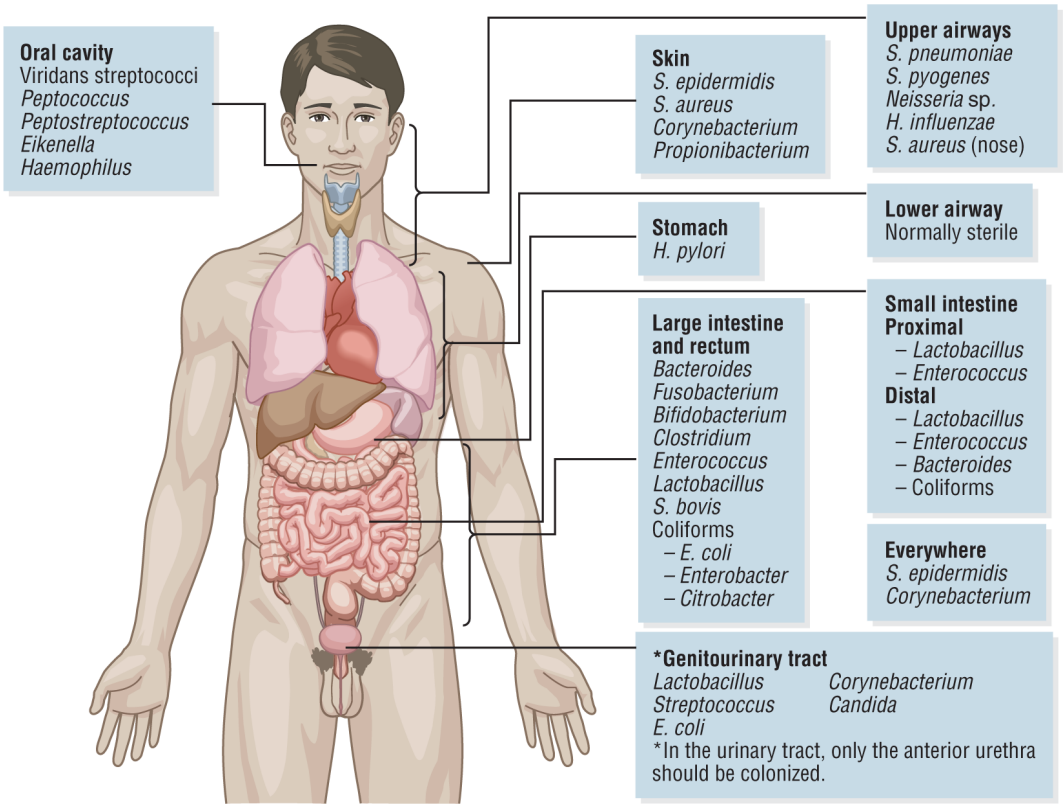


Figure 16-1 Normal human flora.

Description

Generally, the antimicrobial agents exert their effects through one of the following mechanisms: inhibition of cell wall synthesis, inhibition of protein synthesis, inhibition of nucleic acid function, or inhibition of certain cell membrane functions. Throughout the following discussion of various antimicrobial substances, the overall mechanism that is appropriate to each drug group will be discussed. Before discussing specific antimicrobial classes, it is necessary to define the following terms:

- *Antimicrobial*: any substance that kills or inhibits the growth of any microorganism
- *Antibacterial*: any substance that inhibits the growth of or destroys bacteria
- *Bacteriostatic*: an antibiotic that inhibits or retards the growth of bacteria
- *Bactericidal*: an antibiotic that kills bacteria

- *Antiviral*: any substance that kills or inhibits growth of a virus
- *Antifungal*: any substance that kills or inhibits growth of a fungus
- *Spectrum*: the specificity or selectivity of antibiotics regarding the type of bacteria that they are effective against

Principles in the Appropriate Use of Antibiotics

An **antibiotic** is a compound that kills or inhibits the growth of bacteria. The most common types of bacteria that antibiotics are used for are **gram-positive** and **gram-negative**. The gram stain is a method for categorizing different types of bacteria by using a purple stain and viewing the ability of the bacteria's cell wall to retain the color through a microscope (**Figure 16-2**). Some antibiotics will treat only gram-positive or gram-negative bacteria and some will treat both. Antibiotics that treat many types of gram-positive and gram-negative bacteria are considered **broad-spectrum** antibiotics.

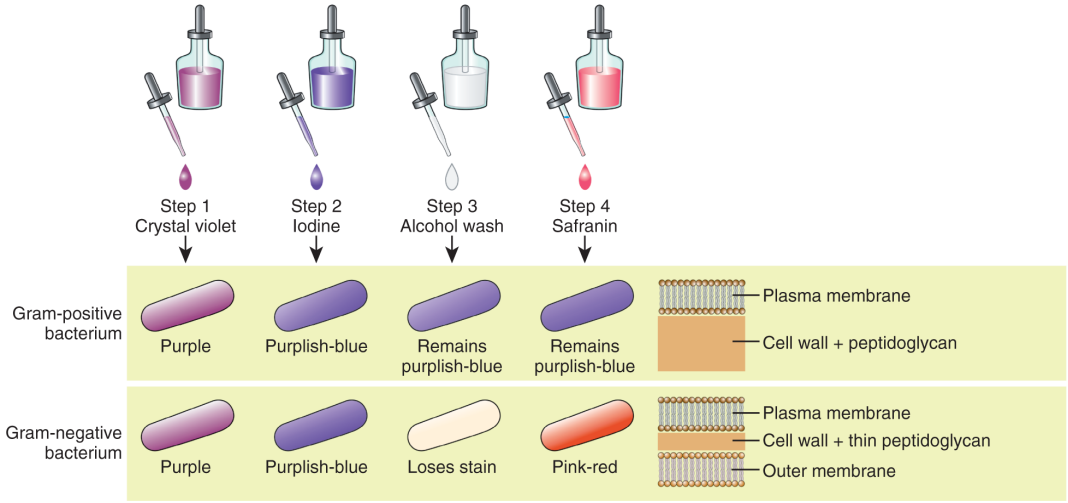


FIGURE 16-2 Gram stain used to differentiate between gram-positive and gram-negative bacteria.

Description

When using antibiotic therapy, it is important to identify the organism involved and select the most appropriate drug. **Table 16-1** includes some commonly encountered infections and antibiotics of choice that are used to treat them. Also, in the course of treatment,

many antibiotics become ineffective, usually because the organism develops a resistance to that drug. In order to minimize these problems, the following steps should be considered when selecting and administering antibiotic therapy:

TABLE 16-1
Microorganisms Responsible for Commonly Encountered Infections and Drugs of Choice

Infection Type	Microorganism Responsible for Causing Infection	First-Line Treatments
Community-acquired pneumonia	*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila*	Outpatient: doxycycline, azithromycin, clarithromycin, levofloxacin, and moxifloxacin Inpatient: IV third-generation cephalosporin plus doxycycline, azithromycin, and clarithromycin or levofloxacin and moxifloxacin
Healthcare-associated pneumonia	Less than 5 days after hospitalization: *Streptococcus pneumoniae*, *H. influenzae*, MSSA, *Escherichia coli*, and *Klebsiella pneumoniae* More than 5 days after hospitalization: same as above, plus MRSA, *Enterobacter* sp., *Proteus* sp., *Serratia* sp., and *Pseudomonas aeruginosa*	Ceftriaxone, ampicillin/sulbactam, ertapenem, levofloxacin, and moxifloxacin Beta-lactam with *Pseudomonas* sp. activity plus levofloxacin or ciprofloxacin plus vancomycin or linezolid
Otitis media	*Streptococcus pneumoniae*, *H. influenzae*, and *Moraxella catarrhalis*	Amoxicillin, cefuroxime, cefpodoxime, and azithromycin
Pharyngitis	*Streptococcus pyogenes* and viruses	Penicillin VK, cephalexin, or azithromycin
Urinary tract infections	*Escherichia coli*, *Proteus* sp., *K. pneumoniae*,	TMP/SMX, ciprofloxacin, levofloxacin, nitrofurantoin, and fosfomycin

	Staphylococcus saprophyticus, and *Enterococcus* sp.	Complicated: ciprofloxacin, levofloxacin, ceftriaxone, or ertapenem
Skin and soft tissue infections	*Streptococcus pyogenes* and *Staphylococcus aureus* (MSSA/MRSA)	Cefazolin, nafcillin, cephalexin, or dicloxacillin High-risk MRSA: vancomycin, linezolid, and clindamycin

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible strains of *Staphylococcus aureus*; TMP/SMX, trimethoprim/sulfamethoxazole.

1. When possible, collect a sample at the site of infection (e.g., urine, sputum, and cerebral spinal fluid) for identification of a causative organism and to determine potential antimicrobial susceptibilities.
2. Start **empiric** antimicrobial therapy targeted to treat the probable causative organisms depending on suspected site of infection.
3. Identify the causative organisms by obtaining **cultures and sensitivities (C & S)**.
4. Initiate appropriate **definitive therapy** according to the identified organism and its sensitivities, the history or presence of drug allergy, drug safety profile, and cost.
5. Continue therapy for the shortest effective duration of treatment.
6. Avoid unnecessary use of antibiotics when a bacterial infection is unlikely in order to prevent the development of resistant pathogens.

NEED TO KNOW

When a physician orders “Sputum for C & S,” a sputum specimen is tested for bacteriologic culture (to determine the organism is present in it) and sensitivity (to determine which specific antimicrobial will be effective against that organism).

Causes of Failure in Antibacterial Therapy

The causes of failure in the use of antibacterial therapy are as follows:

1. The drug being used is not effective against the organism causing the infection.
2. Development of resistance or presence of “super bug,” or resistant organism such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* sp. (VRE), and so on.
3. Inadequate drug regimen:
   a. Inadequate dose
   b. Inappropriate route of administration
   c. Drug unable to penetrate site of infection
4. Failure to use adjuvant surgical and supportive measures (drainage and surgery).

Antibiotic-resistant bacteria have developed over the past decade and are commonly responsible for life-threatening infections. Multidrug-resistant (MDR) bacteria are bacteria that are resistant to multiple different antibacterial classes of drugs and therefore have limited treatment options. MDR bacteria are a result of the overuse of antibiotics and considered a public health threat by the Centers for Disease Control. These bacteria are responsible for more than 2 million infections, 20,000 deaths, and a significant economic burden. These infections can manifest as pneumonia, urinary tract, bloodstream, and skin and soft tissue infections. Examples of resistant bacteria are provided in **Table 16-2**.

TABLE 16-2
Drug-Resistant Bacteria

Bacterial Group	Specific Resistant Organisms
Gram-negative	Multidrug-resistant: *Pseudomonas aeruginosa* *Acinetobacter* sp.
	Extended-spectrum: β-lactamase–producing *Klebsiella*

	pneumoniae and *Escherichia coli* Carbapenemase-producing Enterobacteriaceae
Gram-positive	Methicillin-resistant *Staphylococcus aureus*
	Vancomycin-resistant *Staphylococcus aureus*
	Vancomycin-resistant *Enterococcus* sp.

Categories of Antibiotic Drugs

Antibiotics are a category of drugs that either inhibit or cease bacterial growth. The three main categories of bacteria that will be discussed are gram-positive, gram-negative, and anaerobic bacteria.

Beta-Lactam Antibiotics

The β-lactam antibiotics are the most frequently used class of antibiotics. Categories of β-lactam antibiotics include the penicillins, cephalosporins, carbapenems, and monobactams. These substances all have a four-member β-lactam ring as part of their chemical structure (**Figure 16-3**). It is this chemical structure (β-lactam ring) that is responsible for the antibacterial activity of all four groups. They all have in common the β-lactam ring, with various substitutions made at different parts of the ring (**Figure 16-4**). It is not necessary to memorize the individual structures, but they are presented in order to show how all the β-lactam antibiotics are related.

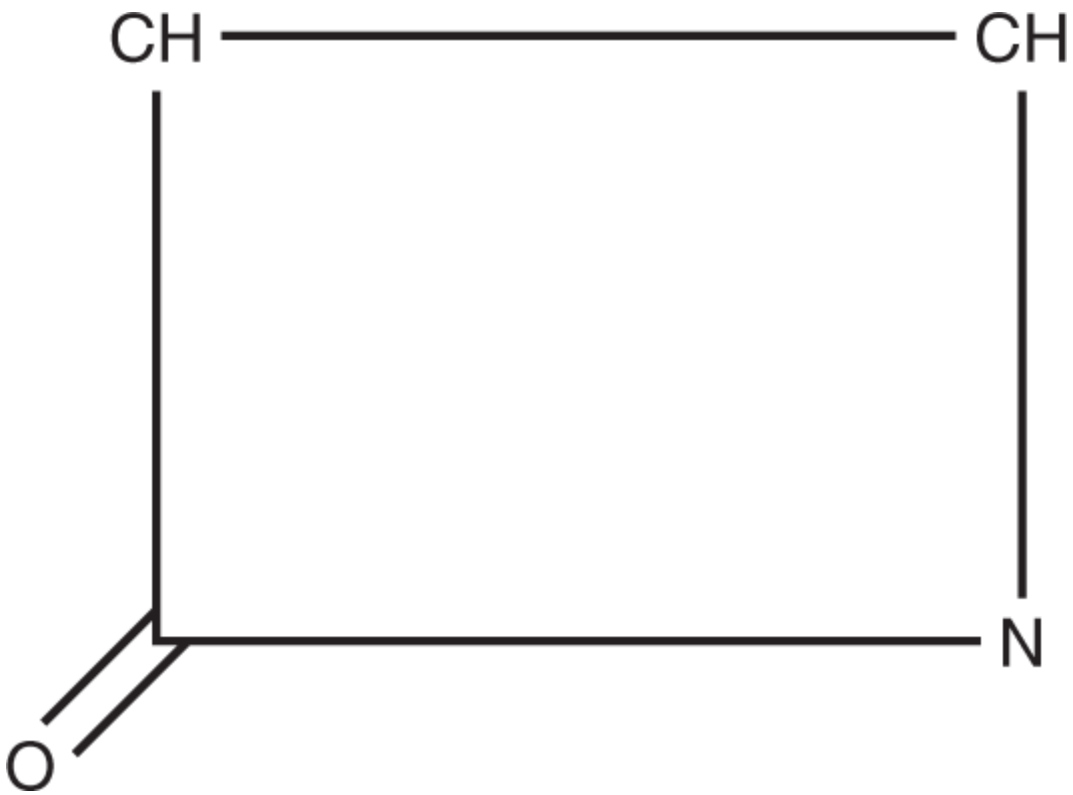


FIGURE 16-3 Beta-lactam ring.

Description

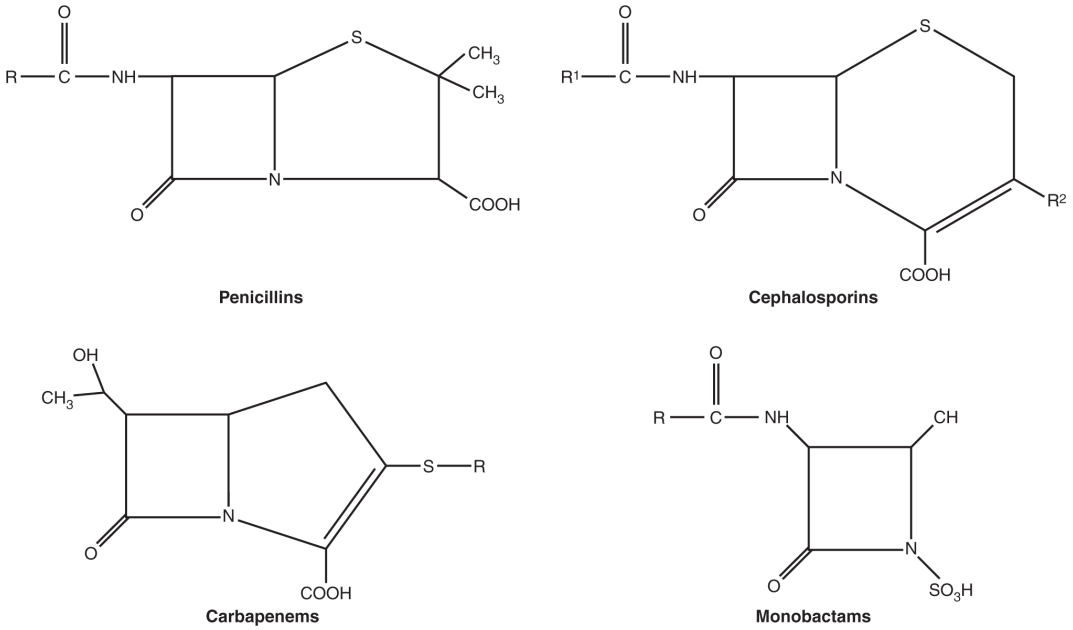


FIGURE 16-4 Beta-lactam antibiotic structures.

Description

The bacterial cell wall is made of substances called peptidoglycans that provide structure to the cell wall (**Figure 16-5**). The β-lactam antibiotics interfere with the synthesis of these peptidoglycans by binding to an enzyme referred to as penicillin-binding protein. This action prevents the synthesis of peptidoglycan and the cell dies. Because this substance does not occur in human or mammalian cells, most antibiotics are not toxic to human cells.

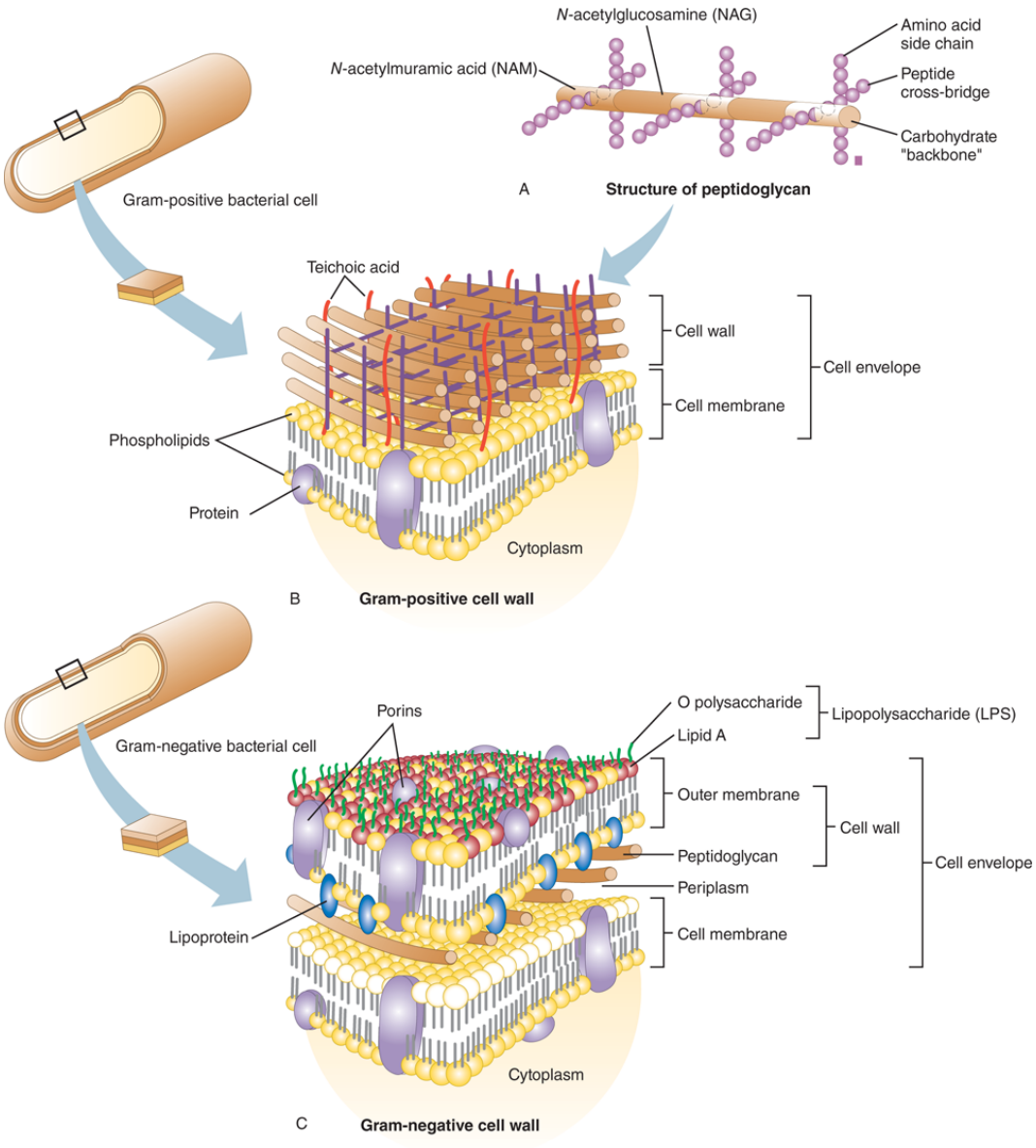


FIGURE 16-5 (**A**) Structure of peptidoglycan. (**B**) Gram-positive cell structure. (**C**) Gram-negative cell structure.

Description

One of the major problems associated with the use of β-lactam antibiotics and all antibiotics is the development of bacterial resistance to the drugs. There are a number of mechanisms that are operational in the development of resistance, but the most important one is that some bacteria produce enzymes that inactivate various drugs. These enzymes are called β-lactamases, and they cleave the carbon–nitrogen bond in the β-lactam ring, which destroys the antibacterial activity. There are several β-lactamases produced by various gram-positive and gram-negative organisms, and this phenomenon has necessitated the development of newer-generation β-lactams that are effective against the β-lactamase–producing bacteria. Beta-lactamase enzyme inhibitors are available and formulated with some antibiotics in order to preserve the efficacy of these drugs against β-lactamase–producing bacteria. The various β-lactam antibiotics are discussed, and the antibiotics that are resistant to the effects of β-lactamases are identified. In addition, the β-lactamase inhibitors, used in combination with the β-lactams, are described.

NEED TO KNOW

All β-lactam antibiotics contain a β-lactam ring in their structure and work by inhibiting peptidoglycan synthesis in bacterial cell walls. Penicillins, cephalosporins, monobactams, and carbapenems are all considered as β-lactam antibiotics.

Penicillins

The discovery of penicillin in 1928 by Alexander Fleming was one of the most important events in medical history. Because the original natural penicillins came from a mold (a living organism), the penicillins are considered true antibiotics. All the various penicillins have the same basic structure, and the different classes are determined by modifications made at the *R* side chain (see Figure 16-3).

Some of the penicillins are effective by the oral route, but there is some variability in absorption (e.g., penicillin G is unstable in the low-pH environment of the stomach and penicillin V is acid-stable). Most

penicillins are rapidly eliminated from the body by the kidneys in an unchanged form; however, some penicillins are metabolized by the liver. Overall, penicillins are well tolerated. The major adverse effects of the penicillins are gastrointestinal (GI) upset and a high incidence of allergic reactions. These can range from an acute anaphylactic reaction to a milder delayed reaction, but regardless of the extent of the allergy, there is cross-allergenicity among all penicillins (i.e., allergy to one penicillin may mean allergy to all in the class). Other allergic type reactions that may occur with penicillins include hives, fever, interstitial nephritis (cause of renal failure), and hemolytic anemia. At high doses, penicillins may cause seizures. The categories of penicillins include natural penicillins, penicillinase-resistant penicillins, amino penicillins, and extended-spectrum penicillins. The following discussion includes examples, spectrum of activity, clinical use, and adverse effects distinctive to each class of penicillins (see **Table 16-3**).

