



GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION

Updated 2019

© 2019 Global Initiative for Asthma



Global Strategy for Asthma Management and Prevention (2019 update)

The reader acknowledges that this report is intended as an evidence-based asthma management strategy, for the use of health professionals and policy-makers. It is based, to the best of our knowledge, on current best evidence and medical knowledge and practice at the date of publication. When assessing and treating patients, health professionals are strongly advised to use their own professional judgment, and to take into account local or national regulations and guidelines. GINA cannot be held liable or responsible for inappropriate healthcare associated with the use of this document, including any use which is not in accordance with applicable local or national regulations or guidelines.

This document should be cited as: Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. Available from: www.ginasthma.org

Table of contents

Tables and figures	5
Preface.....	7
Members of GINA committees (2018)	8
Methodology.....	9
What's new in GINA 2019?.....	12
Peer-reviewed publications about the GINA report	14
SECTION 1. ADULTS, ADOLESCENTS AND CHILDREN 6 YEARS AND OLDER	15
Chapter 1. Definition, description, and diagnosis of asthma	15
Definition of asthma	16
Description of asthma	16
Making the initial diagnosis	17
Confirming the diagnosis of asthma in patients already taking controller treatment	22
Differential diagnosis.....	24
How to make the diagnosis of asthma in other contexts	25
Chapter 2. Assessment of asthma.....	27
Overview	28
Assessing asthma symptom control	29
Assessing future risk of adverse outcomes	33
Role of lung function in assessing asthma control.....	33
Assessing asthma severity	35
Chapter 3. Treating asthma to control symptoms and minimize risk.....	37
Part A. General principles of asthma management	38
Long-term goals of asthma management	38
The patient-health care provider partnership.....	39
Control-based asthma management.....	40
Part B. Medications and strategies for symptom control and risk reduction.....	43
Asthma medications.....	44
Reviewing response and adjusting treatment.....	54
Treating other modifiable risk factors.....	57
Other therapies	58
Non-pharmacological strategies	60
Indications for referral for expert advice	68
Part C. Guided asthma self-management education and skills training	69
Overview	69
Skills training for effective use of inhaler devices	69

Adherence with medications and other advice	70
Asthma information	72
Training in guided asthma self-management	73
Part D. Managing asthma with comorbidities and in specific populations.....	75
Managing comorbidities	75
Managing asthma in specific populations or settings	78
Part E. Difficult-to-treat and severe asthma in adults and adolescents.....	84
Definitions: uncontrolled, difficult-to-treat and severe asthma.....	84
Prevalence: how many people have severe asthma?	85
Importance: the impact of severe asthma	85
Investigate and manage adult and adolescent patients with difficult-to-treat asthma.....	91
Assess and treat severe asthma phenotypes.....	93
Manage and monitor severe asthma treatment.....	98
Chapter 4. Management of worsening asthma and exacerbations	101
Overview	103
Diagnosis of exacerbations.....	104
Self-management of exacerbations with a written asthma action plan	104
Management of asthma exacerbations in primary care.....	108
Management of asthma exacerbations in the emergency department	111
Chapter 5. Diagnosis and initial treatment of asthma, COPD and asthma-COPD overlap (ACO)	119
Objective	120
Background to diagnosing asthma, COPD and asthma-COPD overlap	121
Definitions	121
Stepwise approach to diagnosis of patients with respiratory symptoms	122
Future research.....	128
SECTION 2. CHILDREN 5 YEARS AND YOUNGER	129
Chapter 6. Diagnosis and management of asthma in children 5 years and younger.....	129
Part A. Diagnosis	130
Asthma and wheezing in young children	130
Clinical diagnosis of asthma.....	131
Tests to assist in diagnosis	134
Differential diagnosis	135
Part B. Assessment and management	137
Goals of asthma management.....	137
Assessment of asthma	137
Medications for symptom control and risk reduction	139

Reviewing response and adjusting treatment	144
Choice of inhaler device	144
Asthma self-management education for carers of young children	145
Part C. Management of worsening asthma and exacerbations in children 5 years and younger	146
Diagnosis of exacerbations	146
Initial home management of asthma exacerbations	147
Primary care or hospital management of acute asthma exacerbations.....	149
Chapter 7. Primary prevention of asthma	153
Factors contributing to the development of asthma in children	154
Factors associated with increased or decreased risk of asthma in children.....	154
Advice about primary prevention of asthma	157
SECTION 3. TRANSLATION INTO CLINICAL PRACTICE.....	159
Chapter 8. Implementing asthma management strategies into health systems.....	159
Introduction	160
Adapting and implementing asthma clinical practice guidelines.....	160
Barriers and facilitators	162
Examples of high impact implementation interventions.....	162
Evaluation of the implementation process	162
How can GINA help with implementation?	163
REFERENCES	164

Tables and figures

DIAGNOSIS

Box 1-1.	Diagnostic flowchart for clinical practice – initial presentation	18
Box 1-2.	Diagnostic criteria for asthma in adults, adolescents, and children 6–11 years	19
Box 1-3.	Steps for confirming the diagnosis of asthma in a patient already taking controller treatment	23
Box 1-4.	How to step down controller treatment to help confirm the diagnosis of asthma	23
Box 1-5.	Differential diagnosis of asthma in adults, adolescents and children 6–11 years	24

ASSESSMENT

Box 2-1.	Assessment of asthma in adults, adolescents, and children 6–11 years	29
Box 2-2.	GINA assessment of asthma control in adults, adolescents and children 6–11 years	31
Box 2-3.	Specific questions for assessment of asthma in children 6–11 years	32
Box 2-4.	Investigating a patient with poor symptom control and/or exacerbations despite treatment	36

MANAGEMENT

Box 3-1.	Communication strategies for health care providers	39
Box 3-2.	The control-based asthma management cycle	40
Box 3-3.	Population level versus patient level decisions about asthma treatment	42
Box 3-4.	Initial asthma treatment - recommended options for adults and adolescents	45
Box 3-5A.	Personalized management for adults and adolescents to control symptoms and minimize future risk	46
Box 3-5B.	Personalized management for children 6–11 years to control symptoms and minimize future risk.....	47
Box 3-6.	Low, medium and high daily doses of inhaled corticosteroids	48
Box 3-7.	Options for stepping down treatment once asthma is well controlled	56
Box 3-8.	Treating modifiable risk factors to reduce exacerbations	57
Box 3-9.	Non-pharmacological interventions - summary	60
Box 3-10.	Effectiveness of avoidance measures for indoor allergens	64
Box 3-11.	Indications for considering referral for expert advice, where available	68
Box 3-12.	Strategies to ensure effective use of inhaler devices	70
Box 3-13.	Poor medication adherence in asthma	71
Box 3-14.	Asthma information	72
Box 3-15.	What proportion of adults have difficult-to-treat or severe asthma?	85
Box 3-16A.	Decision tree – investigate and manage adult and adolescent patients with difficult-to-treat asthma	87
Box 3-16B.	Decision tree – assess and treat severe asthma phenotypes	88
Box 3-16C.	Decision tree – consider add-on biologic Type 2 targeted treatments	89
Box 3-16D.	Decision tree – monitor and manage severe asthma treatment	90

EXACERBATIONS

Box 4-1.	Factors that increase the risk of asthma-related death	103
Box 4-2.	Self-management of worsening asthma in adults and adolescents with a written asthma action plan	107
Box 4-3.	Management of asthma exacerbations in primary care (adults, adolescents, children 6–11 years)	109
Box 4-4.	Management of asthma exacerbations in acute care facility, e.g. emergency department	113
Box 4-5.	Discharge management after hospital or emergency department care for asthma	117

ASTHMA-COPD OVERLAP

Box 5-1.	Current definitions of asthma and COPD, and clinical description of asthma-COPD overlap	122
Box 5-2a.	Usual features of asthma, COPD and asthma-COPD overlap	124
Box 5-2b.	Features that if present favor asthma or COPD	124
Box 5-3.	Spirometric measures in asthma, COPD and asthma-COPD overlap	125
Box 5-4.	Summary of syndromic approach to diseases of chronic airflow limitation for clinical practice	127
Box 5-5.	Specialized investigations sometimes used in distinguishing asthma and COPD	128