TABLE 16-3
Commonly Used Penicillins

Penicillin Class/Drugs in Class	Route	Common Clinical Uses
Natural Penicillins		
Penicillin G	IV, IM	Pharyngitis (other upper respiratory tract infections), meningitis, syphilis, and anthrax
Penicillin G procaine	IM	
Penicillin G benzathine	IM	
Penicillin V	PO	
Penicillin-Resistant Penicillins		
Oxacillin	IV, IM	Endocarditis*, bloodstream infections, and skin and soft tissue infections caused by MSSA
Nafcillin	IV	

Dicloxacillin	PO	
Aminopenicillins		
Ampicillin	PO, IV	Sinusitis, otitis media, LRTIs/pneumonia, and meningitis caused by *Listeria monocytogenes*
Amoxicillin	PO	
Extended-Spectrum Penicillins		
Ticarcillin	IV, IM	Hospital-acquired pneumonia, urinary tract infections, diabetic foot infections, and intra-abdominal infections with suspected *Pseudomonas aeruginosa* or resistant gram-negative organisms
Piperacillin	IV, IM	

*Oral drugs (dicloxacillin) not used to treat endocarditis.

LRTIs, lower respiratory tract infections; MSSA, methicillin-susceptible strains of *Staphylococcus.*

Natural Penicillins

These penicillins include penicillin G (benzylpenicillin) and penicillin V (phenoxymethylpenicillin). Because penicillin G is not stable in an acid environment, it is most often given by intravenous injection four to six times per day. There are other formulations of penicillin G (procaine and benzathine) that are administered through the intramuscular (IM) route. Penicillin V is acid-stable and is given orally. *Spectrum*: Gram-positive *Streptococcus* sp., *Neisseria meningitidis*, *Listeria monocytogene*s, some *Enterococcus* sp., non-β-lactamase–producing anaerobes, *Treponema pallidum*, and *Bacillus anthracis*.

Penicillinase-Resistant Penicillins

These semisynthetic penicillins include methicillin, nafcillin, oxacillin, and dicloxacillin. Methicillin is no longer used because of the high rate of adverse effects. Dicloxacillin is used for mild-to-moderate infections and is only available orally. The other agents are used parenterally. *Spectrum*: Gram-positive β-lactamase–producing *Staphylococcus* sp., also effective against *Streptococcus* sp.

including penicillin-susceptible strains of *Streptococcus pneumoniae*. They are the drugs of choice for patients with methicillin-susceptible strains of *Staphylococcus aureus* (MSSA).

Aminopenicillins

These drugs include ampicillin and amoxicillin. Ampicillin is not as stable or well tolerated as amoxicillin when given orally and therefore should be taken on an empty stomach. *Spectrum*: These agents have greater activity against gram-positive organisms than penicillin and are also effective against some gram-negative organisms. They are able to more effectively penetrate the gram-negative outer membrane. Examples are methicillin-susceptible and penicillin-resistant *Staphylococcus* sp.; *Enterococcus* sp., also effective against *Streptococcus* sp. including *S. pneumoniae*; and susceptible gram-negatives including *Escherichia coli*, *Salmonella* sp., and *Haemophilus influenzae*. *Adverse effects*: Skin rashes, diarrhea, and pseudomembranous colitis are more common with ampicillin; amoxicillin is better tolerated.

Extended-Spectrum Penicillins

This group of drugs includes ticarcillin and piperacillin. None of these agents are absorbed from the GI tract and therefore must be given by injection. Ticarcillin and piperacillin are only available in combination with β-lactamase inhibitors to improve the spectrum against gram-negatives. *Spectrum*: As the name implies, these agents are effective not only against gram-positive organisms (similar spectrum to amino penicillins) but also against a number of gram-negative aerobic organisms, including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *E. coli*, *Enterobacter* sp., *Citrobacter* sp., and *Serratia* sp. *Adverse effects*: Piperacillin has been associated with acute kidney injury when used with vancomycin compared with other β-lactams.

Beta-Lactamase Inhibitors

The production of β-lactamase by bacteria is one of the main methods that bacteria use in creating resistance. To prevent this resistance, there are two agents that are specific β-lactamase inhibitors: avibactam, clavulanic acid, sulbactam, tazobactam, and vaborbactam. These substances have no antibacterial action themselves, but are used in combination with other β-lactam drugs to broaden their antibacterial spectrum against gram-positives and gram-negative β-lactamase–producing organisms. Avibactam is available intravenously combined with ceftazidime (Avycaz). Clavulanic acid is available by oral route in combination with amoxicillin (Augmentin®) and combined with ticarcillin (Timentin®) for IV use. Sulbactam is available in combination with ampicillin (Unasyn®) for parenteral use. Tazobactam is available in combination with piperacillin (Zosyn), ceftolozane (Zerbaxa), and vaborbactam, which is available with meropenem (Vabomere). These combination agents also have coverage against anaerobic organisms (except Zerbaxa and Avycaz).

Cephalosporins

The structure of the cephalosporins is very similar to that of penicillin, except that the cephalosporin nucleus is more resistant to β-lactamase (see **Figure 16-6** for basic structure). The two *R* positions provide sites for a variety of modifications to the basic structure. The cephalosporins are classified into five groups or generations on the basis of their activity against gram-positive and gram-negative organisms. In general, first-generation agents are effective against MSSA, *Streptococcus* sp. and some gram-negative organisms, and second-generation drugs cover less gram-positive bacteria and more gram-negative organisms. Third-generation drugs have little coverage against *Staphylococcus* sp., while retaining good activity against *Streptococcus* sp. and gram-negatives. The fourth-generation cephalosporins are very active against MSSA, *Streptococcus* sp., and many gram-negative organisms including *P. aeruginosa*. **Table 16-4** lists examples of each generation with its route of administration and spectrum.

TABLE 16-4
First- to Fifth-Generation Cephalosporins

Category Generic (Brand)	Route	Spectrum
First-Generation		
Cephalexin (Keflex®)	Oral	Greater effectiveness against gram-negative organisms than penicillin G and more effective against a wider variety of gram-positive agents and used for pharyngitis, urinary tract infections, cellulitis, and infections caused by MSSA
Cefazolin (Ancef®, Kefzol®)	IV, IM	
Second-Generation		
Cefaclor (Ceclor®) Cefprozil Cefuroxime (Ceftin)	Oral	Increased effectiveness against gram-negative organisms and against β-lactamase producers, less effective against gram-positive organisms, used in sinusitis, otitis media, and LRTIs
Cefotetan (Cefotan) Cefoxitin	IV, IM	Similar activity as above with additional anaerobic coverage; and used to treat mild intra-abdominal infections
Third-Generation		
Cefotaxime (Claforan®) Ceftriaxone (Rocephin) Ceftazidime (Ceftaz)* Ceftazidime/avibactam (Avycaz)**	IV	Broader gram-negative and decreased gram-positive spectrum, less resistant to β-lactamases, and used to treat more resistant causes of otitis media, pneumonia, urinary tract infections, and only IV agents used to treat meningitis and endocarditis
Cefdinir (Omnicef®) Cefpodoxime Ceftibuten Cefditoren (Spectracef) Cefixime (Suprax)	Oral	
Fourth-Generation		
Cefepime (Maxipime®)	IM, IV	Useful against methicillin-sensitive *Staphylococcus epidermidis* and MSSA effective against many gram-negative organisms (i.e., *Escherichia coli*, *Proteus*

		sp., and *Klebsiella* sp.), including *Pseudomonas aeruginosa* used for hospital-acquired pneumonia, central nervous system infections, urinary tract infections, and intra-abdominal infections with an anaerobic drug
Fifth-Generation		
Ceftaroline (Teflaro)	IV	Gram-negative coverage similar to third-generation agents but also effective against MRSA, used in community-acquired pneumonia, bloodstream infections, and skin and soft tissue infections

*Ceftazidime is the only third-generation cephalosporin with activity against *P. aeruginosa*.

**Reserved for patients with infections resistant to carbapenems.

LRTIs, lower respiratory tract infections; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible strains of *Staphylococcus aureus*.

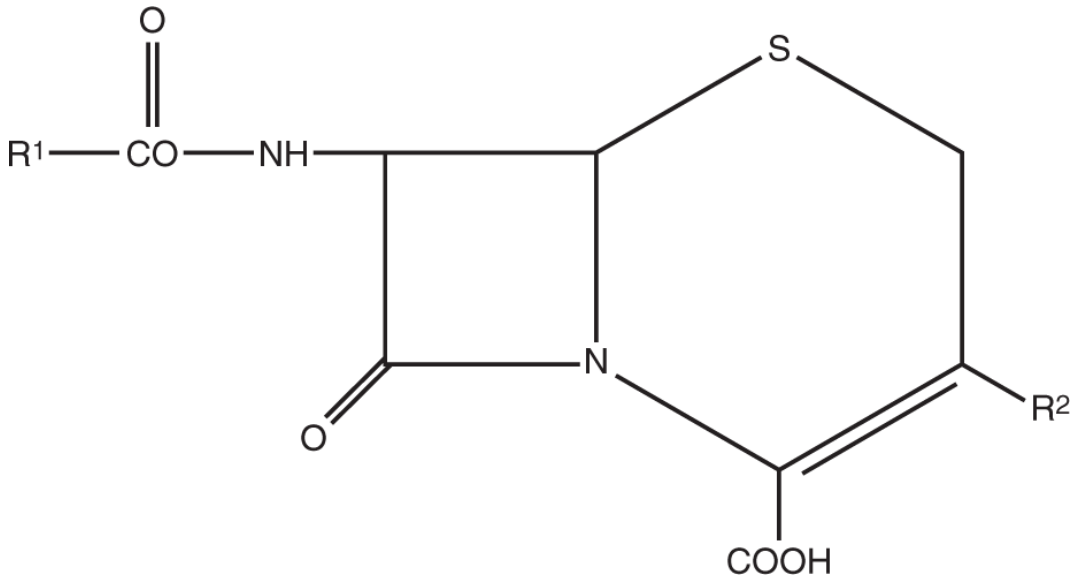


FIGURE 16-6 Structure of cephalosporins.

Description

The mechanism of action is similar to that of penicillin. Like penicillins, they can cause allergic reactions, rash, hives, anaphylaxis, and hemolytic anemia. Patients with a history of anaphylaxis to penicillins may develop a reaction to cephalosporins but the cross-reactivity may be lower than 1% and is more common with first-generation drugs. Third-, fourth-, and fifth-generation cephalosporins

may still be given to patients with a penicillin allergy but monitoring is required. In general, the cephalosporins are fairly safe, except for a low risk of renal toxicity and allergic reactions.

NEED TO KNOW

There are five generations of cephalosporins. The spectrum of action decreases in gram-positive coverage and increases in gram-negative coverage as you move from the first-generation to the third-generation cephalosporins. The cefepime, a fourth-generation agent has excellent gram-positive and gram-negative activity including *P. aeruginosa*. The fifth-generation agent has gram-positive activity including MRSA and gram-negative activity similar to the third-generation drugs.

Carbapenems

This category of β-lactams is similar in structure to penicillins, but with modification of the chemical structure, they are much less affected by β-lactamase enzymes. There are four drugs available in this class: ertapenem, doripenem, imipenem/cilastatin, and meropenem. Imipenem is partially broken down and inactivated in the kidneys. It is formulated with cilastatin to block tubular metabolism and to retain its antimicrobial activity. *Spectrum*: This class has activity against most gram-negative rods, including *P. aeruginosa* (except ertapenem), gram-positives, and anaerobes. Carbapenems should only be reserved to treat infections caused by bacteria resistant to other classes of antibiotics and β-lactams. These drugs are only administered IV or IM. *Adverse effects*: The most common side effects include pain at the injection site, nausea, vomiting, diarrhea, and allergic reactions. At high concentrations, imipenem may cause seizures. The cross-reactivity between penicillins and carbapenems is very low.

Monobactams

This drug group has only a single ring in its structure, and hence the name monobactam. It is structurally similar to ceftazidime. It is generally safe to use monobactams in penicillin allergic patients but

should be avoided in patients allergic to ceftazidime. *Spectrum*: Monobactam is a synthetic antibiotic and is only effective against aerobic gram-negative bacteria including *P. aeruginosa*. The only monobactam currently available in the United States is aztreonam (Azactam®), which is not absorbed by the oral route and must be given IV. Aztreonam is reserved for use in treating severe pneumonia, meningitis, and urinary tract infections caused by gram-negative organisms. *Adverse effects*: Allergies, rash, and elevated liver enzymes are rarely seen with aztreonam.

NEED TO KNOW

Aztreonam can be used safely in patients who have experienced anaphylaxis to other β-lactam drugs. It should be avoided in patients with an allergy to ceftazidime.

Quinolones

Quinolones (e.g., fluoroquinolones) are an important and commonly used class of antibiotics that have been shown to be effective against a variety of gram-positive and gram-negative bacteria, atypical bacteria, mycobacteria, and some anaerobic bacteria. Quinolones are bactericidal through inhibition of DNA topoisomerases, enzymes responsible for winding and unwinding of the double-helical structure of DNA. Inhibition of this enzyme can cause a fracture of DNA leading to cell death. *Spectrum*: Quinolones (except ciprofloxacin) have been shown to be effective and most commonly used in the treatment of upper and lower respiratory tract infections/community-acquired pneumonia (CAP) associated with *Streptococcus pneumoniae*, *H. influenzae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*. *Adverse effects*: In general, the quinolones are well tolerated but as their use has increased so has the reporting of serious side effects associated with them. They can cause dizziness, confusion, and hallucinations, and arrhythmias associated with QT prolongation, muscle pain, tendon rupture, and photosensitivity. This class should not be used in pregnant women

and in children for risk of developmental owing to skeletal muscle dysfunction, but benefit may outweigh the risk in these populations. Fluoroquinolones are metabolized and cleared by the kidney, and dosage may be adjusted in patients with renal insufficiency. **Table 16-5** provides a summary of quinolones and their clinical uses. All orally administered quinolones should be administered at least 2 hours before or 6 hours after antacids containing magnesium or calcium, aluminum, sucralfate, metal cations (e.g., iron), and multivitamins containing zinc or iron. This interaction can significantly decrease absorption of these agents. All these agents, except delafloxacin, are also available in ophthalmic drops, in addition to besifloxacin, norfloxacin, and gatifloxacin for the treatment of bacterial conjunctivitis.

TABLE 16-5
Quinolones

Drug	Route	Spectrum of Action	Clinical Uses
Ciprofloxacin (Cipro®)	IV, PO	*Escherichia coli*, *Proteus* sp., *Klebsiella* sp., *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*	UTIs, infectious diarrhea, and intra-abdominal infection (with metronidazole)
Delafloxacin (Baxdela)	IV, PO	MSSA, MRSA, *E. coli*, *Proteus* sp., *Klebsiella* sp., *P. aeruginosa*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *M. pneumoniae*, *L. pneumophila*, *Chlamydophila pneumoniae*, and anaerobes	Skin and soft tissue infections
Levofloxacin (Levaquin®)	IV, PO	*E. coli*, *Proteus* sp., *Klebsiella* sp., *P. aeruginosa*, *S. pyogenes*, *S. pneumoniae*, MSSA, *H. influenzae*, *M. pneumoniae*, *L. pneumophila*, and *C. pneumoniae*	CAP, sinusitis, COPD exacerbations, UTIs, skin infections, and intra-abdominal infection (with metronidazole)
Moxifloxacin (Avelox®)	PO	*E. coli*, *Proteus* sp., *Klebsiella* sp., *S. pyogenes*, *S. pneumoniae*, MSSA, *H. influenzae*, *M. pneumoniae*, *L. pneumophila*, *C. pneumoniae*, and *anaerobes*	*Cannot be used for UTIs CAP, sinusitis, COPD exacerbations, skin and soft tissue infections, and intra-abdominal infections

CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible strains of *Staphylococcus aureus*; UTIs, urinary tract infections.

Case Study 16-1

Anaphylaxis

An 8-year-old female is being seen in the emergency department for severe rash, severe dyspnea, and possible anaphylactic reaction. She was administered epinephrine 0.5 mg IV immediately.

History and Physical Examination

History: She was diagnosed with otitis media 5 days ago and was prescribed amoxicillin 500 mg suspension every 12 hours.
Vital signs: Heart rate, 125 beats/min; respiratory rate, 20 breaths/min; blood pressure, 89/40 mm Hg; and temperature, 38°C.
Neurologic: Pupils equal and react to light and accommodation.
Cardiovascular: Tachycardia.
Respiratory: Inspiratory and expiratory wheezes and decreased breath sounds and use of accessory muscles.

Home Medications

Amoxicillin 500 mg oral suspension every 12 hours
Multivitamin

Respiratory Care

1. High flow oxygen
2. Albuterol 2.5 mg/ipratropium 0.5 mg aerosol solution/3 mL nebulized now

Day 2: The patient's symptoms have improved and she is feeling better.

Questions

1. What was the most likely cause of this patent's anaphylaxis?
2. What alternative antibiotic would be appropriate to treat otitis media in this patient now?
3. Explain why a tetracycline antibiotic would not be an ideal choice of therapy for this patient.

Macrolides

Erythromycin is the prototype macrolide, but clarithromycin (Biaxin) and azithromycin (Zithromax) are the most commonly used agents in this class. This class is most frequently used in the outpatient setting. These drugs are good alternatives for patients allergic to penicillin. The common clinical use of this class is in the outpatient treatment of upper and lower respiratory tract infections caused by *S. pneumoniae* and atypical organisms. Azithromycin is also used in addition to a third-generation cephalosporin (ceftriaxone) for the inpatient treatment of CAP. Macrolides exert their bacteriostatic effects by binding to the 50S subunit of bacterial ribosomes,

preventing protein synthesis. *Spectrum*: *Streptococcus* sp., *H. influenzae*, and atypical organisms. *Adverse effects*: Significant nausea, vomiting, and diarrhea are commonly associated with this class and most with erythromycin. Hepatic failure has rarely been reported with macrolides. Erythromycin and clarithromycin interact with many drugs and have an increased risk of developing arrhythmias. Because of high incidence of GI effects and drug interactions as well as multiple daily doses with erythromycin and clarithromycin, azithromycin is the most frequently prescribed agent in this class.

Sulfonamides

Trimethoprim/sulfamethoxazole (TMP/SMX) is the most commonly used amide antibiotics. It is considered first-line for many infections but has fallen out of favor for common infections such as uncomplicated urinary tract infections because of emergence of resistance. Sulfadiazine is an uncommonly used sulfonamide recommended in combination with pyrimethamine for *Toxoplasma gondii*. TMP/SMX is recommended as a first-line agent in the treatment and prophylaxis of *Pneumocystis jirovecii* (causes pneumonia in HIV and immunocompromised patients) and prophylaxis of *T. gondii (*central nervous system infection in HIV-infected patients). Sulfonamides are derivatives of para-aminobenzoic acid (PABA). PABA is a precursor to folic acid, which is an essential substance in the DNA synthesis of bacterial cells. Sulfonamides inhibit dihydropteroate synthase, the enzyme responsible incorporating PABA in order to form a precursor of folic acid. When trimethoprim is added to sulfamethoxazole, this blocks the second step responsible for the formation of tetrahydrofolic acid and ultimately leads to inhibition of DNA synthesis. The sulfonamides are readily and completely absorbed in the GI tract, but they also have the ability to penetrate the cerebrospinal fluid as well as the placental barrier. *Spectrum*: Wide range of activity against *Staphylococcus* sp. (including MRSA), *Stenotrophomonas* sp., *H. influenzae*, and *P.*

jirovecii and moderate *E. coli*, *Proteus* sp., and *Klebsiella* sp. coverage; however, resistance is quite common with many strains of bacteria. *Adverse effects*: Allergic rashes are the most common adverse effect, but some rashes develop into life-threatening skin reactions called Stevens-Johnson syndrome and toxic epidermal necrolysis. Photosensitivity, drug fever, dose-dependent bone marrow suppression, liver failure, and renal dysfunction may also occur. The trimethoprim component of TMP/SMX may cause hyperkalemia.

In addition to the sulfonamides already mentioned, the following are other sulfonamide antibiotics used:

- *Sulfacetamide* (*Sulamyd*®): used topically for various eye infections
- *Sulfasalazine* (*Azulfidine*®): used in treating ulcerative colitis
- *Silver sulfadiazine* (*Silvadene*®): used in treating burn patients with bacterial infection

Tetracyclines and Glycylcyclines

The tetracyclines are a family of related compounds that were introduced in the late 1940s, and the use of these agents has decreased owing to resistance until recently with two new approved drugs. Tetracycline, doxycycline, and minocycline are older agents in this class, and eravacycline and omadacycline were approved in late 2018. Tigecycline is the only glycylcycline, derivative of tetracycline, available. Tetracycline is only available orally and minocycline and doxycycline are available IV and orally and newer agents are only available intravenously. These drugs bind to the bacterial ribosome at the 30S subunit and interfere with protein synthesis. The oral drugs are chelated, leading to decreased absorption, and should not be taken with drug products or vitamins that contain aluminum, calcium, magnesium, iron, and dairy. Although the tetracyclines have a broad spectrum, they are used for a fairly limited number of infections that include *Rickettsia* (causes spotted fever) *Borrelia burgdorferi* (cause Lyme disease), *Chlamydia* sp. (cause acne), and *Plasmodium* sp.

(cause malaria and brucellosis). They are also used for bronchitis and CAP. Eravacycline and omadacycline are more effective against resistant bacteria. *Spectrum*: Effective against a wide range of gram-positive (including MRSA) and gram-negative organisms and atypicals responsible for CAP. Tigecycline has additional activity against MRSA, *Enterococcus* sp. (including VRE), and more reliable gram-negative activity compared with tetracyclines. *Adverse effects*: GI and esophageal irritation are the most common side effects but have optimal absorption when taken on an empty stomach. Tigecycline IV can cause significant nausea and vomiting. Patients should avoid the sun and wear sunscreen while taking these agents. They can cause significant photosensitivity and sunburn. These drugs have a good ability to penetrate certain tissues, particularly bones and developing teeth, which can cause permanent discoloration. This class should not be used in pregnant patients and in children under age 8 owing to risk of teeth discoloration.

Aminoglycosides (Amikacin, Gentamicin, Plazomicin, Streptomycin, and Tobramycin)

Aminoglycosides are a class of antibiotics that are reserved only for use in severe infections because of their severe ototoxicity and renal toxicity. These antibiotic substances were derived from various *Streptomyces* species in 1943. The mechanism of action is the inhibition of protein synthesis by binding to the 30S ribosomal subunit.

They are poorly absorbed orally and are given IM or IV. They have a low therapeutic index and must be monitored carefully in terms of plasma concentration. Their use is reserved for critically ill hospitalized patients with severe gram-negative infections. Amikacin and streptomycin are also used for **tuberculosis (TB)**. Aerosolized amikacin and tobramycin are also used for cystic fibrosis patients and sputum colonization with *Pseudomonas* sp. *Spectrum*: Effective against most gram-negative bacilli, including *Pseudomonas* sp., *Acinetobacter*, and mycobacteria (amikacin and streptomycin only). *Adverse effects*: Primarily result from accumulation of drug in the

middle ear, causing potentially irreversible hearing loss and balance problems. Nephrotoxicity and renal dysfunction can also occur but more frequently in patients on high doses and/or other nephrotoxic drugs. These drugs sometimes are administered in combination with other β-lactams for critically ill patients.

NEED TO KNOW

Toxicities associated with aminoglycosides are hearing loss, vestibular (balance) toxicity, and nephrotoxicity.

Glycopeptides

There are four glycopeptides used in the United States: vancomycin, the most commonly used, telavancin, dalbavancin, and oritavancin. All drugs are only available as intravenous agents, except for vancomycin. Vancomycin is the drug of choice for MRSA infections, including hospital-associated MRSA pneumonia or in patients with MSSA and a severe β-lactam allergy. Oral vancomycin is the drug of choice and only used for *Clostridium difficile*–associated diarrhea infection. The other three agents are used for complicated skin and soft tissue infections. Dalbavancin and oritavancin have a long duration of action and are given either as one dose or once weekly. Glycopeptides inhibit bacterial cell wall synthesis by preventing the formation of peptidoglycan. *Spectrum*: Gram-positive cocci and particularly *Staphylococcus* sp. that are resistant to penicillin or cephalosporins. *Adverse effects*: Vancomycin, especially at high doses, and telavancin are associated with the development of renal dysfunction. All glycopeptides can cause an IV infusion-related reaction that causes flushing, rash, and hypotension. Telavancin can cause ventricular arrhythmias caused by QTc prolongation. Oral vancomycin is minimally absorbed and therefore not associated with adverse effects. Vancomycin plasma concentrations are usually monitored in order to assure efficacy and to avoid renal dysfunction.