CHILDREN 5 YEARS AND YOUNGER

Box 6-1.	Probability of asthma diagnosis in children 5 years and younger	131
Box 6-2.	Features suggesting a diagnosis of asthma in children 5 years and younger	132
Box 6-2A.	Questions that can be used to elicit features suggestive of asthma.....	133
Box 6-3.	Common differential diagnoses of asthma in children 5 years and younger	136
Box 6-4.	GINA assessment of asthma control in children 5 years and younger	138
Box 6-5.	Personalized management of asthma in children 5 years and younger	143
Box 6-6.	Low daily doses of inhaled corticosteroids for children 5 years and younger.....	144
Box 6-7.	Choosing an inhaler device for children 5 years and younger.....	145
Box 6-8.	Primary care management of acute asthma or wheezing in children 5 years and younger	148
Box 6-9.	Initial assessment of acute asthma exacerbations in children 5 years and younger.....	149
Box 6-10.	Indications for immediate transfer to hospital for children 5 years and younger.....	150
Box 6-11.	Initial management of asthma exacerbations in children 5 years and younger	151

PRIMARY PREVENTION OF ASTHMA IN CHILDREN

Box 7-1.	Advice about primary prevention of asthma in children 5 years and younger	157
----------	---	-----

IMPLEMENTATION OF THE GINA STRATEGY

Box 8-1.	Approach to implementation of the Global Strategy for Asthma Management and Prevention	161
Box 8-2.	Essential elements required to implement a health-related strategy	161
Box 8-3.	Examples of barriers to the implementation of evidence-based recommendations	162
Box 8-4	Examples of high-impact interventions in asthma management.....	162

Preface

Asthma is a serious global health problem affecting all age groups. Its prevalence is increasing in many countries, especially among children. Although some countries have seen a decline in hospitalizations and deaths from asthma, asthma still imposes an unacceptable burden on health care systems, and on society through loss of productivity in the workplace and, especially for pediatric asthma, disruption to the family.

In 1993, the National Heart, Lung, and Blood Institute collaborated with the World Health Organization to convene a workshop that led to a Workshop Report: Global Strategy for Asthma Management and Prevention.¹ This was followed by the establishment of the Global Initiative for Asthma (GINA), a network of individuals, organizations, and public health officials to disseminate information about the care of patients with asthma, and to provide a mechanism to translate scientific evidence into improved asthma care. The GINA Assembly was subsequently initiated, as an *ad hoc* group of dedicated asthma care experts from many countries. The Assembly works with the Science Committee, the Board of Directors and the Dissemination and Implementation Committee to promote international collaboration and dissemination of information about asthma. The GINA report (“Global Strategy for Asthma Management and Prevention”), has been updated annually since 2002, and publications based on the GINA reports have been translated into many languages. In 2001, GINA initiated an annual World Asthma Day, raising awareness about the burden of asthma, and becoming a focus for local and national activities to educate families and health care professionals about effective methods to manage and control asthma.

In spite of these efforts, and the availability of effective therapies, international surveys provide ongoing evidence for suboptimal asthma control in many countries. It is clear that if recommendations contained within this report are to improve care of people with asthma, every effort must be made to encourage health care leaders to assure availability of, and access to, medications, and to develop means to implement and evaluate effective asthma management programs. To this end, the major revision of the GINA report published in May 2014 not only reflected new evidence about asthma and its treatment, but also integrated evidence into strategies that would be both clinically relevant and feasible for implementation into busy clinical practice, and presented recommendations in a user friendly way with extensive use of summary tables and flow-charts. For clinical utility, recommendations for clinical practice are contained in the core GINA Report, while additional resources and background supporting material are provided online at www.ginasthma.org. New recommendations about treatment of mild asthma, described in the present report, represent the outcome of more than a decade of work by GINA members and others, and may be considered the most fundamental change in asthma management in the past 30 years.

It is essential that we acknowledge the superlative work of all who have contributed to the success of the GINA program, and the many people who have participated in it; in particular, the outstanding and dedicated work of Drs Suzanne Hurd as Scientific Director and Claude Lenfant as Executive Director over the many years since GINA was first established, until their retirement in December 2015. Through their tireless contributions, Dr Hurd and Dr Lenfant fostered and facilitated the development of GINA. In January 2016, we were delighted to welcome Ms Rebecca Decker, BS, MSJ, as the new Program Director for GINA and GOLD, and we appreciate the commitment and skills that she has brought to this demanding role.