Oxazolidinones

Currently, linezolid and tedizolid are the only available members of this class. Both drugs are available orally and IV. Pneumonia and skin and soft tissue infections caused by resistant gram-positive infections are the main uses. They can be initiated in the hospital and transitions to the oral formulation as an outpatient. They inhibit protein synthesis by binding to the 50S ribosomal subunit blocking a complex forming with 70S. *Spectrum*: They have excellent activity against gram-positives, including MRSA and VRE. They are also used for *Mycobacterium tuberculosis*. *Adverse effects*: When used for more than 2 weeks, it can cause bone marrow suppression, peripheral neuropathy, and lactic acidosis. These effects are more common with linezolid. Both agents may interact with monoamine oxidase inhibitors and selective serotonin reuptake inhibitors (discussed in Chapter 14).

Cyclic Lipopeptides (Daptomycin)

Daptomycin is the only available drug in this class. It works by binding to the cell membrane of gram-positive bacteria and causes a pore or “hole” to form, allowing intracellular potassium to leak out of the organism. This results in cell depolarization, a cessation of RNA and DNA synthesis, and cell death. One unique feature of this drug is that although it enters lung tissue very well, it binds to pulmonary surfactant which inactivates the drug. Therefore, it should not be used to treat any pulmonary infections or pneumonia. It is used for the treatment of skin and soft tissue infection caused by resistant gram-positive bacteria and endocarditis of the tricuspid valve caused by *Staphylococcus aureus*. *Spectrum*: Gram-positive organisms, including MRSA and VRE. *Adverse effects*: Daptomycin can affect skeletal muscle and causes muscle soreness or weakness. A fever and eosinophilic pneumonia have also been reported with this drug.

NEED TO KNOW

Daptomycin cannot be used for the treatment of pneumonia or lower respiratory tract infections. It is inactivated by pulmonary surfactant.

Agents for Anaerobic Infections

Anaerobes are primarily found in the oral cavity and the lower GI tract. It is in these locations that anaerobic infections will occur. The most prevalent anaerobic bacterium found in the GI tract is *Bacteroides fragilis*. There are multiple agents that will treat anaerobic infections, including carbapenems, tigecycline, ampicillin/sulbactam, piperacillin/tazobactam, and moxifloxacin. *Clostridium difficile*, which causes infectious diarrhea, is also an anaerobe but is only treated with oral vancomycin and metronidazole. This section will discuss clindamycin, which has some anaerobic and gram-positive activity as well as metronidazole. Metronidazole has clinical activity primarily against anaerobic organisms.

Lincosamide

The only available lincosamide is clindamycin (Cleocin®). It is a synthetic derivative of lincomycin and is used as an alternative in treating penicillin-susceptible gram-positive infections in patients with a β-lactam allergy. It is an inhibitor of protein synthesis by binding to the 50S ribosome. It is used for skin and soft tissue infections as well as dental or oral infections. It can also be used topically for acne. It may also be used in combination with other agents for the second-line treatment of malaria and *P. jirovecii* pneumonia. It is usually administered orally but can be given by injection for serious anaerobic infections. *Spectrum*: Gram-positive cocci, in particular *Streptococcus pyogenes* and *S. aureus* and in some cases MRSA. Clindamycin also has activity against anaerobic bacteria. *Adverse effects*: Include high incidence of diarrhea and, in some individuals, antibiotic-associated colitis.

Nitroimidazoles

Metronidazole and less commonly used tinidazole are synthetic agents that are effective against both parasitic and anaerobic bacterial infections. Susceptible organisms activate part of these drugs and create free radicals. The free radicals cause damage to the organism DNA, leading to cell death. Metronidazole is effective orally with good GI absorption and is distributed to tissues and fluids such as vaginal secretions, seminal fluid, saliva, breast milk, and cerebrospinal fluid. Tinidazole is newer, more expensive, and only available orally. These drugs can be used for abdominal infections in combination with drugs that have activity against gram-negative organisms. It may be used for mild *C. difficile* infections. *Spectrum*: They are effective against gram-positive and gram-negative anaerobic bacteria and antiparasitic against vaginal *Trichomonas*, amoebiasis, and giardiasis. *Adverse effects*: The most common side effects include nausea, vomiting, and diarrhea and a metallic taste. Liver dysfunction and pancreatitis can occur but are rare. Peripheral neuropathy can occur with prolonged use. Patient should be instructed to avoid alcohol when taking these drugs because the drugs can react with alcohol, which may lead to severe vomiting.

Tuberculosis

TB is caused by the **acid-fast bacilli (AFB)**, *M. tuberculosis*. It is diagnosed through a combination of symptoms, risk factors, bacteriologic identification of sputum cultures, and radiologic evidence. Throughout the world, TB is one of the top 10 causes of death. TB is very difficult to treat because the bacteria replicate and grow more slowly than other organisms and drugs used must be able to get into the cells in order to be active. The cell walls of these bacteria are difficult to penetrate (**Figure 16-7**) and structurally different from other bacteria. In the United States, more than half of the new cases of TB are seen in foreign-born individuals, particularly those from Mexico, India, Vietnam, and the Philippines. TB tends to be a chronic disease that is often identified in patients who are in generally poor health, have poor nutrition, and have inadequate defense mechanisms. The resistant strains have been increasing owing to expansion in homeless populations and the incidence of HIV/AIDS and other immunocompromised populations. Patients with active TB infection will have a bad cough lasting multiple weeks, chest pain, bloody sputum, fever, night sweats, and weight loss. This infection most commonly affects the lungs but can also occur on other parts of the body and lymph nodes. The goal of treatment is to cure the disease, stop the transmission to other individuals, and avoid the development of drug resistance.

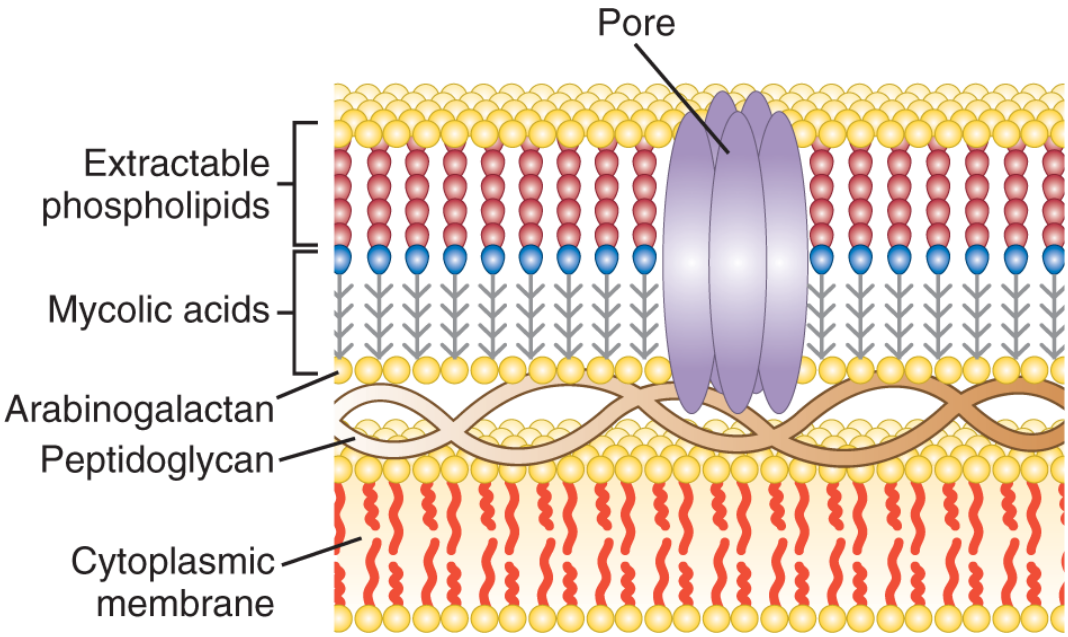


FIGURE 16-7 Mycobacterium cell wall.

Description

NEED TO KNOW

When a physician orders "Sputum for AFB," there is a suspicion that the patient may have TB. Strict precautions and respiratory isolation should be observed.

Drugs Used in the Treatment of TB

Treatment of active TB often requires combination therapy to minimize the development of resistance. The duration of treatment in most cases is at least 6–9 months, and in patients with MDR, TB treatment can last for 2 years. The most recent clinical protocol includes four-drug treatment with "first-line" agents. These agents seem to give the best efficacy with an acceptable degree of toxicity. They include isoniazid, a rifamycin (i.e., rifampin, rifapentine, and rifabutin), ethambutol, and pyrazinamide (PZA). The usual protocol for these agents includes isoniazid, rifampin, and PZA for the first 2 months. These are followed by isoniazid and rifampin for the remaining 4 months. It is thought that the increased incidence of drug-resistant TB may be partially because of failure of the initial treatment

regimen. Some of the patients in the high-risk populations are unable or unwilling to maintain the medications over a 6-month period, leading to an unresolved active infection and organisms that have developed resistance to isoniazid and rifampin. TB that is resistant to isoniazid and rifampin is referred to as multiple drug-resistant TB (MDR-TB). The newest and most resistant form of TB is extensively drug-resistant TB, in which the TB is resistant to isoniazid, rifampin, and other first- and second-line antitubercular drugs. The drugs used in the treatment of TB and MDR-TB are listed in **Table 16-6**. Only the first-line drug therapies will be discussed in further detail in this chapter.

TABLE 16-6
Anti-Tuberculosis Drugs

First-Line Agents	Second-Line Agents
Isoniazid	Levofloxacin/moxifloxacin
Rifampin (also rifapentine and rifabutin)	Streptomycin sulfate
Ethambutol	Amikacin/kanamycin (not available in the United States
Pyrazinamide	Ethionamide
	Para-aminosalicylic acid
	Cycloserine
	Capreomycin
	Bedaquiline

Isoniazid

Isoniazid is one of the two most important drugs in the treatment of TB. Isoniazid prevents the production of mycolic acids in the cell wall

of *Mycobacterium tuberculosis*. The adverse reactions that one should be aware of include development of peripheral neuropathy. Patients are instructed to take pyridoxine (vitamin B_6) to prevent this from occurring. Rash, fever, optic neuritis, and rarely seizures can occur. All first-line agents used for TB can cause hepatotoxicity.

Rifamycins

The rifamycins are another important drug class used in the treatment of TB. There are three drugs in this class: rifampin (most commonly used), rifabutin, and rifapentine. Rifamycins can also be used to treat *Mycobacterium avium* complex (MAC) (lung infection that develops in immunocompromised patients) and in combination therapy to treat *S. aureus*. They inhibit protein synthesis by preventing RNA transcription, a part of the DNA is copied to make RNA. This class interacts with many drug classes and can lead to increased clearance of drugs from the body and in turn a decreased effect of that drug. Rifabutin has less potent drug interactions and because of that is used in patients with TB and HIV to decrease the likelihood of drug interactions. Rifamycins color bodily fluids an orange-red color. They can also cause rash, fever, nausea, and hepatotoxicity.

Pyrazinamide

PZA is usually used only for the first 2 months of TB therapy. PZA diffuses into mycobacteria and is converted to pyrazinoic acid. This acid accumulates and prevents fatty acid synthesis, and may also inhibit RNA translation and prevents protein synthesis. The major adverse effects are hyperuricemia and hepatotoxicity.

Ethambutol

Ethambutol is used in the treatment of TB and MAC. It inhibits the production of arabinogalactan, a component of the cell wall. This drug may cause optic neuritis (loss of vision and color blindness), which is usually reversible. Hepatic toxicity and rash can occur as well.

Antifungal Drugs

Mycotic or fungal infections can occur in superficial areas of the body, including the skin and mucous membranes, as well as systemically. Fungal skin and mucocutaneous infections are the most common sites of fungal infections. Systemic fungal infections occur less frequently, but when present, incur high mortality. Immunocompromised patients are at a higher risk of fungal infections. Fungi can be divided into three classifications: yeast (e.g., *Candida* and *Cryptococcus*), dimorphic fungi (e.g., *Histoplasma*, *Blastomyces*, and *Coccidies*), and mold (e.g., *Aspergillus* and *Zygomycetes*). Drug classes used to treat systemic fungal infections and *Aspergillus* pulmonary infections will be discussed in this chapter. Drugs used to treat superficial fungal infections will be mentioned.

Antifungals Used in Systemic Fungal Infections

The most common classes of drugs used in the treatment of systemic fungal infections include the azoles, polyenes, and echinocandins. The polyenes are the most toxic class and are reserved for use in resistant *Candida* or mold infections. Many of the azoles are available in oral and IV formulations. This makes it easy to transition the treatment of these infections to an outpatient setting. The echinocandins are the newest class of antifungals and now considered first-line treatment in systemic *Candida* infections.

Polyenes

Amphotericin B and nystatin are the available drugs in this class. Aerosolized amphotericin is described in detail in Chapter 10. This drug class increases fungal cell permeability, inhibiting growth at low concentrations. Amphotericin is given IV for systemic *Candida*, *Aspergillus*, *Cryptococcus*, dimorphic fungi, and mold infections. Nystatin is usually topically for the treatment of fungal skin infections

and orally for treatment of oral cavity fungal infections (thrush). Amphotericin comes in three formulations, amphotericin B conventional and two lipid formulations. The lipid formulations are preferred, have less adverse effects, and better tolerated overall. *Adverse effects* (amphotericin): Hypokalemia, hypomagnesaemia, and infusion-related reactions, which include fever, chills, and rigors, are most common with conventional amphotericin. Acetaminophen and diphenhydramine are given before the IV infusion to decrease infusion-related reactions. Nephrotoxicity is common and limits the use of these agents. The lipid formulations have less nephrotoxicity.

Flucytosine

This drug has a narrower spectrum against fungi than amphotericin B. It is used in clinical practice in combination with other antifungals for the treatment of cryptococcal meningitis. It can be given orally and often is given in combination with amphotericin B. *Adverse effects*: Include nausea, rashes, diarrhea, and hepatic diseases; some bone marrow suppression also can occur, which can be fatal.

Azoles

The drug development of antifungals has recently been active. There are five drugs in this class that are used to treat systemic infections: fluconazole, itraconazole, isavuconazonium, posaconazole, and voriconazole. Fluconazole, posaconazole, isavuconazonium, and voriconazole are available in IV and oral formulations. Terconazole is used topically to treat vaginal *Candida* infections. They work by inhibiting fungal cytochrome P450, leading to a decrease in ergosterol production in the fungal cell membrane. All azoles treat *Candida* sp., and itraconazole, isavuconazonium, posaconazole, and voriconazole also have activity against dimorphic fungi and are considered first-line for the treatment of pulmonary aspergillosis. The newer agents isavuconazonium and posaconazole have activity against more difficult to treat mold infections. *Adverse effects*: Azoles are generally well-tolerated class. They can cause QT prolongation, hepatotoxicity,

rash, and interaction with many medications. Voriconazole can cause reversible visual effects and visual hallucinations. Itraconazole can worsen heart failure. This class of medications has significant drug interactions with many medications. They can increase the concentration of interacting medications, leading to toxicity.

Echinocandins

Anidulafungin, caspofungin, and micafungin are the agents available in this class. They inhibit the synthesis of 1,3-D-β-glucan. This is essential for cell wall formation and without it results in cell lysis. All three agents have similar spectrums of activity. They provide excellent activity against *Candida*, but unlike azoles only come in an IV formulation. They also have some activity against *Aspergillus* but are used in refractory cases. *Adverse effects*: This class is very well tolerated and may rarely cause infusion-related reactions and hepatotoxicity.

Antiviral Agents

Viruses are highly contagious organisms. Because viruses are intracellular obligate parasites requiring an intact host cell for reproduction, they are not affected by antibiotics. The structure of a virus can be found in Figure 10-2. The treatment of viruses has been approached by three basic modalities: prevention of infection through immunization and the development of antiviral drugs. There is no treatment for the most common respiratory virus, rhinovirus (common cold). Only drugs used to treat influenza and cytomegalovirus (CMV) pneumonitis will be discussed in this chapter.

Antiviral Drugs

Immunization has been the most effective approach for the treatment of most viral infections. Effective vaccines are available against diseases such as measles, mumps, polio, and rubella. The development of effective antiviral drugs has occurred in recent years, but because drugs that inhibit viral replication also affect the host cells, clinical usefulness is somewhat limited. The general mechanism of action of antiviral drugs is basically the same—they work by inhibiting viral cell replication by altering DNA synthesis. Some of the commonly used antiviral drugs are listed below, along with their main therapeutic uses and adverse effects.

Neuraminidase Inhibitors

The three available neuraminidase inhibitors used in the treatment or prevention of influenza A and B are oseltamivir (Tamiflu), peramivir (Rapivab), and zanamivir (Relenza). Oseltamivir is available orally, peramivir is administered intravenously, and zanamivir is used as an inhaled formulation (Chapter 10). They are most effective when used in the first 48–72 hours of influenza infection when viral replication is highest. Drugs in this class inhibit the enzyme neuraminidase, which

prevents the release of viral particles from infected cells. *Adverse effects*: This class is generally well tolerated. They can cause nausea, vomiting, fatigue, and headache.

Endonuclease Inhibitor

This is a new class of antiviral agents. Baloxavir (Xofluza) is the only available agent in this class and is only approved for the oral treatment of influenza infection. It inhibits endonuclease, which is required for viral transcription and prevents replication of the virus. *Adverse effects*: In clinical trials, the most common side effects were diarrhea and nasopharyngitis. This drug is very new and clinical use will reveal any other toxicities.

Acyclovir (Zovirax®) and Valacyclovir (Valtrex)

These agents are primarily used in the treatment of herpes simplex virus infections and *Varicella zoster* (VZV). It is effective in the membranous lesions of genital herpes and also in other herpetic diseases. Acyclovir can be applied topically in ointment form or taken orally as a prophylactic agent. These drugs do not appear to be a cure, but it can decrease healing time and duration of the illness when used early. In addition to oral and topical forms, acyclovir can be given IV and is used multiple times daily. Valacyclovir is an oral agent developed to improve tolerability and adherence with only twice daily dosing. These drugs stop viral replication but act as a nucleoside and get incorporated into the viral DNA. *Adverse effects*: Crystals may form in the urine with these drugs, causing renal insufficiency. They can also cause acute interstitial nephritis. Nausea, vomiting, and rash are most common and seizures can occur rarely.

Ganciclovir (Cytovene) and Valganciclovir (Valcyte)

CMV may affect immunocompetent patients but will only cause active infection in immunocompromised patients, specifically transplant recipients and uncontrolled HIV patients. They are nucleoside analogs

and work similarly to acyclovir and valacyclovir. They are used to treat and prevent CMV infection as well as VZV. Ganciclovir is available intravenously and orally but the oral formulation is not used because of poor absorption. Valganciclovir is formulated in an oral preparation with better absorption. *Adverse effects*: These agents have dose-related bone marrow suppression, nephrotoxicity, nausea, vomiting, and diarrhea. These agents are teratogenic. Pregnant patients should avoid taking this class and pregnant healthcare professionals should avoid handling this class of medications.

Case Study 16-2

Hospital-Acquired Pneumonia

A 66-year-old man was admitted to the hospital 10 days ago with a complication from a lung transplant. He has been on mechanical ventilation for the past 10 days and now developed fever, increased oxygen requirements, and increased thick sputum production. The patient is diagnosed with pneumonia.

History and Physical Examination

History: Chronic obstructive pulmonary disease, single lung transplant 6 months prior, hypertension, and hypothyroidism.
Allergies: Penicillin: rash/hives.
Vital signs: Heart rate, 101 beats/min; respiratory rate, 14 breaths/min; blood pressure, 140/90 mm Hg; and temperature, 39°C.

Laboratory Values

Chest radiograph: New right lower lobe pulmonary infiltrate.
Electrolytes: Na^+ = 139 mEq/L; K^+ = 4.6 mEq/L; Cl^- = 95 mEq/L; HCO_3^- = 30 mEq/L.
Hematology: Hgb = 10 g/dL; white blood cell (WBC) count = 18,500/mm^3.

Current Medications

Ipratropium/albuterol nebulization solution every 6 hours
Amlodipine 10 mg via tube daily for hypertension
Levothyroxine 88 µg via tube daily for hypothyroid
Tacrolimus 1.5 mg sublingually every 12 hours for transplant immunosuppression
Valganciclovir oral suspension 900 mg via tube daily antiviral
Prednisone 5 mg via tube daily for transplant immunosuppression
Enoxaparin 40 mg subQ daily for deep vein thrombosis prophylaxis
Ranitidine 150 mg IV every 8 hours for GI ulcer prevention
Aztreonam 2 g every 8 hours
Daptomycin 500 mg IV daily
Levofloxacin 750 mg IV daily
Propofol IV continuous infusion 30 µg/kg/min for intensive care unit sedation

Respiratory Care

Collect sputum for culture and sensitivity
Hypertonic saline 7% 5 mL nebulized every 12 hours
Ipratropium/albuterol 0.5 mg/2.5 mg nebulization solution every 6 hours
Day 2: The patient is not improving despite broad-spectrum antimicrobial therapy. His fever and WBC have increased and now is in shock on norepinephrine.
Day 3: Sputum culture: *Staphylococcus aureus*. Sensitive: vancomycin, linezolid, and daptomycin. Resistant: clindamycin, tetracycline, and penicillin.

Questions

1. Explain why this patient appears to failing therapy with daptomycin?
2. How would you change this patient's antibiotic regimen at this time?
3. What is the rationale for using valganciclovir in this patient?

Review Questions

1. Define the terms antimicrobial, bacteriostatic, and bactericidal.
2. Differentiate between narrow- and broad-spectrum antibacterial agents and explain the benefits of using narrow-spectrum agents for definitive therapy.
3. Describe the basic mechanism of action of the β-lactam antibiotics. Relate this action to chemical structures of the cell wall.
4. List the most common organisms known to cause lower respiratory tract infections or pneumonia and list one antibiotic regimen used to treat this infection.
5. List at least one example of each of the four categories of the β-lactam antibiotics and discuss the most common adverse effects associated with each.
6. Describe how the spectrum of activity changes from first-generation cephalosporins to fifth-generation cephalosporins and list an example in each of the five generations.
7. What clinical adverse effect associated with aminoglycosides limits their wide spread use?
8. Compare the mechanisms of action and clinical uses of fluoroquinolones, tetracyclines, and macrolides.
9. List the first-line primary antimicrobials used in the treatment of TB and the usual duration of therapy. What side effect may occur with use of all the first-line anti-TB drugs?
10. Which antifungal drugs can be used for the treatment of pulmonary aspergillosis?
11. What are the main clinical uses of acyclovir, oseltamivir, and valganciclovir and list side effects of each?

Posttest

For each of the following questions, try to select the *one* best answer from the choices given.

1. The term *bactericidal* indicates that a drug slows down the growth of bacteria. True or False?
2. A patient is started on ceftriaxone to treat severe pharyngitis. The culture comes back to reveal the causative organism is *S. pyogenes* and susceptibilities show it is sensitive to penicillin. The ceftriaxone is changed to penicillin VK. This is considered what part of the approach to infectious disease is described?
   a. Empiric
   b. Prophylaxis
   c. Definitive
   d. Resistance
3. Which of the following antimicrobials are part of the standard anti-TB treatment regimen?
   a. Kanamycin and amikacin
   b. Isoniazid and rifampin
   c. Penicillin and ribavirin
   d. Vancomycin and tobramycin
4. Which of the following is not a penicillin?
   a. Nafcillin
   b. Amoxicillin
   c. Ampicillin
   d. All of these are correct.
5. Which of the following is a third-generation cephalosporin?
   a. Cefotaxime (Claforan®)
   b. Cefaclor (Ceclor®)
   c. Ceftaroline (Teflaro®)
   d. Cephalexin (Keflex®)
6. Which of the following β-lactams would be safe to use in a patient with a proven anaphylactic shock to penicillin?
   a. Aztreonam

   b. Nafcillin
   c. Cephalexin
   d. Ampicillin
7. The most serious side effect of the aminoglycosides is severe renal and ototoxicity. True or False?
8. Which of the following antifungals are associated with renal toxicity?
   a. Amphotericin B
   b. Voriconazole
   c. Nystatin
   d. Micafungin
9. Which of the following antifungal drugs are used to treat pulmonary aspergillosis?
   a. Voriconazole
   b. Fluconazole
   c. Terconazole
   d. Nystatin
10. Which of the following antivirals are used in the treatment of influenza?
   a. Acyclovir
   b. Ganciclovir
   c. Oseltamivir
   d. Valganciclovir

References/Recommended Readings

Broyles BE, Reiss BS, *Pharmacological Aspects of Nursing Care*. Clifton Park, NY: Delmar Cengage Learning; 2013.

Brunton LL, Lazo JS, Parker KL, eds. *Goodman and Gilman's the Pharmacological Basis of Therapeutics*. 13th ed. New York, NY: McGraw-Hill Medical Publishing; 2018.

Center for Disease Dynamics, Economics & Policy. *State of the World's Antibiotics*. Washington, DC: CDDEP; 2015.

Fiore AE, Fry A, Shay D, et al; Centers for Disease Control and Prevention (CDC). Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60(1):1–24.

Flor de Lima B, Tavares M: Risk factors for extensively drug-resistant tuberculosis: a review. *Clin Respir J.* 2013;8(1):11–23.

Gallagher JC, MacDougall C. *Antibiotics Simplified*. 3rd ed. Burlington, MA: Jones and Bartlett; 2014.

Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. *N Engl J Med*. 2018;379(10):913–923.

Hitner H, Nagle BT: *Pharmacology: An Introduction*. 6th ed. San Jose, CA: Glencoe Publishing Co; 2011.

Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of American and the American Thoracic Society. *Clin Infect Dis*. 2016;63:e61–e111. doi:10.1093/cid/ciw353.

McCance, K, Huether S, Brashers V, et al. *Pathophysiology: The Biologic Basis for Disease in Adults and Children.* 6th ed. Maryland Heights, MO: Mosby-Elsevier; 2010.

Murase Y, Maeda S, Yamada H, et al. Clonal expansion of multidrug-resistant and extensively drug-resistant tuberculosis, Japan. *Emerg Infect Dis.* 2010;16(6):948–954.

Nahid P, Dorman S, Alipanah N, et al. Executive summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug susceptible tuberculosis. *Clin Infect Dis*. 2016;63:853–867.

O'Donnell JA, Gelone SP. Fluoroquinolones. *Infect Dis Clin North Am*. 2000;14:498.

Rainforth Collins, S. *Mosby's Drug Reference for Health Professionals.* 6th ed. St. Louis, MO: Mosby-Elsevier; 2018

Rybak JM, Marx KR, Nishimoto AT, Rogers PD. Isavuconazole: pharmacology, pharmacodynamics, and current clinical experience with a new triazole antifungal agent. *Pharmacotherapy*. 2015;35(11):1037–1051.

Shah NS, Pratt R, Armstrong L, et al. Extensively drug-resistant tuberculosis in the United States, 1993-2007. *JAMA*. 2008;300(18):2153–2160.

Spratto GR, Woods AL. *Nurse's Drug Handbook*. Clifton Park, NY: Delmar Cengage Learning; 2013.

Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis*. 2018;18:318–377.

van de Beek D, Cabellos C, Dzupova O. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. *Clin Microbiol Infect*. 2016;22:S37–S62.

Velayati AA, Masjedi MR, Farnia P, et al. Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. *Chest.* 2009;136(2):420–425.

Wargo KA, Edwards JD. Aminoglycoside-induced nephrotoxicity. *J Pharm Pract*. 2014;27(6):573–577

Weiderhold NP. The antifungal arsenal: alternative drugs and future targets. *Int J Antimicrob Agents*. 2018;51(3):333–339.

World Health Organization. The top 10 causes of death. News facts sheet. http://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death. Published May 24, 2018. Accessed November 2, 2018.

Zhanel GG, Cheung D, Adam H, et al. Review of eravacycline, a novel fluorocycline antibacterial agent. *Drugs*. 2016;76(5):567–588.

© Anna RubaK/ShutterStock, Inc.

Abbreviation	Definition	Abbreviation	Definition
ARDS	Acute respiratory distress syndrome	O_2	Oxygen
CBC	Complete blood count	PEFR	Peak expiratory flow rate
CF	Cystic fibrosis	PPD	Purified protein derivative
CO_2	Carbon dioxide	RDS	Respiratory distress syndrome
COPD	Chronic obstructive pulmonary disease	RV	Residual volume
CPAP	Continuous positive airway pressure	SIDS	Sudden infant death syndrome
CPR	Cardiopulmonary resuscitation	SMR	Submucosa resection
CT	Computed tomography	SOB	Shortness of breath
EIA	Enzyme immunoassay	TB	Tuberculosis
ET	Endotracheal tube	TLC	Total lung capacity
FVC	Forced vital capacity	$\dot{V}/\dot{Q}$	Ventilation/Perfusion
IRT	Immunoreactive trypsinogen		

Reproduced from Stanfield's Essential Medical Terminology, Fifth Edition (16026-0).

© Anna RubaK/ShutterStock, Inc.

A

Absorption a term in pharmacokinetics of a drug, means “pass through” or “soak in.” A process in which a drug passes through a barrier or membrane

Acetylcholine (ACh) a neurotransmitter that affects the motor neurons of the peripheral nervous system at the skeletal muscle

Acid-fast bacillus (AFB) bacteria that retain the color of a stain after an acid wash (acid-fast, e.g., *Mycobacterium tuberculosis*)

Adrenergic a term derived from adrenaline, which also called sympathomimetic; often used to describe drugs that mimic the action of the sympathetic nervous system and stimulate release of norepinephrine or epinephrine (e.g., albuterol))

Advanced cardiovascular life support (ACLS) a training course that includes a set of clinical algorithms performed during cardiac and respiratory medical emergencies

Adverse reaction also called side effects; a response to a drug that is harmful, excessive, and unintended

Aerosol a suspension of liquid droplets or solid particles in air or gas that is generated by a device

Afterload the force the heart must work against to pump or eject blood out of the heart during systole

Agonists drugs that combine with specific receptors to cause a drug action

Airway hyperresponsiveness (AHR) a hallmark trait of asthma where there is increased reactivity of the airways that causes bronchoconstriction in response to exposure to multiple stimuli or allergens

Aldosterone a steroid hormone from the adrenal cortex; it increases the reabsorption of sodium and water into the bloodstream, elevating the blood volume and increasing the blood pressure

Allergy an adverse reaction caused by triggering the immune system that results from an exposure to a drug, food, or chemical

Analgesia a state where there is absence of pain (loss of sensation of pain)

Analgesic a drug used to achieve analgesia, that is, relief from pain without the intention to cause loss of consciousness

Angina also called angina pectoris; a cardiovascular disease marked by severe pain in the chest that spreads to the shoulders, arms, and neck. Angina is caused by an insufficient supply of blood to the heart muscle

Angiotensin II a powerful vasoconstrictor that is released into the bloodstream by a series of chemical reactions triggered by the release of renin. Angiotensin II promotes the release of aldosterone that causes sodium and water retention

Antagonists also called blocking agent; drugs that combine with receptors and cause no action or block an effect, for example, naloxone, which blocks the effects of narcotics. Antagonists and agonists often compete for the same receptor site

Antiadrenergic also called adrenergic blockers; agents that block a receptor from norepinephrine or epinephrine having an effect

Antiasthmatic monoclonal antibodies the newest antiasthma drug class that block immunoglobulins from binding to mast cells and basophils, thus inhibiting the progression of an inflammatory response; recommended as an adjunct or add-on therapy in patients with severe asthma

Antibacterials compounds that kill or inhibit the growth of bacteria

Antibiotic *see* Antibacterials

Antibody also called immunoglobulin; a large number of high-molecular-weight proteins produced by the immune system in response to the presence of a foreign substance (pathogens)

Anticholinergic agents that block a receptor for ACh or prevent the release of ACh

Antidepressant a drug used in the treatment modality of moderate-to-severe major depressive disorders

Antifungals antimicrobial drugs used to treat and prevent fungal and mold infections

Antigen a substance that triggers an allergic or anaphylactic reaction and can include a number of substances, such as animal products, mold, dust, and drugs

Antimicrobials an agent that causes an effect on various microscopic organisms by being selectively toxic to them (e.g., antibiotics, antivirals, antifungals)

Antimuscarinics agents that specifically block the muscarinic receptor sites

Antiprotozoals antimicrobial agents that are used to treat infections caused by protozoans that are single-cell organisms

Antipsychotics a group of agents that are used to treat various types of psychosis and the prototype drugs are the phenothiazines

Antipyretic drugs that are used to lower body temperature (when elevated), reducing fever

Antivirals antimicrobial drugs that kill virus or affect the viral replication process, inhibiting the release of the virus into the host cell cytoplasm or outside of the host cell

Anxiolytic also called an antianxiety agent; drugs that reduces the feeling of anxiousness

Arrhythmia an irregularity or loss of rhythm of the electrical activity in the heart

Asthma one of the most common chronic lung diseases affecting individuals of all ages and in all degrees. The major characteristics of asthmatics include airway obstruction due to bronchospasm, inflammation, and excess mucus production

Atherosclerosis hardening (fibrosis) of the arteries, which causes narrowing of all the vessels, especially the coronary arteries

B

Bactericidal an antibiotic that kills bacteria

Bacteriostatic an antibiotic that inhibits or retards the growth of bacteria

Biotransformation also called metabolism; the process by which drugs and other foreign chemicals that enter the body are altered, changed, inactivated, and prepared for elimination

Bland aerosol medications in the form of aerosols that do not have a direct effect on the mucus molecule but are used to improve secretion clearance by providing humidification with saline solutions

Broad-spectrum antibiotics : antibiotics that treat many types of gram-positive and gram-negative bacteria

Bronchial provocation testing a procedure done in the pulmonary function laboratory to provide the physician with information regarding the reactivity of the patient's airway when exposed to an irritant. This testing provides both pathophysiologic and clinical information about a patient's pulmonary disease

Bronchoconstriction a condition in which the diameter (lumen) of the airway is reduced or constricted, thereby decreasing expiratory flow. This condition may be due to bronchospasm, airway inflammation/airway wall thickening, mucosal edema, or the presence of secretions (or a combination of these)

Bronchorrhea a condition associated with excess thin and watery pulmonary secretions, which is similar to the rhinorrhea process in the nose

Bronchoscopy the direct visualization of the tracheobronchial tree by a rigid or flexible scope that allows the clinician to visualize the upper and lower respiratory tracts for the diagnostic management of several pulmonary diseases involving the airways and lungs

Bronchospasm a reversible contraction of the bronchial smooth muscle leading to decreases in pulmonary function, for example, forced expiratory volume in 1 second (FEV_1) and peak expiratory flow rate (PEFR)

C

Carcinogen drugs or substances that cause malignant neoplasms or cancers

Catecholamine a monoamine neurotransmitter or neurohormone produced in the adrenal gland. Catecholamines affect the adrenergic receptors and are metabolized by catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO)

Chamber a device that has been developed to provide a reservoir of aerosol to improve medication delivery using pressurized metered-dose inhalers. The primary purpose of this device is to hold the aerosol in suspension for a longer period while giving the patient time to inhale when ready

Chlorofluorocarbon (CFC) an organic compound that contains carbon, chlorine, and fluorine; it is used as a propellant device to deliver aerosolized medications (in pressurized metered-dose inhalers); devices using these agents have not been sold in the United States since 2008

Cholesterol an organic molecule (steroid alcohol); a type of lipid that is essential for the formation of cell membranes, nerve tissue, and lipoproteins; high cholesterol levels permit the formation of fatty deposits in the walls of arterial blood vessels

Cholinergic drugs that affect a ganglion, parasympathetic neuroeffector site, or muscular junction by stimulating the release of ACh

Chronotropic influencing the rate of rhythmic movements, especially of the heartbeat

Concentration the ratio of the amount of drug or ingredient in the product; expressed in many units—mg/mL, g/mL, etc.

Congestive heart failure (CHF) a condition in which the heart pumps less blood than it receives, the blood volume increases inside the chambers causing enlargement, and the rest of the body also receives less blood; characterized by generalized edema throughout the body

Conscious sedation a procedure in which a patient who is undergoing an invasive procedure, such as a bronchoscopy, colonoscopy, or cardiac catheterization, is given medications to reduce the pain and anxiety of such procedures while allowing the patient to follow verbal commands and maintain his or her own airway

Coronary artery disease (CAD) a condition that results from decreased blood flow to the coronary circulation and is associated with several cardiovascular diseases (e.g., atherosclerosis, angina pectoris)

Corticosteroid a collective term that represents the three different hormones produced by the adrenal cortex (the glucocorticoids, the mineralocorticoids, and the gonadocorticoids)

Croup laryngotracheitis usually caused by a viral infection affecting the upper airway that obstructs breathing and causes runny nose and a characteristic barking cough

Cultures and sensitivities (C&S) term often used in microbiological samples; “culture” refers to the test that finds which microorganism is causing a particular infection and “sensitivity” is the result of the a test that determines which antibiotics can be used to treat the specific microorganism that is identified

Cyclic 3',5'-adenosine monophosphate (cAMP) a derivative of adenosine triphosphate. When a sympathetic nerve in the bronchial tree is stimulated, it promotes the conversion of adenosine triphosphate to cAMP, causing bronchial smooth muscle relaxation and dilation

Cyclic 3',5'-guanosine monophosphate (cGMP) a cyclic nucleotide derived from guanosine triphosphate. When a parasympathetic nerve in the bronchial tree is stimulated, acetylcholine (ACh) is released to the postganglionic site converting guanosine triphosphate (GTP) to **cGMP**, promoting bronchoconstriction

Cystic fibrosis a genetic disorder in which there is a deficiency of pancreatic digestive enzymes (usually leading to malabsorption of nutrients from the diet) and a mutation of a gene associated with the movement of chloride ions through cell membranes, which also results in excessive thick secretions and respiratory infections

D

Definitive therapy antibiotics given after knowing that it will be effective against organisms causing the infection

Deposition the process by which aerosol particles (drugs) accumulate on surfaces within the respiratory system or lungs

Diabetes mellitus a disease caused by pancreatic cell dysfunction. This chronic metabolic disorder is characterized by having complete lack of insulin production, a relative lack of insulin production, or insulin resistance. Without the body's proper utilization of insulin, glucose cannot be utilized for energy and thus hyperglycemia occurs

Diastolic blood pressure blood pressure measured between contractions of the heart

Diuretics drugs that reduce the amount of fluid in the body (increase the excretion of urine)

Dornase alfa (Pulmozyme) a DNA enzyme (recombinant human deoxyribonuclease) that selectively cleaves DNA present in sputum and decreases viscosity when administered as an aerosol; improves pulmonary function regardless of baseline lung function and may reduce the risk of bacterial infection only in patients with CF; not recommended to use dornase alfa for any airway disease other than CF

Drug a biologically active substance or chemical that modifies cellular function or produces a physiologic effect when introduced into the body

Drug dependence state in which a person requires a drug or substance to function normally. When the substance or drug is removed or withheld, it will result in physical or psychological symptoms

Dry-powder inhaler (DPI) inspiratory flow-driven inhalers that deliver a dry powder into the lungs

E

Empiric comes from Greek word "empeiria," meaning experience; starting therapy based on clinical "educated guess" when a complete or perfect information about the infection is not available

Eosinophils immune cells (white blood cell) that fight against infection and inflammation

Equianalgesic dose a dose of an analgesic that provides almost the same degree of analgesia as another analgesic or the doses of more than one analgesic that produces the same degree of pain relief

Excretion a pharmacokinetic term; the process by which living organisms eliminate or expel waste matter from the body. There are several different sites where drugs are excreted from

the body (kidneys, respiratory system, and GI tract)

Expectorant an agent that increases the amount of fluid in the respiratory tract and thus stimulates discharge of mucus with a cough

Extrapyramidal symptoms (EPS) drug-induced movement disorders; side effects associated with first-generation antipsychotics (FGAs) that include acute and tardive symptoms

G

Ganglion cells a group of neurons that receive signals from the nervous system and the send signals to organs and muscles of the body

General anesthetic a drug that induces the absence of all sensation

Generic name a term referring to the chemical structure of a drug

Glucocorticoids a steroid hormone produced by the adrenal cortex that is responsible for carbohydrate and protein metabolism; possesses anti-inflammatory and immunosuppressive properties

Gluconeogenesis a metabolic process that stimulates the breakdown of protein through the conversion of amino acids to glucose to produce sugar from a non-carbohydrate precursor

Gram-negative bacteria lose the crystal violet stain (and take the color of the red counterstain) in Gram's method of staining because of the thin layer of peptidoglycan cell wall in the bacteria

Gram-positive bacteria retain the crystal violet stain (appear in blue color when viewed under a microscope) in Gram's method of staining because of the thick layer of peptidoglycan cell wall in the bacteria

H

Heart failure a complex syndrome that impairs the ability of the ventricle to fill with or eject blood

Heart failure with reduced ejection fraction (HFrEF) also called systolic heart failure; a condition due to loss of contractility of the cardiac muscle that leads to an inefficient pump

Histamine an important organic nitrogenous compound that is found in some of the body cells. It is responsible for most of the symptoms of an allergic reaction

Homeostasis the ability or tendency of an organism to maintain internal stability to compensate for environmental changes

Hormones chemicals released by the endocrine system directly into the bloodstream from various glands located throughout the body to regulate various functions of the body; in contrast to nervous control, hormones have a slower onset and a longer duration of action

Hospital-acquired pneumonia (HAP) pneumonia or a lower respiratory infection contracted by a patient in a hospital at least 48 hours after admission

Hydrofluoroalkane (HFA) an organic compound containing halogen atoms instead of hydrogen atoms in an alkane that are used as pMDIs (with the standard dosage of the active ingredient medications but incorporating a carrier gas that contains no CFCs); have significantly higher lung deposition of the active drug than CFC-containing devices and deliver a warmer aerosolized mist than CFC-driven pMDIs

Hygroscopic a phenomenon of tending to attract humidity by the aerosol droplets as they travel in suspension and therefore become larger in size

Hypertension a condition of elevated blood pressure

Hypnotic drug that produces drowsiness and facilitates the onset of sleep

I

ICS inhaled corticosteroid; medications taken consistently by using an inhaler to treat asthma and some allergic conditions

Idiosyncratic reaction a type of adverse drug reaction; it is an unexplained or unpredictable reaction to a drug and can be manifested as an accelerated, toxic, or inappropriate response to the usual therapeutic dose

Induction a state of anesthesia before intubation, always precedes paralysis owing to the risk of inadequate sedation. The goals of induction therapy are to provide rapid sedation, pain control, and amnesia without changes in hemodynamics

Inhaled nitric oxide (INO) a pulmonary vasodilator that regulates vascular muscle tone; used for the treatment of assessment of pulmonary hypertension as well as in the treatment of pulmonary hypertension and acute respiratory distress syndrome; the only FDA-approved drug for the treatment of term or near-term newborns with acute hypoxic respiratory failure associated with pulmonary hypertension

Inotropes agents that alter the force of cardiac muscular contraction

Inotropic influence on contractility of cardiac muscular tissue

Instillation one of the two primary routes to deliver medications in respiratory care, where drugs are directly administered through an ET tube or intratracheal catheter by injecting a bolus (3–5 mL) of a drug directly into the tracheobronchial tree via a tube or catheter; typically used for wetting agents or mucolytics, surface-active agents, and advanced cardiac life-support drugs during cardiac resuscitation

Intravenous means “into a vein;” a parenteral route for administration of a drug by a needle

L

LABA (long-acting β_2-agonist/long-acting β_2-adrenergic agonist) a class of adrenergic bronchodilators used in the chronic treatment of COPD and in combination with inhaled corticosteroids (ICSs) in the chronic management of asthma. This has a long bronchodilating effect lasting from 12 to 24 hours

LAMA (long-acting antimuscarinic agent/long-acting muscarinic antagonist) drugs that bind to M1-, M2-, and M3-receptors, but detach most rapidly from M2-receptors;these agents dissociate slowly from the M3-receptors, causing a longer duration of bronchodilatory effect. It is used in the chronic treatment of COPD, and the duration of activity ranges from 12 to 24 hours

Leukotriene inhibitors or antagonists an antiasthmatic drug that targets inflammation. They either prevent leukotrienes from binding to a receptor or they inhibit the synthesis of leukotrienes; used in the management of asthma

Low-density lipoprotein (LDL) a class of lipoproteins that has relatively low density; transports cholesterol to the tissues

M

Mass median aerodynamic diameter (MMAD) the particle size above and below which 50% of the mass of the particles is contained; the higher the MMAD, the more larger particles are contained in the aerosol; a major determinant of lung deposition

Mast cells contained in the connective tissue that release histamine and other substances (mediators) during inflammatory and allergic reactions

Mast-cell stabilizers a class of antiasthmatic drugs that are inhaled to deposit into the pulmonary tree; prevent the mast cells from degranulating, preventing the release of histamine and related mediators

Metabolism *see* Biotransformation

Metered-dose inhaler (MDI) a device used in the treatment of asthma and other respiratory conditions to administer aerosol medications in a defined dose that are inhaled into the respiratory tract

Methylxanthines a class of bronchodilator that are derived from the purine base xanthine. It is produced naturally by both plants and animals; may inhibit phosphodiesterase to maintain the level of cAMP and has weak bronchodilating effect

Mucoactive agents that are used in respiratory care to help loosen, thin, and clear pulmonary secretions; used to encourage mucus clearance

Mucokinetic a medication or solution that increases the movement of mucous by ciliary activity or by increasing cough by improving expiratory airflow

Mucolytic agents that disrupt the mucus molecule and damage gels contained in the mucus; causes the breaking apart (lysis) of the mucus molecule itself by degrading mucin polymers, DNA, or fibrin in airway secretions

Mucosal edema airway inflammation; accumulation of fluid within the mucosal membrane

Multidrug-resistant (MDR) a microorganism resistant to more than one antimicrobial drug

Myocardial infarction (MI) a “heart attack” that is a result of an occlusion (coronary occlusion) of the blood supply to the cardiac muscle leading to an infarct (muscle tissue death)

N

N-acetyl-L-cysteine (NAC) an antioxidant drug that has been primarily used in the treatment of liver injury; it has the ability to hydrolyze and break apart sulfide bonds found in mucin, so used as a mucolytic; it is thought to decrease the viscosity of mucus, making it easier to clear

Nebulizer a device that converts liquid to fine spray (aerosol)

Negative feedback a control mechanism that alerts the body to inhibit or prevent any further release when a hormone is released and reaches a certain blood level

Neuroeffector junction a site or a synapse between a neuron and the effector organ or secretory cell it innervates; a motor neuron releases a neurotransmitter in this site

Neurohormonal activation of hormone release by nerve cells and production within specialized nerve cells called neurosecretory cells

Neuromuscular blocking agent (NMBA) peripheral acting muscle relaxants; they interact with nicotinic-2 receptors at the skeletal neuromuscular junction causing muscle weakness and paralysis

Neurotransmitters chemical substances that “transmit messages” (electrical signals to other nerves) across synaptic clefts and neuroeffector junctions

Nicotine replacement therapy (NRT) therapy used to help with quitting smoking or stopping chewing tobacco by taking nicotine by means other than tobacco

Non–cystic fibrosis bronchiectasis (NCFB) a type of bronchiectasis (permanent dilation of the airways of the lungs) that arises as a result of chronic inflammation and is not due to cystic fibrosis; characterized by persistent cough and excessive sputum production

Norepinephrine (NE) a naturally occurring catecholamine hormone; one of the two main neurotransmitters of the ANS at the neuroeffector site

O

Off-label a drug use that is non–FDA-approved

P

Parasympathetic one of the two main divisions of the autonomic nervous system (nerves arising from the brain and the lower end of the spinal cord and supplying the internal organs, blood vessels, and glands); the interruptions (synapses) between the CNS and the receptor sites occur in autonomic ganglia that are located close to the effector site; it has the opposite activity of the sympathetic nervous system

Parasympatholytic a drug that reduces the activity of the parasympathetic nervous system

Parenteral routes other than mouth and alimentary canal for administering drug in the body (e.g., intradermal, subcutaneous, intramuscular, and intravenous)

Particle size a term used to compare the dimensions solid, liquid, and gaseous particles; defined through a particle’s diameter (spherical) and volume, area, and weight (nonspherical);

for aerosols, diameter is used

Pediatric Advanced Life Support (PALS) a training program for pediatric healthcare provider that includes a series of protocols to guide responses to life-threatening clinical events

Percent solution the amount of the active ingredient in 100 parts of the product; found on the label or in the product information

Pharmacodynamics study of the actions of drugs on living organisms, that is, what the drug does to the body

Pharmacokinetics study of what the body does to the drug related to absorption, duration of action, distribution in the body, metabolism, and method of excretion

Pharmacology the study of drugs—their origin, properties, how they work, and affect living organisms. As a discipline, it is one of the important basic sciences of medicine and other health professions. In the health care, pharmacology is the study of substances that are used to prevent, diagnose, and treat diseases

Pharmacotherapy a therapy that uses a specific medicine or drug to treat a specific disease

Pharmacy the practice of compounding, preparing, and dispensing drugs and assuring rational medication use

Phlegm viscid mucus secreted in the respiratory passages in states of inflammation; contains inflammatory cells, bacteria, and DNA

Phosphodiesterase (PDE) an enzyme that breaks a phosphodiester bond; these enzymes break down cAMP into an inactive form AMP

Placebo a substance, chemical or otherwise, that contains no active ingredient but can cause modification of effects in either a positive or negative manner, purely on the basis of suggestion

***Pneumocystis carinii* pneumonia (PCP)** infection that occurs in immunosuppressed populations (e.g., AIDS patients) caused by the fungus *Pneumocystis jirovecii*

Postganglionic a neuron leads from the synapse to the organ or gland being affected

Preganglionic a neuron leads from the vertebrae to a synapse outside the spinal cord

Preload the volume of blood in the ventricles at the end of diastole (filling)

Priming process of running the fluids in an intravenous bag through the tubing before it is administered to the patient to assure there is no air in the tubing

Prophylactic treatment also called preventive treatment; a treatment designed to prevent a disease, for example, medications administered within 30 minutes of birth to prevent premature infants at a high risk of developing RDS

R

Racemic epinephrine a mixture of dextro- and levo-isomers of epinephrine, a sympathomimetic amine, that stimulates production of cAMP; typically is administered by small-volume nebulizer or in-line for mechanically ventilated patients; used for upper airway edema and bronchoconstriction associated with mucosal edema

Rapid sequence intubation (RSI) a procedure in which appropriate medications are administrated to facilitate an endotracheal intubation and to reduce adverse effects; used to facilitate emergency airway management

Ratio strength strength of drug products; a ratio of 1 to another quantity that is larger than 1 and may be easier to understand if changed into a percentage. For example, ratio strength of 1:1000 is 1 part into 1000 parts or 1/1000, which is 0.001 or 0.1%

RDS (respiratory distress syndrome of the newborn) a syndrome in premature newborns caused by pulmonary surfactant deficiency and dysfunction; infants born with a surfactant deficiency quickly develop alveolar collapse and difficulty breathing as a result of the effort required to overcome surface tension on each breath

Receptor a part of a cell or organism that will respond in a specific way when combined with a hormone, neurotransmitter, or drug

Reconstituted using a powder or concentrated form of a drug and adding a solvent to reconstitute (or return) the drug to a liquid form of a specific concentration, for example, antibiotics and synthetic surfactants

Releasing hormones hormones that are produced in the hypothalamus that control hormones of the adenohypophysis

Renin a hormone released from the kidney into the bloodstream when renal blood flow is reduced; leads to the formation of angiotensin and is involved in the control of blood pressure

Rescue treatment also called salvage therapy; a treatment given after a condition does not respond to standard therapy, for example, medications administered within first few hours (2–3 hours) of life to prevent premature infants with established RDS

S

SABA (short-acting β_2-agonist/short-acting β_2-adrenergic agonist) a class of adrenergic (sympathomimetic) bronchodilators primarily used for the acute treatment of bronchospasms; provide quick or “rescue” relief from acute bronchoconstriction

SAMA (short-acting antimuscarinic agent/short-acting muscarinic antagonist) a class of anticholinergic bronchodilators that produce bronchodilation by blocking ACh at muscarinic receptors, therefore blocking the direct constrictor effects of ACh on bronchial smooth muscle; effects are seen within 15 minutes, for example, ipratropium

Sedation a process of inducing a relaxed calm state or sleep by using medications (sedatives)

Sedative drug that produces a calming effect, drowsiness, and decreases CNS activity

Septic shock a subset of sepsis (a life-threatening organ dysfunction caused by a dysregulated host response to infection that causes organ dysfunction) with hypotension and is associated with a higher risk of mortality

Shock a medical emergency characterized by tissue hypoperfusion and commonly associated with hypotension. It is a reversible state when identified and treated early, but can progress to severe organ dysfunction

Sinoatrial (SA) node a specialized group of cells located in the heart that initiate the normal rate of contraction

Small-volume nebulizer (SVN) a device that nebulizes medications for aerosol delivery (maximum volume about 10 mL)

Solute a substance dissolved in a solvent to form a solution

Solvent a substance that is able to dissolve other substances to form a solution

Spacer a device that have been developed to provide a reservoir of aerosol to improve medication delivery by pMDI

Sputum expectorated phlegm

Status asthmaticus a severe condition in which a patient exhibits severe dyspnea, hypoxemia, and airway obstruction that is not responding to aggressive bronchodilator therapy

Stimulant drugs that are used for narcolepsy, treatment of obesity, and in managing attention-deficit/hyperactivity disorder (ADHD) and increases the activity of the central nervous system. This group of drugs usually includes the amphetamines, mixed amphetamine salts, and methylphenidate

Strength the amount of drug in a given dosage form, usually expressed as ratios, fractions, decimals, or percentages

Subcutaneous a route of drug administration in which drugs are injected into the fatty layer of tissue beneath the dermis of the skin

Sublingual means under the tongue; a route of drug administration in which the drugs are placed under the tongue where it diffuse through the tissues into blood

Surface tension the physical property that creates tension at a fluid–air interface; like molecules at the surface of a liquid attract (cohesion) each other when a liquid is in contact with gas, the liquid molecules on the surface are attracted inward; thus, the liquid contracts to minimize its surface area (e.g., the tendency of the lungs to return to a resting state)

Surfactant the naturally occurring (endogenous) detergent (a mixture of phospholipids and surfactant proteins) that reduces and regulates alveolar surface tension of the liquid that lines the alveoli; forms a liquid film along the water–air alveolar surface, which reduces surface tension, decreases collapsing pressure, and allows the alveoli to expand

Sympathetic one of the two main divisions of the autonomic nervous system; regulates the body's unconscious actions. The interruptions (synapses) between the CNS and the receptor sites occur in autonomic ganglia that are located close to the spinal cord; associated with the "fight-or-flight" response

Sympathomimetic *see* Adrenergic

Synapse a gap formed in the nervous system between the nerves or between the nerve and the organ that is innervated when nerves communicate with other nerves or neuroeffector sites

Synaptic cleft a gap between the nerves or between the nerve and the organ that is innervated in which neurotransmitters "transmit messages" are released

Systolic blood pressure blood pressure measured when the heart contracts

T

Tachyphylaxis the rapid development of tolerance to a drug, making it less effective

Tardive dyskinesia an irreversible disorder that causes abnormal involuntary movements that usually affect the tongue, jaw, and limbs resulting from long-term use of FGAs

Teratogen drugs or substances that are known to cause birth defects

Therapeutic effect the intended effect of a drug (e.g., pain relief from morphine or sedation from midazolam)

Tolerance a phenomenon, occurring after a period of use of some drugs, that necessitates an increase in dosage to maintain an effect

Toxicology study of harmful effects of drugs on living organisms, tissues, and the human body

Trade name the trademark name or commercial trade name of a drug

Triglyceride (TG) lipids that are esters formed from one molecule of glycerol and three molecules of one or more fatty acids

Tropic hormones hormones that are released from the anterior lobe and affect other endocrine glands

Tuberculosis (TB) a disease caused by the acid-fast bacilli, *Mycobacterium tuberculosis*; this organism usually infects the lungs

U

Uricosuria means uric acid in the urine

V

Vasopressor agents that are used to improve cardiac output and blood pressure, oftentimes in the setting of shock. They work by causing constriction of blood vessels, therefore increasing systemic vascular resistance and increasing blood pressure

Ventilator-associated pneumonia (VAP) pneumonia or lung infection caused by the invasion of the lower respiratory tract and lung parenchyma by microorganisms that develops 48 hours after endotracheal intubation and mechanical ventilation

© Winui/Shutterstock.

Note: “Page numbers followed by *f*, or *t* indicate material in figures, or tables, respectively.”

A

abciximab (ReoPro), 188*t*
absorption, drugs, 10, 12–13
abuse of prescription drugs, 6
acarbose (Precose), 222*t*, 223
ACE inhibitors
  for heart failure, 176–177, 177*t*
  for hypertension, 173, 173*f*
acetaminophen (Tylenol), 208, 209
acetazolamide (Diamox), 172
acetylcholine (ACh), 21, 29, 29*t*
ACh. *See* acetylcholine
acid-fast bacilli (AFB), 241
aclidinium (Tudorza Pressair), 31, 31*t*, 69, 69*t*
ACLS. *See* advanced cardiovascular life support
acute asthma episode, management, 87–88
acute pulmonary edema, 172
acute severe asthma, 67
acyclovir (Zovirax), 244
adenosine, 163–164, 163*t*
ADHD. *See* attention-deficit/hyperactivity disorder
adherence, patient, 15
adrenal gland, 215, 215*f*
adrenergic (sympathomimetic) bronchodilators
  β_2-adrenergic agonists, 63–66, 63*f*, 64*t*, 66*f*
  actions and side effects, 62*t*
  nonselective sympathomimetics, 62–63, 63*t*
  sympathomimetic drug interactions, 66–67, 68*t*
adrenergic agents, 23, 24–25
  for hypertension, 174, 175*t*
adrenergic neuronal activators and blockers, 28

adrenergic receptors, 24*t*
adrenergic/anticholinergic combination, 70–71, 71*t*
adrenergic/corticosteroid combination, 70–71, 71*t*
adults, asthma management in, 83, 84*f*, 85*t*
Advair, 70, 91*t*
advanced cardiovascular life support (ACLS), 152
  cardiac arrest
    causes of, 160–161, 161*t*
    post–cardiac arrest care, 164
    rhythm-based management during, 161–164, 162*f*
  medication use and route of administration, 161
  oxygenation, 161
  ventilation and capnography, 161
adverse reaction, 4
Aerolizer, 54*f*
Aeroneb Solo Nebulizer System, 140
aerosol, 48
aerosolized antimicrobials, 121–132
  categories, 123*t*
    antibacterial (antibiotic) drugs, 123–126, 124*t*
    antifungal drugs, 126–127, 127*f*
    antiprotozoal drugs, 129–130
    antiviral drugs, 127–129
  clinical indications for, 122
  factors associated with efficacy and safety of, 122–123
  limitations of, 130–131
  rationale for, 122
aerosolized bronchodilators, 70–71
aerosolized corticosteroids
  advantages and disadvantages of, 89
  side effects/adverse reactions of, 89–91
aerosolized medications administration
  adverse effects of, 49
  disadvantages and limitations of, 48
  dry powder aerosols, 53, 54*f*
  liquid nebulizers, 49–50, 49*f*
  metered-dose inhalers
    during mechanical ventilation, 55
    multiple medications, 53
    pressurized, 50–51, 51*f*
    priming of, 51
    technique for treatment, 52
  small-volume nebulizers, 49–50, 49*f*
    during mechanical ventilation, 55
    technique for, 50
    ventilator parameters during, 55
  spacers and holding chambers, 52, 52*f*
AFB. *See* acid-fast bacilli

afterload, 176
age, altering drug effect, 16
agonists, 13
  and antagonist receptor relationship, 14*f*
AHFS Drug Information, 6
AHR. *See* airway hyperresponsiveness
AirDuo RespiClick, 91*t*
airway hyperresponsiveness (AHR), 138
  mannitol, 138–139
  methacholine, 138
airway mucus, 100*f*
albiglutide (Tanzeum), 222*t*, 224
albuterol (Proventil, Ventolin, salbutamol), 27, 27*t*, 62*t*, 64, 64*t*, 65
alcohol (ethanol), 197–198
aldosterone, 169
  antagonists, for heart failure, 177–178
alfuzosin, 26, 26*t*
allergy, 4
allopurinol (Zyloprim), 73*t*
alogliptin (Nesina), 222*t*, 223
α-adrenergic drugs, 25, 25*t*
α-adrenergics, 61*t*
α-blocking drugs, 25–26, 26*t*
α-methyldopa (Aldomet), 28
alpha-1-receptor antagonists, 174
alpha-2-receptor agonists, 174
alpha-adrenergic sympathomimetic drugs, 81
alpha-glucosidase inhibitors, 222*t*, 223
alprazolam (Xanax), 196*t*
amikacin, 123, 240
amiloride (Midamor), 172
aminoglycosides, 240
aminopenicillins, 235, 235*t*
aminophylline, 73
amiodarone, 162–163, 163*t*, 183*t*
amoxicillin (Augmentin), 235, 235*t*, 236
amphotericin B (Fungizone, Abelcet, and AmBisome), 122, 123*t*, 127, 127*f*, 243
ampicillin (Unasyn), 235, 235*t*, 236
amylase, 219
anaerobic infections, agents for, 241
analgesia, 152, 205
  ICU care, 155–157, 157*t*
analgesics, 196
  and pain management, 204
    non-opioid analgesics, 207–208, 208*t*
    opioid analgesics, 205–207, 206*t*
anaphylactic shock, 159, 224
anaphylaxis, 238

angina, 174
beta-blockers in, 180
calcium channel blockers in, 180
nitrates, 179, 179*t*
ranolazine, 180
angiotensin II, 169
angiotensin II receptor blockers (ARBs)
for heart failure, 177, 177*t*
for hypertension, 173–174, 173*f*
angiotensin receptor-neprilysin inhibitor, for heart failure, 177
anidulafungin, 243
Anoro Ellipta, 70, 71*t*
ANS. *See* autonomic nervous system
antagonists, 14, 80
anti-IgE antibody, 94
anti-IL5 antibodies, 94, 94*t*
antiadrenergic/adrenergic blockers, 23
antiallergic agent, 225–226, 226*t*
antiasthmatic drugs, 92–93, 92*f*
immunomodulators, 93–94, 94*t*
leukotriene modifiers, 93
mast-cell stabilizers, 93
“antibacterial,” defined, 230
antibacterial therapy, causes of failure, 232
antibiotics, 123–126, 124*t*
principles in appropriate use of, 231–232, 231*t*
antibody, 224
anticholinergic bronchodilators, 67–68, 68*f*, 69*t*
anticholinergic drug interactions, 70
long-acting antimuscarinic agents, 69–70
short-acting antimuscarinic agents, 69
anticholinergic drugs, 23, 30–31, 31*t*
interactions, 70
anticholinergics, 60, 61*t*
anticholinesterase drugs/cholinesterase inhibitors, 30, 30*t*
anticoagulant drugs, 184–186, 186*t*
direct thrombin inhibitors, 185
factor Xa inhibitors, 185
low-molecular-weight heparins, 185
oral anticoagulants
direct-acting oral anticoagulants, 186, 186*t*
warfarin, 185–186
unfractionated heparins, 184–185
antidepressants, 198*t*, 200–201, 200*t*
antiepileptic drugs, 203–204
carbamazepine, 203
ethosuximide, 204
lacosamide, 203

levetiracetam, 204
phenobarbital, 204
phenytoin, 203
topiramate, 204
valproic acid, 203
“antifungal,” defined, 230
antifungal drugs, 123, 126–127, 127*f*
azoles, 243
echinocandins, 243
flucytosine, 243
polyenes, 243
antigen, 224
antigen–antibody reactions
antihistamines and antiallergic agent, 225–226, 226*t*
histamine
effects of, 224–225, 225*t*
receptors, 225
antihistamines, 225–226, 226*t*
antimicrobial agents and definitions, 230
antibacterial therapy, causes of failure in, 232
antibiotics, principles in appropriate use of, 231–232
antimicrobial pharmacology, 229–246
antibiotic drugs, categories of
aminoglycosides, 240
anaerobic infections, agents for, 241
beta-lactam antibiotics. *See* beta-lactam antibiotics
cyclic lipopeptides, 240
glycopeptides, 240
macrolides, 239
oxazolidinones, 240
quinolones, 237–239, 238*t*
sulfonamides, 239
tetracyclines and glycylcyclines, 239–240
antifungal drugs, 242
in systemic fungal infections, 243
antimicrobial agents and definitions, 230
antibacterial therapy, causes of failure in, 232
antibiotics, principles in appropriate use of, 231–232, 231*t*
antiviral agents, 243–244
tuberculosis, 241
drugs used in treatment of, 242
antimicrobials
aerosolized. *See* aerosolized antimicrobials
defined, 230
antimuscarinic agents
long-acting, 69–70
short-acting, 69
antimuscarinic antagonists, 67

antimuscarinic drugs, 29
antiprotozoal drugs, 123, 129–130
antipsychotics, 198*t*, 199–200, 199*t*
antipyretic effect, 207
antithyroid drugs, 218*t*
antiviral drugs, 123, 127–129, 243
  acyclovir and valacyclovir, 244
  endonuclease inhibitor, 244
  ganciclovir, 244
  neuraminidase inhibitors, 244
  valganciclovir, 244
anxiolytic drugs, 195
apixaban (Eliquis), 186, 186*t*
apnea of prematurity, 141–142
ARBs. *See* angiotensin II receptor blockers
arformoterol (Brovana), 27, 27*t*, 62*t*, 64*t*
aripiprazole (Abilify), 199*t*
arrhythmias, 174
  antiarrhythmic drugs, 183–184*t*
    Class I, 181–182
    Class II, 182
    Class III, 182
    Class IV, 182
  definitions, 181
  reasons for converting and causes of, 181
  types of, 181, 181*t*
aspart (NovoLog), 221*t*
aspirin (acetylsalicylic acid), 186–187, 187*t*, 208*t*, 209
asthma, 81–82
  acute and chronic, 91–92
  acute asthma episode, management, 87–88
  adults and youths, management in, 83, 84*f*, 85*t*
  children, management in, 83, 86–87, 86*t*
  mucous dysfunction and, 100–101
  peak flow monitoring, 87, 87*f*, 88*t*
atenolol (Tenormin), 27, 27*t*, 175*t*, 183*t*
atracurium, 155*t*
atropine, 30, 31*t*, 69*t*, 152, 163*t*
attention-deficit/hyperactivity disorder (ADHD), 202, 202*t*
autonomic nervous system (ANS), 19–32
  function and anatomy of, 20–21
  general physiologic functions controlled by, 23, 24*t*
  nervous system, 20, 20*f*, 21*f*
  neurotransmitters, 21–23, 23*f*
  origin and distribution of, 22*f*
  parasympathetic division, overall effects of
    anticholinergic drugs, 30–31, 31*t*
    anticholinesterase drugs/cholinesterase inhibitors, 30, 30*t*

cholinergic drugs, 29–30, 29*t*
parasympathetic nerve ending, 28–29, 28*f*
sites of action, NTs, and receptors of, 23*t*
sympathetic nervous system
α-adrenergic drugs, 25, 25*t*
α-blocking drugs, 25–26, 26*t*
adrenergic drugs, sites of action of, 24–25
adrenergic neuronal activators and blockers, 28
β-adrenergic drugs, 26–27, 26*t*, 27*t*
β-blocking drugs, 27–28, 27*t*
sympathetic nerve ending, 23–24, 24*f*, 24*t*
avibactam, 235
azithromycin (Zithromax), 239
azoles, 243
aztreonam (Azactam, Cayston), 122, 123*t*, 124, 124*t*, 236, 237

B

bacterial cell wall, 233, 234*f*
“bactericidal,” defined, 230
bactericidal activity, 124
“bacteriostatic,” defined, 230
bacteriostatic antibiotics, 124
Bacteroides fragilis, 241
baloxavir (Xofluza), 244
barbiturates, 73*t*, 195–196, 195*f*, 196*t*
basal insulin, 220, 220*f*
beclomethasone MDI (QVAR), 85*t*, 90*t*
bedaquiline, 242*t*
Behavioral Pain Scale, 156
benralizumab (Fasenra), 94, 94*t*
benzodiazepines (Valium, Librium, Xanax, Halcion, and Dalmane), 73*t*, 136, 157, 157*t*, 196–197, 196*t*
benzylpenicillin. *See* penicillin G
beractant (Survanta), 114, 115–116, 115*t*
beta-adrenergic antagonists, 174
β-adrenergic drugs, 26–27, 26*t*, 27*t*, 60, 61*t*
beta-adrenergic blockers, for heart failure, 177, 177*t*
beta-blockers, 27–28, 27*t*
in angina, 180
beta-lactam antibiotics, 232–233, 232–233*f*
beta-lactamase inhibitors, 235–236
carbapenems, 236
cephalosporins, 236, 236*f*, 237*t*
monobactams, 236
penicillins, 233–234
aminopenicillins, 235, 235*t*
extended-spectrum, 235, 235*t*

natural, 235, 235*t*
penicillinase-resistant, 235, 235*t*
beta-lactamase, 233
inhibitors, 235–236
betamethasone, 216*t*
β_2-adrenergic agents, 105
β_2-adrenergic agonists, 63–66, 63*f*, 64*t*, 66*f*
bethanechol (Urecholine), 29*t*, 30
Bevespi Aerosphere, 71*t*
biguanides, 221–222, 222*t*
bile acid sequestrants, 189, 189*t*
biotransformation, 14
bisoprolol, 27, 27*t*, 175*t*, 177*t*
bland aerosols, 101
hypertonic saline, 101–102
hypotonic saline, 101
normal saline, 101
sterile distilled water, 102
blood flow, 14
blood pressure (BP), 168–169
blood–brain barrier, 13
bolus insulin, 220, 220*f*
BP. *See* blood pressure
brain stem, 194, 194*f*
brain, structure of, 194*f*
breath-enhanced nebulizer system, 122–123
Breo Ellipta, 70, 91*t*
broad-spectrum antibiotics, 231
bronchial cells, sympathetic stimulation of, 60*f*
bronchial provocation, 138
bronchial provocation testing, 138
bronchoconstriction, 60
and bronchodilation
neurochemical mediators in, 60–61, 60*f*, 61*f*
relief of bronchospasm, 61, 61*t*
relief of mucosal edema, 61
and mucosal edema, 80–81, 80*f*, 81*t*
bronchodilation, bronchoconstriction and
neurochemical mediators in, 60–61, 60*f*, 61*f*
relief of bronchospasm, 61, 61*t*
relief of mucosal edema, 61
bronchodilator β_2-agonist drugs, 27*t*
bronchodilator therapy, 59–76
adrenergic (sympathomimetic) bronchodilators
β_2-adrenergic agonists, 63–66, 63*f*, 64*t*, 66*f*
actions and side effects, 62*t*
nonselective sympathomimetics, 62–63, 63*t*

sympathomimetic drug interactions, 66–67, 68*t*
adrenergic/anticholinergic and adrenergic/corticosteroid, 70–71, 71*t*
anticholinergic bronchodilators, 67–68, 68*f*, 69*t*
anticholinergic drug interactions, 70
long-acting antimuscarinic agents, 69–70
short-acting antimuscarinic agents, 69
bronchoconstriction and bronchodilation
neurochemical mediators in, 60–61, 60*f*, 61*f*
relief of bronchospasm, 61, 61*t*
relief of mucosal edema, 61
magnesium, 74
methylxanthines and PDE inhibitors, 71–73, 73*t*
bronchorrhea, 106
bronchoscopy, 136–137
diagnostic, 137
bronchospasm, 60
relief of, 61, 61*t*
budesonide (Pulmicort Respules, and Pulmicort Flexhaler), 85*t*, 90*t*
bumetanide (Bumex), 171*t*
buprenorphine (Buprenex, Belbuca), 206*t*
bupropion, 201
buproprion (Zyban), 142, 144
butorphanol (Stadol), 206*t*

C

CA inhibitors, 172
CAD. *See* coronary artery disease
caffeine, 72
in newborns, 142
calcitonin, 217
calcium channel blockers (CCBs)
in angina, 180
for hypertension, 174
calcium chloride, 163*t*
calcium gluconate, 163*t*
calfactant (Infasurf), 114, 115*t*, 116–117
cAMP. *See* cyclic 3’,5’-adenosine monophosphate
canagliflozin (Invokana), 222*t*, 224
candesartan, 177*t*
capillary endothelia, 12
capnography, ventilation and, 161
capreomycin, 242*t*
captopril, 177*t*
carbamazepine (Tegretol), 73*t*, 201, 203
carbapenems, 236
carcinogens, 4
cardiac arrest

causes of, 160–161, 161*t*
post–cardiac arrest care, 164
rhythm-based management during, 161–164, 162*f*
cardiac glycosides, for heart failure, 178–179
cardiac workload, 176
cardiogenic shock (CS), 158–159
cardiovascular and renal pharmacology, 168–191
angina
beta-blockers in, 180
calcium channel blockers in, 180
nitrates, 179, 179*t*
ranolazine, 180
arrhythmias
antiarrhythmic drugs, 181–182, 183–184*t*
definitions, 181
reasons for converting and causes of, 181
types of, 181, 181*t*
coagulation process, 182, 184
anticoagulant drugs, 184–186, 186*t*
antiplatelet drugs, 186–187, 187–188*t*, 187*f*
heart, conduction system of, 180–181, 180*f*
heart disease, 175
heart failure and GDMT, 175–176, 176*t*
ACE inhibitors for, 176–177, 177*t*
aldosterone antagonists for, 177–178
angiotensin II receptor blockers for, 177, 177*t*
angiotensin receptor-neprilysin inhibitor for, 177
beta-adrenergic blockers for, 177, 177*t*
cardiac glycosides, digoxin, 178–179
cardiac workload, 176
hydralazine and isosorbide dinitrate for, 178, 178*t*
neurohormonal activation, 176
hypertension
ACE inhibitors for, 173, 173*f*
adrenergic agents for, 174, 175*t*
angiotensin II receptor blockers for, 173–174, 173*f*
calcium channel blockers for, 174
direct-acting vasodilator drugs for, 175
factors controlling BP, 168–169
stages of, 168*t*
therapeutic approach to, 169
lipids, 187–188, 188*t*
hyperlipidemia, drugs used in treatment of, 188–189, 189*t*
nephron, 169
diuretics and therapeutic role, 170–172, 171*t*
filtration, 170
function of, 169*f*
tubular reabsorption, 170

tubular secretion, 170
cardiovascular system, opioids and, 205
carvedilol (Coreg), 27, 27*t*, 175*t*, 177*t*
caspofungin, 243
catecholamine, 62
CCBs. *See* calcium channel blockers
cefaclor (Ceclor), 237*t*
cefazolin (Ancef, Kefzol), 237*t*
cefdinir (Omnicef), 237*t*
cefditoren (Spectracef), 237*t*
cefepime (Maxipime), 237*t*
cefixime (Suprax), 237*t*
cefotaxime (Claforan), 237*t*
cefotetan (Cefotan), 237*t*
cefoxitin, 237*t*
cefpodoxime, 237*t*
cefprozil, 237*t*
ceftaroline (Teflaro), 237*t*
ceftazidime (Ceftaz), 123*t*, 237*t*
ceftazidime/avibactam (Avycaz), 235, 237*t*
ceftibuten, 237*t*
ceftolozane (Zerbaxa), 236
ceftriaxone (Rocephin), 237*t*
cefuroxime (Ceftin), 237*t*
celecoxib (Celebrex), 208*t*
central nervous system (CNS), 193–211
adverse effects of opioids, 205
analgesics and pain management, 204
non-opioid analgesics, 207–208, 208*t*
opioid analgesics, 205–207, 206*t*
effects of drugs on, 194–195
epilepsy, 202–203
antiepileptic drugs, 203–204
general anatomy of, 194*f*
brain stem, 194
cerebellum, 194
cerebrum, 194
diencephalon, 194
general anesthetics, 209*t*
conscious sedation, 210
ideal, characteristics of, 209*t*
ideal, properties of, 209, 209*t*
inhaled, 209, 210*t*
preanesthetic medications, 209–210
psychopharmacologic drugs, 198, 198*t*
antipsychotics, 199–200, 199*t*
depression, treatment of, 200–201, 200*t*
mood stabilizers, 201–202

stimulants, 202, 202*t*
sedative hypnotics and antianxiety drugs
alcohol (ethanol), 197–198
barbiturates, 195–196, 195*f*, 196*t*
benzodiazepines, 196–197, 196*t*
cephalexin (Keflex), 237*t*
cephalosporins, 236, 236*f*, 237*t*
cerebellum, 194, 194*f*
cerebrum, 194, 194*f*
cetirizine (Zyrtec), 226, 226*t*
CF. *See* cystic fibrosis
CFC. *See* chlorofluorocarbon
cGMP. *See* cyclic 3',5'-guanosine monophosphate
chambers, 52, 52*f*
chemical name, of drug, 4
CHF. *See* congestive heart failure
children, asthma management in, 83, 86–87, 86*t*
chlordiazepoxide (Librium), 196, 196*t*
chlorofluorocarbon (CFC), 50
chlorothiazide (Diuril), 171, 171*t*
chlorpheniramine (Chlor-Trimeton), 226*t*
chlorpromazine (Thorazine), 199*t*
chlorthalidone (Hygroton), 171*t*
cholesterol, 168
absorption inhibitors, 189, 189*t*
choline esters, 29, 29*t*
cholinergic drugs, 23
definitions of, 29–30
mechanism of action of, 29
chronic obstructive pulmonary disease (COPD), 74
mucous dysfunction and, 100–101
chronotropic effect, 180
ciclesonide MDI (Alvesco), 90*t*
cimetidine (Tagamet), 14, 73*t*
ciprofloxacin (Cipro), 16, 73*t*, 123*t*, 238*t*
Circulaire II, 49
cisatracurium (Nimbex), 155*t*
clarithromycin (Biaxin), 73*t*, 239
clavulanic acid, 235–236
clindamycin (Cleocin), 241
clonazepam (Klonopin), 196*t*
clonidine (Catapres), 28
clopidogrel (Plavix), 187*t*
Clostridium difficile, 241
clotting cascade, 184, 185*f*
clozapine (Clozaril), 199*t*
CNS. *See* central nervous system
coagulation process, 182, 184

anticoagulant drugs, 184–186, 186*t*
antiplatelet drugs, 186–187, 187–188*t*, 187*f*
codeine, 206*t*
colistimethate (Colomycin/Coly-Mycin M), 123*t*, 124–125, 124*t*
colistin DPI, 122
Combivent, 71*t*
concentration, 36
congestive heart failure (CHF), 170
conscious sedation, 210
continuous aerosol dosages, 41
COPD. *See* chronic obstructive pulmonary disease
coronary artery disease (CAD), 174
corticosteroids, 80, 88–89, 215
aerosolized
advantages and disadvantages of, 89
side effects/adverse reactions of, 89–91
anti-inflammatory activity of, 216*t*
function of, 216*t*
glucocorticoids, 216–217, 217*t*
inhaled, 89, 90*t*. *See also* inhaled corticosteroids
LABAs/LAMA combination preparations, 91*t*
mineralocorticoids, 217
cortisone, 216*t*
Critical-Care Pain Observation Tool, 156
critical care pharmacotherapy
ICU analgesia and sedation, 155–156
opioids, 156, 156*t*
sedation, 156–157, 157*t*
neuromuscular blockade, 153–154
depolarizing NMBAs, 154*f*, 154–155, 154*t*
interactions with, 155*t*
nondepolarizing NMBAs, 154*f*, 154*t*, 155
properties of, 155*t*
shock
cardiogenic, 158–159
distributive, 159
hypovolemic, 159
obstructive, 159–160, 160*t*
cromolyn sodium, 93
croup, 80
CS. *See* cardiogenic shock
cultures and sensitivities (C & S), 232
cyclic 3’,5’-adenosine monophosphate (cAMP), 60
cyclic 3’,5’-guanosine monophosphate (cGMP), 60
cyclic lipopeptides, 240
cycloserine, 242*t*
cystic fibrosis (CF), 105–106, 126, 219
mucous dysfunction and, 100–101

D

dabigatran (Pradax), 186, 186*t*
dalbavancin, 240
dapagliflozin (Farxiga), 222*t*, 224
daptomycin, 240
definitive therapy, 232
degludec (Tresiba), 221*t*
delafloxacin (Baxdela), 238*t*
deposition, 48
depression, 200–201, 200*t*
desflurane (Suprane), 209, 210*t*
desloratadine (Clarinex), 226, 226*t*
detemir (Levemir), 221*t*
dexamethasone, 216*t*
dexmedetomidine, 157, 157*t*
dexmethylphenidate, 202*t*
dextroamphetamine, 202*t*
dextroamphetamine/amphetamine, 202*t*
diabetes mellitus (DM), 219–220, 220*t*
  type 1 diabetes, treatment of, 220–221, 220*f*, 221*t*
  type 2 diabetes, treatment of, 221–224, 222*t*
diastolic blood pressure, 168
diazepam (Valium), 157, 157*t*, 196*t*
diclofenac (Voltaren), 208*t*
dicloxacillin, 235, 235*t*
dicyclomine (Bentyl), 31, 31*t*
diencephalon, 194
digoxin, 178–179
dihydropyridine calcium channel blockers, 174
diltiazem, 184*t*
diluents, 70
dimenhydrinate (Dramamine), 225, 226*t*
dipeptidyl peptidase-4 inhibitors (DPP-4), 222*t*, 223
diphenhydramine (Benadryl), 226*t*
dipyridamole (Aggrenox), 187*t*
direct-acting oral anticoagulants (DOACs), 186, 186*t*
direct-acting vasodilator drugs, for hypertension, 175
direct thrombin inhibitors, 185
Diskhaler, 53, 54*f*
Diskus, 53, 54*f*
disopyramide, 183*t*
distributive shock, 159
disulfiram (Antabuse), 73*t*
diuretics, 168
  CA inhibitors, 172
  classes and mechanism of action, 171*t*

loop, 171
osmotic, 172
potassium-sparing, 171–172
thiazide and thiazide-like, 170–171
DM. *See* diabetes mellitus
DOACs. *See* direct-acting oral anticoagulants
dobutamine (Dobutrex), 26*t*, 160*t*
dofetilide, 184*t*
dopamine (Intropin), 26–27, 26*t*, 160*t*
doripenem, 236
dornase alfa (Pulmozyme), 102–103, 103*f*, 104*t*
dosage calculations and problem solving, 35–44
continuous aerosol dosages, 41
dosage guidelines for infants and children, 42–43
dosage units, 36*t*, 37*t*
dosage frequencies, 37, 37*t*
Joint Commission–approved abbreviations, 37, 38*t*
systems of measure, 36–37
other drug dosage calculations, 41–42
problem solving, drug concentration calculations, 38–41
dosage frequencies, 37, 37*t*
dosage guidelines for infants and children, 42–43
dosage units, 36*t*, 37*t*
dosage frequencies, 37, 37*t*
Joint Commission–approved abbreviations, 37, 38*t*
systems of measure, 36–37
dose–response curve, 10–11, 11*f*
doxazosin, 26, 26*t*
doxycycline, 239
DPIs. *See* dry powder aerosols
DPP-4. *See* dipeptidyl peptidase-4 inhibitors
dronedarone (Multaq), 182, 183*t*
Drug Information Handbook, 6
drug interaction, 16
drug ionization, 13
drug-resistant bacteria, 232*t*
drug–receptor relationship, 13, 13*f*
drugs, 4. *See also specific drugs*
absorption, 12–13
abuse of prescription drugs, 6
dependence, 4
development, 5*f*
phase I studies, 5
phase II studies, 5
phase III studies, 5
phase IV studies, 5
in vitro and animal studies, 5
distribution, 14

doses, 10–12
effects on central nervous system, 194–195
excretion, 15
information, sources of, 6
mechanisms, 13–14
metabolism, 14–15
names of. *See specific names*
nomenclature, 4
routes of administration, 10, 11*t*
schedules, 6*t*
dry mouth, 220, 220*t*
dry powder aerosols (DPIs), 53, 54*f*
dulaglutide (Trulicity), 222*t*, 224
Dulera, 70, 91*t*
DuoNeb, 71*t*

E

echinocandins, 243
edoxaban (Savaysa), 186, 186*t*
edrophonium (Tensilon), 30, 30*t*
Ellipta, 53
empagliflozin (Jardiance), 222*t*, 224
empiric antimicrobial therapy, 232
enalapril, 177*t*
endocrine system, 213–227
antigen–antibody reactions
antihistamines and antiallergic agent, 225–226, 226*t*
histamine, effects of, 224–225, 225*t*
histamine receptors, 225
corticosteroids, 215
anti-inflammatory activity of, 216*t*
function of, 216*t*
glucocorticoids, 216–217, 217*t*
mineralocorticoids, 217
hormone release, control of, 215, 215*f*
pancreas, function of
cystic fibrosis, 219
diabetes mellitus, 219–220, 220*t*
type 1 diabetes, treatment of, 220–221, 220*f*, 221*t*
type 2 diabetes, treatment of, 221–224, 222*t*
pituitary gland and hypothalamus, 214–215, 214*f*, 215*f*
thyroid gland, function of
antithyroid drugs, 218*t*
hyperthyroidism, treatment of, 218
hypothyroidism, treatment of, 217–218
thyroid preparations, 218*t*
endonuclease inhibitor, 244

endotracheal tube (ETT), 116, 117, 118
eosinophils, 81
ephedrine, 25, 25*t*, 26, 26*t*
epilepsy, 202–203
  antiepileptic drugs, 203–204
epinephrine, 25, 25*t*, 26–27, 26*t*, 62–63, 62*t*, 63*t*, 137, 159, 160*t*, 162, 163, 163*t*
eplerenone, 177
epoprostenol sodium (Flolan, Veletri), 140
EPS. *See* extrapyramidal symptoms
eptifibatide (Integrilin), 188*t*
equianalgesic doses, 205
ertapenem, 236
erythromycin, 73*t*, 239
esmolol (Brevibloc), 27, 27*t*, 183*t*
ethacrynic acid (Edecrin), 171*t*
ethambutol, 242, 242*t*
ethanol, 197–198
ethionamide, 242*t*
ethosuximide (Zarontin), 204
etomidate, 153, 153*t*
ETT. *See* endotracheal tube
excretion of drug, 10
exenatide (Byetta), 222*t*, 224
exenatide extended-release (Bydureon), 222*t*, 224
exogenous insulin, 220
exogenous surfactants, 112, 114–115, 115*t*
expectorants, 101, 106
extended-spectrum penicillins, 235, 235*t*
extrapyramidal symptoms (EPS), 199

F

factor Xa inhibitors, 185
Federal Comprehensive Drug Abuse Prevention and Control Act of 1970, 6*t*
fentanyl (Sublimaze, Actiq, Duragesic, Fentora, Ionsys), 136, 152, 156, 156*t*, 206*t*
fexofenadine (Allegra), 226, 226*t*
FGAs. *See* first-generation antipsychotics
fibric acid derivatives, 189, 189*t*
fibrosing colonopathy, 219
filtration, nephron, 170
first-generation antipsychotics (FGAs), 199, 199*t*, 200
first-pass effect, 15
5-french end-hole catheter, 118
flecainide, 183*t*
Flexhaler, 53, 54*f*
flora, human, 230*f*
fluconazole, 243
flucytosine, 243

fludrocortisone, 216*t*, 217
fluid mosaic model, 12, 12*f*
fluphenazine (Prolixin), 199*t*
fluticasone furoate (Arnuity Ellipta), 85*t*, 90*t*
fluticasone propionate (Flovent HFA, Flovent Diskus, and ArmonAir), 90*t*
fluticasone propionate Diskus, 85*t*
fluticasone propionate HFA, 85*t*
fluvoxamine, 73*t*
formoterol (Foradil), 27, 27*t*, 62*t*, 64*t*, 65
fosfomycin, 123*t*
fosinopril, 177*t*
fungal infections, antifungals used in, 243
furosemide (Lasix), 171*t*

G

GABA. *See* gamma-amino butyric acid
gamma-amino butyric acid (GABA), 195, 195*f*
ganciclovir (Cytovene), 244
ganglion cells, 20
GDMT. *See* guideline-directed therapy
gender, altering drug effect, 16
general anesthetics, 209, 209*t*
  conscious sedation, 210
  ideal
    characteristics of, 209*t*
    properties of, 209, 209*t*
  inhaled, 209, 210*t*
  preanesthetic medications, 209–210
generic name, of drug, 4
genetic variations, altering drug effect, 16
genitourinary system, opioids and, 205
gentamicin, 123*t*, 240
GI system, opioids and, 205
glargine (Lantus, Toujeo, Basaglar), 221*t*
glimepiride (Amaryl), 222, 222*t*
glipizide (Glucotrol), 222, 222*t*
GLP-1 RA. *See* glucagon-like peptide-1 receptor agonists
glucagon, 219
glucagon-like peptide-1 receptor agonists (GLP-1 RA), 222*t*, 224
glucocorticoids, 215, 216–217, 216*t*
  adverse effects of, 217*t*
  functions of, 216*t*
gluconeogenesis, 216
glucose-lowering agents, 222*t*
glucosuria, 220, 220*t*
glulisine (Apidra), 221*t*
glyburide (Glynase), 222, 222*t*

glycopeptides, 240
glycopyrrolate (Seebri Neohaler, Lonhala Magnair), 31, 31*t*, 69, 69*t*
glycylcyclines, 239–240
gonadocorticoids, 215, 216*t*
gram-negative bacteria, 231, 231*f*, 232*t*
gram-positive bacteria, 231, 231*f*, 232*t*
gram stain, 231, 231*f*
guaifenesin, 106–107
guideline-directed therapy (GDMT), 168, 175–176

H

haloperidol (Haldol), 199*t*
HandiHaler, 53, 54*f*
heart
  conduction system of, 180–181, 180*f*
  disease, 175. *See also* heart failure
heart effects, histamine, 225
heart failure (HF), 175–176, 176*t*
  ACE inhibitors for, 176–177, 177*t*
  aldosterone antagonists for, 177–178
  angiotensin II receptor blockers for, 177, 177*t*
  angiotensin receptor-neprilysin inhibitor for, 177
  beta-adrenergic blockers for, 177, 177*t*
  cardiac glycosides, digoxin, 178–179
  cardiac workload, 176
  hydralazine and isosorbide dinitrate for, 178, 178*t*
  neurohormonal activation, 176
heart failure with reduced ejection fraction (HFrEF), 173
HF. *See* heart failure
HFA. *See* hydrofluoroalkane
histamine-1, 81
histamine, 224
  effects of, 224–225, 225*t*
  receptors, 225
HIV. *See* human immunodeficiency virus
HMG-Co-A Reductase Inhibitor, 187–188, 188*t*
holding chambers, 52, 52*f*
homeostasis, 214
hormones, 214
  of pituitary gland, 215, 215*f*
  production of the adrenal gland, 215, 215*f*
  release, control of, 215, 215*f*
hospital-acquired pneumonia, 244–246
human flora, 230*f*
human immunodeficiency virus (HIV), 130
Humulin, 221*t*
hydralazine, 178, 178*t*

hydrochlorothiazide (Microzide), 171, 171*t*
hydrocodone (Hysingla ER, Zohydro, Lortab, Vicodin), 206*t*
hydrocortisone, 216*t*
hydrofluoroalkane (HFA), 50
hydromorphone (Dilaudid), 156, 156*t*, 206*t*
hydroxyzine pamoate, HCL (Atarax, Vistaril), 226*t*
hygroscopic, defined, 102
hyperglycemia, 220, 220*t*
hyperlipidemia
  drugs used in treatment of
    bile acid sequestrants, 189, 189*t*
    cholesterol absorption inhibitors, 189, 189*t*
    fibric acid derivatives, 189, 189*t*
    niacin, 189, 189*t*
    omega-3 fatty acids, 189, 189*t*
    statins, 188, 189*t*
hypertension, 168
  ACE inhibitors for, 173, 173*f*
  adrenergic agents for, 174, 175*t*
  angiotensin II receptor blockers for, 173–174, 173*f*
  calcium channel blockers for, 174
  direct-acting vasodilator drugs for, 175
  factors controlling BP, 168–169
  stages of, 168*t*
  therapeutic approach to, 169
hyperthyroidism, 217
  treatment of, 218
hypertonic saline, 101–102
hyperventilation, 50
hypnotic drugs, 195
hypoglycemia, 221
hypothalamus, 214–215, 214*f*, 215*f*
hypothyroidism, 217
  treatment of, 217–218
hypotonic saline, 101
hypovolemic shock, 159

I

ibuprofen (Advil, Motrin), 208*t*
ibutilide, 183*t*
ICSs. *See* inhaled corticosteroids
ICU care, analgesia and sedation, 155–156
idiosyncratic reaction, 4
iloprost (Ventavis), 140–141, 141*f*
imipenem/cilastatin, 236
immunomodulators, 93–94, 94*t*
indacaterol (Arcapta), 27, 27*t*, 62*t*, 64*t*

indomethacin (Indocin), 208*t*
induction, 152
  rapid sequence intubation, 152–153
    etomidate, 153, 153*t*
    ketamine, 153, 153*t*
infant respiratory distress syndrome, 118–119
inhaled corticosteroids (ICSs), 80
  indications for, 89, 90*t*
  use of, 90
inhaled nitric oxide (INO), 139
inhaled vasodilators in acute hypoxemia
  epoprostenol sodium, 140
  iloprost, 140–141, 141*f*
  nitric oxide, 139–140
  treprostinil, 141, 141*f*
INO. *See* inhaled nitric oxide
inotropes, 158, 160*t*
inotropic effect, 178
instillation, 48
  procedure, surfactants, 116*f*
instilled medications administration, 55–56
  disadvantages and limitations of drug delivery, 56
insulin, 219, 221, 224
interferon, 73*t*
intermediate-acting insulins, 221*t*
ipratropium (Atrovent), 31, 31*t*, 69, 69*t*
isavuconazonium, 243
isoflurane (Forane), 209, 210*t*
isoniazid, 73*t*, 242, 242*t*
isoproterenol (Isuprel), 26–27, 26*t*, 62
Isosorbide dinitrate (Isordil), 178, 178*t*, 179*t*
Isosorbide mononitrate (Imdur), 179*t*
itraconazole, 243

J

jet nebulizers, 49
  for nebulized antimicrobials, 122
Joint Commission, 37, 38*t*

K

ketamine, 153, 153*t*
ketorolac, 208*t*
ketosis, 220, 220*t*

L

LABA. *See* long-acting β_2-agonist
labetalol, 27, 27*t*, 175*t*
lacosamide (Vimpat), 203
LAMA. *See* long-acting antimuscarinic agents
LDL. *See* low-density lipoprotein
leukotriene inhibitors, 80
leukotriene modifiers, 93
levalbuterol (Xopenex), 27, 27*t*, 62*t*, 64*t*, 65
levetiracetam (Keppra), 204
levofloxacin (Levaquin), 123*t*, 238*t*
levofloxacin/moxifloxacin, 242*t*
levorphanol, 206*t*
levothyroxine sodium (Levothroid, Synthroid, Unithroid), 218, 218*t*
lidocaine, 136–137, 152, 162, 163*t*, 183*t*
linagliptin (Tradjenta), 222*t*, 223
lincosamide, 241
linezolid, 240
liothyronine sodium (Cytomel), 218*t*
liotrix (Thyrolar), 218*t*
lipase, 219
lipids, 187–188, 188*t*
  hyperlipidemia, drugs used in treatment of, 188–189, 189*t*
  solubility, 13
liquid nebulizers, 49–50, 49*f*
liraglutide (Victoza), 222*t*, 224
lisdexamfetamine, 202*t*
lisinopril, 177*t*
lispro (Humalog), 221*t*
lithium, 73*t*, 201–202
lixisenatide (Adlyxin), 222*t*, 224
LMWHs. *See* low-molecular-weight heparins
long-acting β_2-agonist (LABA), 62, 65–66
  corticosteroid and, 90–91, 91*t*
long-acting antimuscarinic agents (LAMA), 69–70
  corticosteroid and, 90–91, 91*t*
long-acting insulins, 221*t*
loop diuretics, 171, 171*t*
loratadine (Claritin), 226, 226*t*
lorazepam (Ativan), 157, 157*t*, 196*t*, 210
losartan, 177*t*
low-density lipoprotein (LDL), 188, 188*t*
low-molecular-weight heparins (LMWHs), 185
loxapine (Loxitane, Adasuve), 199*t*
lucinactant (Surfaxin), 114, 115*t*
Lugol's solution, 218*t*

M

Mabis Mist II, 49
macrolides, 239
magnesium, 74
magnesium sulfate, 163*t*
major depression. *See* depression
mannitol (Osmitrol), 107, 138–139, 172
MAOIs. *See* monoamine oxidase inhibitors
mass median aerodynamic diameter (MMAD), 48
mast-cell stabilizers, 83, 93
mast cells, 80, 81
master endocrine gland. *See* pituitary gland
MDIs. *See* metered-dose inhalers
MDR. *See* multidrug-resistant
MDR-TB. *See* multiple drug-resistant TB
mechanical ventilation
  metered-dose inhalers during, 55
  small-volume nebulizers during, 55
meclizine (Antivert), 225, 226*t*
meclofenamate (Meclomen), 208*t*
median effective dose, 11
median lethal dose, 11
medication principles, 4
meglitinides, 222*t*, 223
meperidine (Demerol), 206*t*
mepolizumab (Nucala), 94, 94*t*
meropenem (Vabomere), 236
mesh nebulizers, 49
metabolism, 10, 14–15
metaproterenol, 27, 27*t*, 62*t*, 64*t*, 65
metered-dose inhalers (MDIs)
  during mechanical ventilation, 55
  multiple medications, 53
  pressurized, 50–51, 51*f*
  priming of, 51
  with spacer chamber, 52*f*
  technique for treatment, 52
metformin (Glucophage), 221–222
methacholine (Provocholine), 29–30, 29*t*, 138
methadone (Dolophine), 206*t*
methemoglobinemia, 140
methicillin, 235
methimazole (Tapazole), 218, 218*t*
methohexital (Brevital), 196, 196*t*
methyl salicylate (Bengay, Salonpas, Icy Hot), 208*t*
methylphenidate, 202*t*

methylprednisolone, 216*t*
methylxanthines, 61, 61*t*
description of, 73
drug interactions, 73, 73*t*
and PDE inhibitors, 71–73, 73*t*
mechanism of, 72
side effects of, 72–73
therapeutic use of, 72
metolazone (Zaroxolyn), 171*t*
metoprolol (Lopressor), 27, 27*t*, 175*t*, 177*t*, 183*t*
metronidazole, 241
mexiletine, 73*t*, 183*t*
MI. *See* myocardial infarction
micafungin, 243
Micro-Air Omron, 49
Micromedex, 6
midazolam (Versed), 136, 153*t*, 157, 157*t*, 196*t*, 210
miglitol (Glyset), 222*t*, 223
milrinone, 160*t*
mineralocorticoids, 215, 216*t*, 217
MiniHeart Nebulizer, 140
minocycline, 239
MMAD. *See* mass median aerodynamic diameter
mometasone (Asmanex), 85*t*, 90*t*
monoamine oxidase inhibitors (MAOIs), 200, 200*t*, 201
monobactams, 236
monoclonal antibodies, 80
montelukast (Singulair), 93
mood stabilizers, 198*t*, 201–202
morphine, 156, 156*t*, 205, 206*t*
moxifloxacin (Avelox), 238*t*
mucoactive medications, 100
bland aerosols, 101–102
hypertonic saline, 101–102
hypotonic saline, 101
normal saline, 101
sterile distilled water, 102
mucokinetic agents, 105
mucolytic agents
dornase alfa, 102–103, 103*f*, 104*t*
N-acetylcysteine, 102, 104–105, 104*f*
mucokinetic agents, 101, 105
mucolytic agents
dornase alfa, 102–103, 103*f*, 104*t*
N-acetylcysteine, 102, 104–105, 104*f*
mucosal edema
alpha-adrenergic sympathomimetic drugs used in, 81
bronchoconstriction and, 80–81, 80*f*

pulmonary, causes of, 81*t*
relief of, 61
mucous dysfunction, diseases associated with, 100–101
multidrug-resistant (MDR), 122
multiple drug-resistant TB (MDR-TB), 242
mycobacterium cell wall, 241, 241*f*
myocardial infarction (MI), 174

N

N-acetylcysteine (NAC) (Mucomyst), 102, 104–105, 104*f*
nadolol (Corgard), 27, 27*t*, 175*t*
nafcillin, 235, 235*t*
nalbuphine (Nubain), 206*t*
naloxone (Narcan), 206*t*, 207
naltrexone (Vivitrol), 206*t*, 207
naproxen (Naprosyn), 208*t*
narcotic antagonists, 207
nateglinide (Starlix), 222*t*, 223
National Formulary, 6
natural penicillins, 235, 235*t*
nebivolol (Bystolic), 27, 27*t*, 175*t*
nebulizers, 48. *See also specific types*
nedocromil sodium, 93
negative feedback, 215, 215*f*
Neohaler, 53
neonatal respiratory distress syndrome, 114
neostigmine, 30, 30*t*
nephron, 169
diuretics and therapeutic role, 170–172, 171*t*
filtration, 170
function of, 169*f*
tubular reabsorption, 170
tubular secretion, 170
neprilysin, 177
neuraminidase inhibitors, 244
neuroeffector, 20
neurogenic shock, 159
neurohormonal activation, 176
neuromuscular blockade, 153–154
interactions with, 155*t*
neuromuscular blocking agents
depolarizing, 154–155, 154*t*
mechanism of action, 154*f*
nondepolarizing, 154*t*, 155
properties of, 155*t*
neuromuscular blocking agents (NMBAs), 152
depolarizing, 154–155, 154*t*

mechanism of action, 154*f*
nondepolarizing, 154*t*, 155
neuronal activators, 25
neuronal blockers, 25
neurotransmitters, 20, 21–23, 23*f*
neutral protamine hagedorn (Humulin, Novolin), 221*t*
newborns, caffeine and theophylline in, 142
niacin (Niaspan), 189, 189*t*
nicotine replacement products, 142–143
nicotine gum, 143
nicotine inhalers, 143–144
nicotine lozenges, 143
nicotine nasal spray, 144
nicotine patches, 143
nicotine replacement therapy (NRT), 142
nitrates, angina and, 179, 179*t*
nitric oxide (NO), 139–140, 209, 210*t*
Nitro-Bid, 179*t*
nitroglycerin, 179*t*
nitroimidazoles, 241
Nitrol, 179*t*
Nitrostat, 179*t*
NMBAs. *See* neuromuscular blocking agents
NO. *See* nitric oxide
non-dihydropyridine calcium channel blockers, 174
non-opioid analgesics, 207–208, 208*t*
nonselective sympathomimetics, 62–63, 63*t*
nonsteroidal anti-inflammatory drugs (NSAIDs), 207, 208*t*, 209
nonvascular smooth muscle, histamine and, 225
norepinephrine (Levophed), 21, 25, 25*t*, 159, 160*t*
norepinephrine and dopamine reuptake inhibitors, 200*t*, 201
normal saline (NS), 101
Novolin, 221*t*
NRT. *See* nicotine replacement therapy
NS. *See* normal saline
NSAIDs. *See* nonsteroidal anti-inflammatory drugs
nystatin, 243

O

obstructive shock, 159–160, 160*t*
off-label, 6
olanzapine (Zyprexa), 199*t*
olodaterol (Striverdi), 27, 27*t*, 62*t*, 64*t*
omalizumab (Xolair), 94
omega-3 fatty acids, 189, 189*t*
opioids, 136, 156, 156*t*
analgesics, 205–207, 206*t*

oral anticoagulants, 185–186
oritavancin, 240
oseltamivir (Tamiflu), 244
osmotic diuretics, 171*t*, 172
oxacillin, 235, 235*t*
oxazolidinones, 240
oxycodone (Percodan, Percocet, Roxicodone, OxyContin, Oxaydo), 206*t*
oxygenation, 161
oxymorphone (Opana, Opana ER), 206*t*

P

PABA. *See* para-aminobenzoic acid
pain, defined, 204
PALS. *See* Pediatric Advanced Life Support
pancreas, function of
  cystic fibrosis, 219
  diabetes mellitus, 219–220, 220*t*
  type 1 diabetes, treatment of, 220–221, 220*f*, 221*t*
  type 2 diabetes, treatment of, 221–224, 222*t*
pancreatic enzyme replacement therapy (PERT), 219
pancuronium, 155*t*
para-aminobenzoic acid (PABA), 239, 242*t*
parasympathetic nerve ending, 28–29, 28*f*
parasympathetic nervous system, 20, 22*f*
  anticholinergic drugs, 30–31, 31*t*
  anticholinesterase drugs/cholinesterase inhibitors, 30, 30*t*
  cholinergic drugs, 29–30, 29*t*
  parasympathetic nerve ending, 28–29, 28*f*
  stimulation of, 67
parasympatholytic drugs, 30, 61
parenteral route, 10
PARI-LC PLUS, 122–123
paroxysmal supraventricular tachycardia (PSVT), 163
particle size, 48
pathologic state, altering drug effect, 16
PCP. *See Pneumocystis Carinii* pneumonia
PDE. *See* phosphodiesterase
PDR. *See* Physicians' Desk Reference
PEA/asystole rhythm, 162
peak flow monitoring, 87, 87*f*, 88*t*
Pediatric Advanced Life Support (PALS), 160
penicillin G, 235, 235*t*
penicillin G benzathine, 235, 235*t*
penicillin G procaine, 235, 235*t*
penicillin V, 235, 235*t*
penicillinase-resistant penicillins, 235, 235*t*
penicillins, 233–234

aminopenicillins, 235, 235*t*
extended-spectrum, 235, 235*t*
natural, 235, 235*t*
penicillinase-resistant, 235, 235*t*
pentamidine (NebuPent), 122, 123*t*, 130
pentazocine, 206*t*
pentobarbital (Nembutal), 196*t*
peptidoglycans, 233, 234*f*
peramivir (Rapivab), 244
percent solution, 40
percentage strength, 40
peripheral acting muscle relaxants. *See* neuromuscular blocking agents
PERT. *See* pancreatic enzyme replacement therapy
pharmacodynamics, 10*t*
pharmacokinetics, 10
pharmacology, 10
areas of, 10*t*
essential general principles of, 15*f*
drug absorption, 12–13
drug distribution, 14
drug doses, 10–12
drug excretion, 15, 15*f*
drug mechanisms, 13–14
drug metabolism, 14–15
routes of administration, 10, 11*t*
factors altering drug effects
administration with meals, 16
age, 16
drug interaction, 16
gender, 16
genetic variations, 16
pathologic state, 16
patient adherence, 15
placebo effect, 15
general pharmacologic concepts, 9–17
pharmacotherapy, 10*t*
pharmacy, 10*t*
phenobarbital (Luminal), 196, 196*t*, 204
phenoxybenzamine, 26, 26*t*
phenoxymethylpenicillin. *See* penicillin V
phentolamine, 26, 26*t*
phenylephrine, 25, 25*t*, 160*t*
phenytoin (Dilantin), 73*t*, 203
phlegm, 100
phosphodiesterase (PDE), 60
inhibitors, methylxanthines and, 71–73, 73*t*
Physicians' Desk Reference (PDR), 6
physostigmine, 30, 30*t*

pilocarpine (Salagen), 29*t*, 30
pioglitazone (Actos), 222*t*, 223
piperacillin (Zosyn), 235, 235*t*, 236
piroxicam (Feldene), 208*t*
pituitary gland, 214–215, 214*f*, 215*f*
placebo effect, 4, 15
plasma protein binding, 14
plazomicin, 240
pMDIs. *See* pressurized metered-dose inhalers
Pneumocystis Carinii pneumonia (PCP), 122
polydipsia, 220, 220*t*
polyenes, 243
polymyxin B, 123*t*
polyphagia, 220, 220*t*
polyuria, 220, 220*t*
poractant alfa (Curosurf), 114, 115*t*, 117–118
posaconazole, 243
postextubation stridor, 82
postganglionic neurons, 20
potassium iodide and sodium iodide (Lugol's solution), 218*t*
potassium-sparing diuretics, 171–172, 171*t*
potency, 11
prasugrel (Effient), 187, 187*t*
prazosin, 26, 26*t*
prednisolone, 216*t*
prednisone, 216*t*
preganglionic neurons, 20
preload, 176
prescription drugs, abuse of, 6
Pressair, 53, 54*f*
pressurized metered-dose inhalers (pMDIs), 50
pretreatment, purpose of, 152
priming, 51
procainamide, 183*t*
promethazine (Phenergan), 226*t*
propafenone, 183*t*
propantheline (Pro-Banthine)), 31, 31*t*
prophylactic treatment, 114
propofol, 153*t*, 157, 157*t*
propranolol (Inderal), 27, 27*t*, 175*t*, 183*t*
propylthiouracil, 218, 218*t*
protease, 219
PSVT. *See* paroxysmal supraventricular tachycardia
psychopharmacologic drugs, 198, 198*t*
  antipsychotics, 199–200, 199*t*
  depression, treatment of, 200–201, 200*t*
  mood stabilizers, 201–202
  stimulants, 202, 202*t*

pulmonary conditions, agents used in, 135–146
pulmonary vasodilators
  inhaled, in acute hypoxemia
    epoprostenol sodium, 140
    iloprost, 140–141
    nitric oxide, 139–140
    treprostinil, 141
pyrazinamide (PZA), 242, 242*t*
pyridostigmine (Mestinon), 30, 30*t*
PZA. *See* pyrazinamide

Q

quetiapine (Seroquel), 199*t*
quinidine, 183*t*
quinolones, 237–239, 238*t*

R

racemic epinephrine (Micronefrin, Racepinephrine), 62*t*, 63*t*, 81
radioactive iodine (Iodotope I-131), 218*t*
ranolazine (Ranexa), 180
rapid-acting insulins, 221*t*
rapid sequence intubation (RSI), 152
  induction, 152–153
    etomidate, 153, 153*t*
    ketamine, 153, 153*t*
  pretreatment, 152
ratio strength, 41
RDS. *See* respiratory distress syndrome
receptors, 13
reconstituted, meaning of, 38
releasing hormones, 214
remifentanil (Ultiva), 206*t*
renin, 169
repaglinide (Prandin), 222*t*, 223
rescue treatment, 114
reserpine, 28
reslizumab (Cinqair), 94, 94*t*
Respimat soft-mist inhaler, 51*f*
respiratory disease, anti-inflammatory drugs used in, 79–96
  antiasthmatic drugs, 92–93, 92*f*
    immunomodulators, 93–94, 94*t*
    leukotriene modifiers, 93
    mast-cell stabilizers, 93
  asthma, 81–82
    acute asthma episode, management, 87–88
    adults and youths, management in, 83, 84*f*, 85*t*

children, management in, 83, 86–87, 86*t*
peak flow monitoring, 87, 87*f*, 88*t*
bronchoconstriction and mucosal edema, 80–81, 80*f*, 81*t*
corticosteroids, 88–89
aerosolized, advantages and disadvantages of, 89
aerosolized, side effects/adverse reactions of, 89–91
inhaled, indications for, 89, 90*t*
LABAs/LAMA combination preparations, 91*t*
respiratory distress syndrome (RDS), 113
respiratory stimulants, 141–142
respiratory syncytial virus, 43
respiratory system, opioids and, 205
rhythm-based management
during cardiac arrest, 161–162, 162*f*
PEA/asystole, 162
pulseless VF/VT, 162–163
supraventricular tachycardia, 163–164
ribavirin (Virazole), 122, 123*t*, 128–129
rifabutin, 242
rifampin, 14, 73*t*, 242
rifamycins, 242, 242*t*
rifapentine, 242
riociguat, 73*t*
risperidone (Risperdal), 199*t*
ritonavir, 73*t*
rivaroxaban (Xarelto), 186, 186*t*
rocuronium (Zemuron), 155*t*
roflumilast (Daliresp), 72
rosiglitazone (Avandia), 222*t*, 223
RSI. *See* rapid sequence intubation

S

SABA. *See* short-acting β_2-agonist
sacubitril/valsartan (Entresto), 177
salmeterol (Serevent), 27, 27*t*, 62*t*, 64*t*, 65
saturated solution of potassium iodide (SSKI), 106
saxagliptin (Onglyza), 222*t*, 223
scopolamine, 31, 31*t*
second-generation antipsychotics (SGAs), 199–200, 199*t*
sedation, ICU care, 155–157, 157*t*
sedative hypnotics and antianxiety drugs, 195
alcohol (ethanol), 197–198
barbiturates, 195–196, 195*f*, 196*t*
benzodiazepines, 196–197, 196*t*
selective serotonin reuptake inhibitors (SSRIs), 200, 200*t*, 201
semaglutide (Ozempic), 222*t*, 224

sepsis, defined, 159
septic shock, 159
serotonin–norepinephrine reuptake inhibitors (SNRIs), 200*t*, 201
sevoflurane (Ultane), 209, 210*t*
SGAs. *See* second-generation antipsychotics
SGLT2. *See* sodium glucose cotransporter-2 inhibitors
shock, 153
  cardiogenic, 158–159
  distributive, 159
  hypovolemic, 159
  obstructive, 159–160, 160*t*
short-acting β_2-agonist (SABA), 62, 65
short-acting antimuscarinic agents, 69
short-acting insulins, 221*t*
side-port adapter, calfactant administration, 117
silodosin, 26, 26*t*
silver sulfadiazine (Silvadene), 239
sinoatrial (SA) node, 180
sitagliptin (Januvia), 222*t*, 223
skin, opioids and, 205
small-volume nebulizers (SVNs), 49
  liquid nebulizers, 49–50, 49*f*
  during mechanical ventilation, 55
  technique for, 50
  ventilator parameters during, 55
smoking cessation
  general considerations of, 145
  methods, 142
  pharmacologic therapy for, 142–144
SNRIs. *See* serotonin–norepinephrine reuptake inhibitors
sodium bicarbonate, 107
sodium glucose cotransporter-2 inhibitors (SGLT2), 222*t*, 223–224
solute, 40
solution strengths, 41–42
solvent, 36
somatic nervous system, 23*t*
sotalol, 184*t*
spacers, 52, 52*f*
special procedures, agents used in
  airway hyperresponsiveness
    mannitol, 138–139
    methacholine, 138
  bronchoscopy, 136–137
spectrum, defined, 230
spironolactone (Aldactone), 172, 177
sputum, 100
  induction, 102

SSKI. *See* saturated solution of potassium iodide
SSRIs. *See* selective serotonin reuptake inhibitors
statins, 188, 189*t*
status asthmaticus, 82, 87–88
sterile distilled water, 102
stimulants, 198*t*, 202, 202*t*
Stiolto Respimat, 71*t*
strength, 38
streptomycin, 240, 242*t*
subcutaneous injection, 10
sublingual route, 11*t*
succinylcholine (Anectine), 154, 155*t*
sufentanil (Sufenta), 206*t*
sulbactam, 236
sulfacetamide (Sulamyd), 239
sulfadiazine, 239
sulfasalazine (Azulfidine), 239
sulfonamides, 239
sulfonylureas, 222, 222*t*
supraventricular tachycardia (SVT), 163–164
surface tension, 112, 112*f*, 113*f*
surfactant, 105
  agents, 111–120
    exogenous surfactants, indications for, 114–115, 115*t*
    instillation procedure, 116*f*
    surface tension, 112, 112*f*, 113*f*
    surfactant, 112–114, 113*f*
    surfactant replacement drugs, 114–118
  defined, 112–114, 113*f*
surfactant replacement drugs, 114
  beractant, 115–116
  calfactant, 116–117
  poractant alfa, 117–118
SVNs. *See* small-volume nebulizers
SVT. *See* supraventricular tachycardia
Symbicort, 70, 91*t*
sympathetic nerve ending, 23–24, 24*f*, 24*t*
sympathetic nervous system, 20, 22*f*
  α-adrenergic drugs, 25, 25*t*
  β-adrenergic drugs, 26–27, 26*t*, 27*t*
  α-blocking drugs, 25–26, 26*t*
  β-blocking drugs, 27–28, 27*t*
  adrenergic drugs, sites of action of, 24–25
  adrenergic neuronal activators and blockers, 28
  sympathetic nerve ending, 23–24, 24*f*, 24*t*
sympathomimetics, 23, 61
  drug interactions, 66–67, 68*t*
synapse, 20

synaptic cleft, 20
synthetic human insulin, 221
systems of measure, 36–37
systolic blood pressure, 168

T

T_3. *See* triiodothyronine
T_4. *See* thyroxine
tachyphylaxis, 4
tamsulosin, 26, 26*t*
tardive dyskinesia, 199
TB. *See* tuberculosis
TCAs. *See* tricyclic antidepressants
tedizolid, 240
telavancin, 240
temazepam (Restoril), 196*t*
teratogens, 4
terazosin, 26, 26*t*
terbutaline (Bricanyl), 27, 27*t*, 62*t*, 64, 64*t*, 65
tetracycline, 239–240
TG. *See* triglyceride
theophylline, 72–73
  in newborns, 142
therapeutic dose, 11
therapeutic effect, 4
therapeutic index (TI), 12
thiazide and thiazide-like diuretics, 170–171, 171*t*
thiazolidinediones, 222*t*, 223
thioridazine (Mellaril), 199*t*
thyroid gland, function of
  antithyroid drugs, 218*t*
  hyperthyroidism, treatment of, 218
  hypothyroidism, treatment of, 217–218
  thyroid preparations, 218*t*
thyroid hormone (Armour Thyroid), 218*t*
thyroid preparations, 218*t*
thyrotropin-releasing hormone (TRH), 215
thyroxine (T_4), 217
TI. *See* therapeutic index
ticagrelor (Brilinta), 188*t*
ticarcillin (Timentin), 235, 235*t*, 236
tigecycline, 239
Timentin. *See* ticarcillin
timolol (Blocadren), 27, 27*t*, 175*t*
tinidazole, 241
tiotropium (Spiriva), 31, 31*t*, 69

tirofiban (Aggrastat), 188*t*
tissue affinity, 14
TMP/SMX. *See* trimethoprim/sulfamethoxazole
tobacco smoking, 73*t*
tobramycin (TOBI,TOBI Podhaler, Bethkis, Kitabis Pak), 122, 123*t*, 124*t*, 125–126, 240
tolerance, 4
  and dependence, 207
topiramate (Topamax), 204
torsemide (Demadex), 171*t*
toxicology, 10*t*
trade/brand names, of drug, 4
transport mechanisms of drugs, 12–13, 12*f*
TrelegyEllipta, 71*t*, 91*t*
treprostinil (Tyvaso), 141, 141*f*
TRH. *See* thyrotropin-releasing hormone
triamcinolone, 85*t*, 216*t*
triamterene (Dyrenium), 172
triazolam (Halcion), 196*t*
tricyclic antidepressants (TCAs), 200, 200*t*, 201
triglyceride (TG), 168
triiodothyronine (T_3), 217
trimethoprim/sulfamethoxazole (TMP/SMX), 239
tropic hormones, 214
tropicamide (Mydriacyl), 31, 31*t*
tuberculosis (TB), 240, 241
  drugs used in treatment of, 242, 242*t*
    ethambutol, 242
    isoniazid, 242
    pyrazinamide, 242
    rifamycins, 242
tubular reabsorption, nephron, 170
tubular secretion, nephron, 170
type 1 diabetes, treatment of, 220–221, 220*f*, 221*t*
type 2 diabetes, treatment of, 221–224, 222*t*
tyramine, 201

U

UFH. *See* unfractionated heparin
ultrasonic nebulizers, 49
umeclidinium (Anoro Ellipta, Incruse Ellipta), 31, 31*t*, 69, 69*t*
unfractionated heparin (UFH), 184–185
United States Pharmacopeia (USP), 6
uricosuria, 207
Utibron Neohaler, 71*t*

V

vaborbactam, 236
vagal maneuvers, 163–164
valacyclovir (Valtrex), 244
valganciclovir (Valcyte), 244
valproic acid (Depakote, Depakene), 201, 203
valsartan, 177*t*
valved holding chamber, 52, 52*f*, 53
vancomycin, 123*t*, 240
VAP. *See* ventilator-associated pneumonia
varenicline (Chantix), 142, 144
varicella zoster (VZV), 244
vascular effects, histamine, 224–225
vasoactive agents, 159–160, 160*t*
vasodilatory shock, 159
vasopressin, 159, 160*t*
vasopressors, 25, 158
vecuronium (Norcuron), 155*t*
venlafaxine, 201
ventilation, and capnography, 161
ventilator-associated pneumonia (VAP), 122
ventilator management, 158
verapamil, 184*t*
VF/VT rhythm, 162–163, 164
vilanterol, 27, 27*t*, 62*t*, 64*t*, 65
virion, structure of, 128, 128*f*
voriconazole, 243
VZV. *See* varicella zoster

W

warfarin (Coumadin), 184, 185–186
wetting agents and mucoactive drugs, 99–108
  airway mucus, 100*f*
    mucous dysfunction, diseases associated with, 100–101
  expectorants and bronchorrhea agents
    guaifenesin, 106–107
    sodium bicarbonate, 107
  mucoactive medications
    bland aerosols, 101–102
    mucokinetic agents, 105
    mucolytic agents, 102–105, 103*f*, 104*f*, 104*t*
wounds, delayed healing, 220, 220*t*

Y

youths, asthma management in, 83, 84*f*, 85*t*

Z

zafirlukast (Accolate), 93
zanamivir (RelenzaDiskhaler), 122, 123*t*, 129, 244
zileuton (Zyflo), 73*t*, 93
ziprasidone (Geodon), 199*t*

0 to 4 years are spent in vitro and animal studies. 4 to 9 years are spent in phase 1 (Assesses safety and pharmacokinetics) 20 to 100 subjects; phase 2 (Assess drug effectiveness) 100 to 200 patients; and phase 3 (Assess drug effectiveness in a large patient population, double-blinded study design) 1000 to 6000 patients. 9 to 20 years are spent in phase 4 (Postmarketing surveillance) for marketing.

Back to Figure

The curve representing drug A flattens before 0% at 5 milligrams per kilogram, rises steeply to 100% at 10 milligrams per kilogram, and then flattens to form ceiling effect. The curve representing drug B flattens before 0% at 12 milligrams per kilogram, rises steeply to 100% at 18 milligrams per kilogram, and then flattens. Note: All values are estimated.

Back to Figure

In passive transport, cellular transport and diffusion take place. In active transport, facilitated diffusion and drug transporters take place.

Back to Figure

Oligosaccharide (carbohydrate), Phospholipid bilayer, Peripheral protein, Integral proteins, Channel, and Glycolipid

are labeled in the structure of the plasma cell membrane.

Back to Figure

The agonist substance causes drug activity with the receptor site. The antagonist substance does not cause drug activity and blocks drug activity with the receptor site.

Back to Figure

A downward arrow from the Receptor site (site of action) points to Free drug, which further leads to Protein or tissue bond, Metabolism, Metabolites, and Excretion such as Urine, Bile, Feces, Sweat, and Expired air. A downward arrow from Drug points to Absorption, that further leads to Free drug. An upward arrow from Free drug labeled Distribution (plasma) points to the Receptor site.

Back to Figure

In sympathetic division, signals from the central nervous system are sent to a tissue through preganglionic neuron, Acetylcholine, Postganglionic neuron, Norepinephrine, Nicotinic-1 receptor (N1), Alpha receptor, Beta receptor. Text beside the tissue reads: Neuroeffector site: Smooth muscle, Cardiac muscle, Exocrine gland. In parasympathetic division, signals from the central nervous system are sent to a tissue through Dendrite, Preganglionic neuron, Acetylcholine, Muscarinic receptor, Synapse, Nicotinic-1 receptor (N1), Postganglionic neuron. Text beside the tissue

reads: Neuroeffector site: Smooth muscle, Cardiac muscle, Exocrine gland.

Back to Figure

In the illustration, the brain and the spinal cord are labeled. The upper cervical region of the spinal cord is labeled C1, the thoracic region is labeled T1, the lumbar region is labeled L1, and the lower sacral region is labeled S1. The sympathetic chain ganglia is located on either side of the spinal cord. The pons and the medulla oblongata are labeled C1. In the parasympathetic nervous system, nerves from pons and medulla oblongata send signals to the eye. The vagus nerve sends signals to the heart, lungs, gastrointestinal tract, and urinary bladder. The somatic nerve in S1 sends signals to the muscle fiber. In the sympathetic nervous system, nerves from T1 send signals to the eye, blood vessels, heart, and lungs. The nerves in L1 send signals to the skin, blood vessels, adipose tissue, and the gastrointestinal tract. The nerves in L1 and S1 send signals to the urinary bladder.

Back to Figure

In the metered-dose inhaler, the parts, canister, actuator, metering valve, actuator seat, drug and propellant liquid mixture, and actuator nozzle are labeled. In the metered valve function, the parts, canister, metered dose of drug, and actuator seat with closed and open nozzle is shown.

Back to Figure

Inhaler A is doughnut shaped with an opening at the outermost part. Inhaler B is almost conical with an opening at one end. Inhaler C has two parts, the mouthpiece cover and a white tray in the mouthpiece. Inhaler D is almost spherical with an opening at the top. Inhaler E has two parts that are cuboids.

Back to Figure

The outside cell and inside cell are arranged horizontally. A downward arrow from NE slash E points to beta 2 receptor below which G sub S are shown on either side. The G sub S on the right points to adenylyl cyclase below which ATP points to cAMP. The upper part shows a cell labeled constriction and the lower part shows a cell labeled relaxation.

Back to Figure

The postganglionic cholinergic nerve shows M2 that prevents ACh release. Below it, bronchial smooth muscle cell is shown, which results in smooth muscle contraction or bronchoconstriction and increased mucus production.

Back to Figure

The outside cell and inside cell are arranged horizontally. A downward arrow from beta 2 agonist points to beta 2 receptor below which G sub S are shown on either side and

point to adenylyl cyclase that leads to cAMP. The upper part shows a cell labeled constriction and the lower part shows a cell labeled relaxation.

Back to Figure

Inhaler A is doughnut shaped, with an opening at the outermost part. Inhaler B is almost oval in shape, with reading displayed in front. Inhaler C has two parts that are cuboids. Inhaler D is bulky and labeled arcapta neohaler. Inhaler E is L-shaped.

Back to Figure

The receptors in the preganglionic parasympathetic nerve labeled M sub 1 are blocked by antimuscarinic. This results in smooth muscle less constricted or bronchodilation. Its zoomed-in view shows M sub 2, ACh, antimuscarinic, M sub 3, bronchiole smooth muscle cell, and ACh prevented from binding labeled.

Back to Figure

Flowmeter A has a scale on the outer surface with colored markings for various readings. Flowmeter B is supported backward with a scale on top and markings for various readings.

Back to Figure

1 Antigen, IgE antibody, nucleus, mast cell, granule, 2 degranulation, and 3 degranulation blocked by cromolyn are labeled in the illustration.

Back to Figure

The white blood cell in the mucus layers consisting gel and (sol) periciliary layer, the cilium, basement membrane, columnar ciliated cell, submucosal gland, goblet cell, and capillaries of blood supply are labeled in the cross section.

Back to Figure

Part A shows a vertical amino acid chain on either side of sulfur-sulfhydryl bonds. Part B shows two vertical sets of amino acid chains on either side of sulfur-sulfhydryl bonds and an overlapping amino acid chain on either side of sulfur-sulfhydryl bonds on the left. On the right, three vertical amino acid chains on either side of sulfur-sulfhydryl bonds are shown. A rightward arrow between them is labeled, rhDnase disrupts bacteria and cellular debris.

Back to Figure

A vertical amino acid chain on either side of sulfur-sulfhydryl bonds is shown on the left. On the right, a vertical amino acid chain on the left and a slanting amino acid chain on the right of sulfur-sulfhydryl bonds are shown. A rightward arrow between them is labeled, disrupts bonds.

Back to Figure

Illustration shows bidirectional arrows around the center of spherical molecules labeled intermolecular forces and along the surface labeled surface tension. All the molecules together form a spherical water droplet.

Back to Figure

The downward air pressure and the upward surface tension in the water layer are shown. The zoomed-in view of two alveoli are shown above it with outermost water layer and air pressure pointing to the center.

Back to Figure

Part A shows two alveoli, the smaller labeled 1 and the larger labeled 2 with radius shown as r. The air pressure pointing to the center in 1 flow to 2 with equal surface tension. Part B shows two alveoli with the smaller one labeled 3 and the larger one labeled 4. The air pressure flows into both the alveoli and small water particles labeled surfactant is closely packed in 3 and not closely packed in 4. 3 indicates very low surface tension and 4 indicates low surface tension.

Back to Figure

In the first illustration, infant’s head and body are inclined down, with the head turned to the right. In the second illustration, infant’s head and body are inclined down, with the

head turned to the left. In the third illustration, infant's head and body are inclined up, with the head turned to the right. In the fourth illustration, infant's head and body are inclined up, with the head turned to the left.

Back to Figure

Illustration A shows vertical ergosterol in fungal cell membranes with hydrophilic heads upward and hydrophilic tails downward in the upper row and hydrophilic heads downward and hydrophilic tails upward in the lower row. Illustration B shows an oval labeled Amphotericin B, between horizontal ergosterols. Below it, fungal cell membranes with hydrophilic heads upward and hydrophilic tails downward in the upper row with upward pores. Below it, fungal cell membranes with hydrophilic heads downward and hydrophilic tails upward in the lower row with downward pores is shown.

Back to Figure

The innermost part is labeled RNA or DNA. Surrounding the RNA or DNA is the capsid within an envelope. Large protein spikes are shown around the envelope.

Back to Figure

The steps read: Preparation: preparing the patient, equipment, medications, assign roles. Pre-oxygenation: increase oxygen reserves through replacing nitrogen in the lungs with supplemental oxygen to prevent desaturation

during intubation. Pretreatment: use of medications to prophylaxis adverse physiological consequences of intubation. Paralysis with induction: administration of an IV induction agent followed by a paralytic (NMBA). Protection and positioning: positioning the patient for optimal laryngoscopy. Placement of ET tube in trachea with proof: perform the intubation and verification the ET is in the proper position. Post-intubation management: administration of long-term analgesia and sedative medications, as well as NMBAs if indicated.

Back to Figure

In illustration A, Cholinesterase, Succinylcholine, ACh, ACh receptor, and Post-synaptic skeletal muscle membrane are labeled. In illustration B, Nondepolarizing NMBs, ACh, ACh receptor, and Post-synaptic skeletal muscle membrane are labeled.

Back to Figure

A text box labeled 1 reads: Start CPR. Give oxygen and attach monitor or defibrillator. If shockable rhythm and 2, V fib or pulseless V Tach under 3, shock, then try 4, CPR for 2 minutes. If shockable rhythm and 5, shock, then try 6, CPR for 2 minutes, Epinephrine every 3 to 5 minutes, and consider advanced airway, capnography. Else, no signs of ROSC, go to 10 and 11. If shockable rhythm and 7, shock, then try 8, CPR for 2 minutes, amiodarone, and treat causes.

If after 1, starting CPR and giving oxygen, attaching monitor or defibrillator, there is no shockable rhythm, then 9, Asystole or PEA, 10, CPR for 2 minutes, Epinephrine every 3 to 5 minutes, and consider advanced airway, capnography. If there is shockable rhythm, then go to 5 or 7. Else, go to 11, CPR for 2 minutes and treat causes. If shockable rhythm, then go to 5 or 7. If no signs of ROSC, go to 10 and 11.

Back to Figure

The illustration shows tubular glomerulus within a circular structure. An arrow shows the movement toward the spiral tube-like structure, where water gets absorbed at the first spiral, followed by sodium absorption at the next spiral. The tube forms a loop and then goes straight downward with a C-shaped bend. The C-shaped bend is labeled as proximal convoluted tubule (PCT). Chloride and potassium ions get absorbed by the body in this bend, and hydrogen ion gets inside the tube. The immediate part of the tube right below it shows the absorption of bicarbonate ion and glucose into the body. This part of nephron further goes straight down and narrows down. Water gets absorbed into body at this part of the tube. It further bends into a U shape. It is labeled as Loop of Henle. The other side of the U-shaped tube shows the absorption of sodium and chloride into the body. The part of tube above it is broad again and sodium and chloride ions get absorbed from this part. A loop forms above it, opposite to the C-shaped tube. Sodium ion gets absorbed here. Above it, hydrogen ion gets into nephron. Further is a V-shaped tube

labeled as distal convoluted tubule (DCT). Here the sodium ion gets absorbed into the body. This part is followed by another bend, where potassium gets inside the nephron. It further joins a vertical structure that resembles a tree with branches. A highlighted space within, which is the collecting duct (CD), shows absorption of water and antidiuretic hormone (ADH) into the body. A downward-facing arrow shows the direction of the flow.

Back to Figure

Angiotensinogin leads to Angiotensin 1, Angiotensin 2, and Angiotensin 2 receptor. Angiotensin 2 to Angiotensin 2 receptor is blocked by Angiotensin 2 receptor blockers. ACE inhibitor blocks this enzyme leaders to Angiotensin converting enzyme, which in turn leads to Angiotensin 2. Renin leads to Angiotensin 2.

Back to Figure

On the left side, Intrinsic activation (contact between blood and collagen or other substances) is shown. On the right side, Extrinsic activation (tissue damage) is shown. XII leads to Active XII, which further leads to XI, Active XI, IX, Active IX, and X. Injured cells lead to Tissue factor, VII to Active VII, and X. X leads to the conversion of Prothrombin (inactive) to Thrombin (active), which further leads to the conversion of Fibrinogen (monomer in circulation) to Fibrin (ready to polymerize into fibers).

Back to Figure

The illustration shows the cross-sectional view of the region between two layers of cells. The upper most layer of cells is labeled as Endothelial cells. The cell damage in it is shown by a breakage in the cell. ADP gets released from it and further, Clopidogrel Prasugrel Ticagrelor, represented by a red transparent rectangle above the P2Y12 receptor, which is on a platelet, shows the AA with a red dotted cross on COX1 or aspirin changing to TXA2. The P2T12 receptor activates the GIIbIIIa receptor. A two-headed curved arrow below it has one arrow pointing to it, while the other head shows the GIIbIIIa receptor having a red transparent rectangle on it, which is Abciximab Eptifibatide Tirofiban. The cell damage on the lower layer too shows the release of the ADP, which further goes to the P2Y12 receptor in the platelet. This receptor activates the GIIbIIIa receptor, which has an arrow head of fibrinogen facing toward it.

Back to Figure

The hypothalamus, thalamus, cerebrum, cerebellum, spinal cord, midbrain, pons, medulla oblongata in the stem are labeled.

Back to Figure

Ethanol binding, Benzodiazepine binding site, GABA site, and Barbiturate binding site are labeled. A downward arrow along the center is labeled chloride ion.

Back to Figure

The labeled parts read: Neurosecretory cells, Hypothalamus, Releasing hormones, Vessels “portal system,” Anterior (adenohypophysis), TSH, HGH, FSH, LH, Prolactin, MSH, ADH, Oxytocin, and Posterior (neurohypophysis).

Back to Figure

In the pituitary gland, TRH is released from the hypothalamus to TSH in the thyroid gland. Thyroxin in turn produces negative feedback to the hypothalamus.

Back to Figure

The breakfast dose, lunch dose, and dinner dose of insulin shows rapid-acting insulin. Overall dose of insulin shows basal (insulin glargine).

Back to Figure

An arrow from indigestion of food points to GI tract, which in turn points to release of gut hormones—incretins under Active GLP-1 and GIP. An upward arrow from the gut reads: Increasing, stimulates insulin release from beta-cells (GLP-1, GIP) and a downward arrow from the gut reads: Decreasing, suppresses glucagon release (GLP-1). An arrow to the gut reads: GLP-1 receptor agonists. To its right, increase in Glucose uptake by muscles, decrease in Blood glucose and Hepatic glucose production is shown.

Back to Figure

The frontal view of a male shows the following: Oral cavity lists Viridans streptococci, Peptococcus, Peptostreptococcus, Eikenella, Haemophilus. Skin lists *S. epidermidis*, *S. aureus*, Corynebacterium, Propionibacterium. Stomach lists *H. pylori*. Large intestine and rectum lists Bacteroides, Fusobacterium, Bifidobacterium, Clostridium, Enterococcus, Lactobacillus, *S. bovis*, Coliforms: *E. coli*, Enterobacter, Citrobacter. Upper airways list *S. pneumoniae*, *S. pyogenes*, *Neisseria* sp., *H. influenzae*, *S. aureus* (nose). Lower airway lists Normally sterile. Small intestine lists Proximal: Lactobacillus, Enterococcus. Distal lists Lactobacillus, Enterococcus, Bacteroides, Coliforms. Everywhere lists *S. epidermidis*, Corynebacterium. Genitourinary tract lists Lactobacillus, Corynebacterium, Streptococcus, Candida, *E. coli*. In the urinary tract, only the anterior urethra should be colonized.

Back to Figure

Row 1 shows purple, Purplish-blue, Remains purplish-blue, Remains purplish-blue, plasma membrane on top and cell wall + peptidoglycan at the bottom. Row 2 shows purple, Purplish-blue, Loses stain, Pink-red, plasma membrane on top, cell wall + thin peptidoglycan at the center, and outer membrane at the bottom is shown.

Back to Figure

A free oxygen atom with diagonal double bonds joins the lower left of a rectangle. Right above it on the other corner of rectangle is CH. On the same side of the rectangle at the other corner too is a CH. Right below the CH on the bottom right corner of the rectangle is N.

Back to Figure

The chemical structure of Penicillins has a molecule of R attached to C horizontally with a single line, C is vertically connected to O above it, with double lines, C on the other side is connected to NH with a single line. NH is connected with a single line to a square that has N on its right bottom and O outside the square connected by diagonal double lines to the other corner on the same side where N is. N is further connected to a rectangular structure that has S between the upper side, which further connects to CH3, next to it is another CH3. Another side is connected to COOH with a single line to the rectangle.

The chemical structure of Cephalosporins has a molecule of R attached to C horizontally with a single line, C is vertically connected to O above it, with double lines, C on the other side is connected to NH with a single line. NH is connected with a single line to a square which has N on its right bottom and O outside the square connected by diagonal double lines to other corner on the same side where N is. N is further connected to a

Hexagon structure. On the top end of the hexagon is an S, and bottom end is, COOH. The COOH is connected with a single line to N in square, and with a double line to R2 on the side of a hexagon.

The chemical structure of Carbapenems has a molecule of OH, and CH3 attached to a square with a single line diagonally. The square has N on its right bottom and O outside the square connected by diagonal double lines to the other corner on the same side where N is. N is further connected to a pentagonal structure. It has COOH connected to N with a single line, and with a double line to a side from which is connected S in a single line, and further to R in a single line.

The chemical structure of Monobactams has a molecule of R attached to C horizontally with a single line, C is vertically connected to O above it, with double lines, C on the other side is connected to NH with a single line. NH is connected with a single line to a square that has N on its right bottom and O outside the square connected by diagonal double lines to other corner on the same side where N is. N is further connected to SO3H with a single line. On the side above N is CH connected with a single line.

Back to Figure

In the Illustration A, the structure of peptidoglycan has a round tube-like horizontal structure labeled as carbohydrate

“backbone”. The backbone has alternating light and dark portions. The lighter areas are labeled as N-acetylmuramic acid (NAM), while the darker areas are labeled as N-acetylglucosamine (NAG). At the end of every light portion is a vertical beaded structure, which is the Amino acid side chain. Every Amino acid side chain is intersected by a diagonal beads structure, which overlaps the backbone. The diagonal beaded structures are Peptide cross-bridges.

Illustration B shows a Gram-positive bacteria cell, and a magnified view of its cross section. The cross-sectional view shows cytoplasm, round beaded structures arranged next to each other, at the bottom. It has protein in between. It has vertical lines upward toward it. Above it is another similar layer of beaded line with downward facing vertical structures. Both the beaded layers are labeled as Phospholipids. The region between them is labeled as cell membrane. Above this is a layer of brown tube-like structures stacked on one another, called as cell wall. The red curved lines are Teichoic acid. The cell wall and cell membrane region together form the cell envelope.

Illustration C shows a gram-negative bacteria cell, and a magnified view of its cross section. The cross-sectional view shows cytoplasm, round beaded structures or the cytoplasm and cell membrane. Above it is a layer of brown tubes labeled as Peptidoglycan laid in a single row. The space between each Peptidoglycan is labeled as Periplasm. Above this layer is the outer membrane consisting of Lipoprotein between the

rows of beaded structures. The topmost layer consists of many beads of different colors. The purple ones are labeled as porins. The pink ones are labeled as Lipid A. The green hair-like structure from the Lipid A is labeled as O polysaccharide. The Lipid A and O polysaccharide together are called Lipopolysaccharide (LPS). The outer membrane and Peptidoglycan together are called as cell wall. The cell wall, periplasm, and outer membrane together form the cell envelope.

Back to Figure

The chemical structure of Cephalosporins has a molecule of R1 attached to CO horizontally with a single line, CO is vertically connected to O above it, with double lines, CO on the other side is connected to NH with a single line. NH is connected with a single line to a square that has N on its right bottom and O outside the square connected by diagonal double lines to other corner on the same side where N is. N is further connected to a Hexagonal structure. On the top end of the hexagon is an S, and bottom end is, COOH. The COOH is connected with a single line to N in square, and with a double line to R2 on the side of a hexagon.

Back to Figure

Extractable phospholipids, Mycolic acids, Arabinogalactan Peptidoglycan, Cytoplasmic membrane, and pore are shown.

Back to Figure