The work of GINA is now supported only by income generated from the sale of materials based on the report. The members of the GINA Committees are solely responsible for the statements and conclusions presented in this publication. They receive no honoraria or expenses to attend the scientific review meetings, nor for the many hours spent reviewing the literature and contributing substantively to the writing of the report.

We hope you find this report to be a useful resource in the management of asthma and that, in using it, you will recognize the need to individualize the care of each and every asthma patient you see.

Helen K Reddel, MBBS PhD
Chair, GINA Science Committee

Louis-Philippe Boulet, MD
Chair, GINA Board of Directors

Members of GINA committees (2018)

GINA BOARD OF DIRECTORS*

Louis-Philippe Boulet, MD (*Chair*)
Université Laval
Québec, QC, Canada

Eric D. Bateman, MD
University of Cape Town Lung Institute
Cape Town, South Africa.

Guy Brusselle, MD, PhD
Ghent University Hospital,
Ghent, BELGIUM

Alvaro A. Cruz, MD
Federal University of Bahia
Salvador, BA, Brazil

J. Mark FitzGerald, MD
University of British Columbia
Vancouver, BC, Canada

Hiromasa Inoue, MD
Kagoshima University
Kagoshima, Japan

Mark L. Levy, MD
Locum GP
London, UK

Jiangtao Lin, MD
China-Japan Friendship Hospital
Peking University
Beijing, China

Soren Erik Pedersen, MD
University of Southern Denmark and
Kolding Hospital
Kolding, Denmark

Helen K. Reddel, MBBS PhD
Woolcock Institute of Medical Research,
University of Sydney
Sydney, Australia

Arzu Yorgancioglu, MD
Celal Bayar University
Department of Pulmonology
Manisa, Turkey

GINA SCIENTIFIC COMMITTEE*

Helen K. Reddel, MBBS PhD, *Chair*
Woolcock Institute of Medical Research,
University of Sydney
Sydney, Australia

Leonard B. Bacharier, MD
Washington University School of
Medicine,
St Louis, MO, USA

Eric D. Bateman, MD
University of Cape Town Lung Institute
Cape Town, South Africa.

Allan Becker, MD
University of Manitoba
Winnipeg, MB, CANADA

Guy Brusselle, MD, PhD
Ghent University Hospital,
Ghent, BELGIUM

Roland Buhl, MD PhD
Mainz University Hospital
Mainz, Germany

J. Mark FitzGerald, MD
University of British Columbia
Vancouver, BC, Canada

Hiromasa Inoue, MD
Kagoshima University
Kagoshima, Japan

Fanny Wai-san Ko, MD
The Chinese University of Hong Kong
Hong Kong

Jerry A. Krishnan, MD PhD
University of Illinois Hospital & Health
Sciences System
Chicago, IL, USA

Louise Fleming, MBChB MD
Royal Brompton Hospital
London, United Kingdom

Soren Erik Pedersen, MD
Kolding Hospital
Kolding, Denmark

Aziz Sheikh, BSc, MBBS, MSc, MD
The University of Edinburgh
Edinburgh, United Kingdom

GINA PROGRAM

Rebecca Decker, BS, MSJ

EDITORIAL ASSISTANCE

Ruth Hadfield, BSc, DPhil, GCBiostat

GRAPHICS ASSISTANCE

Kate Chisnall

INFORMATION DESIGN

Tomoko Ichikawa, MS
Hugh Musick, MBA
Institute for Healthcare Delivery Design
University of Illinois, Chicago, USA

* Disclosures for members of GINA Board of Directors and Science Committee can be found at www.ginasthma.com

Methodology

GINA SCIENCE COMMITTEE

The GINA Science Committee was established in 2002 to review published research on asthma management and prevention, to evaluate the impact of this research on recommendations in GINA documents, and to provide yearly updates to these documents. The members are recognized leaders in asthma research and clinical practice with the scientific expertise to contribute to the task of the Committee. They are invited to serve for a limited period and in a voluntary capacity. The Committee is broadly representative of adult and pediatric disciplines as well as from diverse geographic regions. The Science Committee meets twice yearly in conjunction with the American Thoracic Society (ATS) and European Respiratory Society (ERS) international conferences, to review asthma-related scientific literature. Statements of interest for Committee members are found on the GINA website www.ginasthma.org.

PROCESSES FOR UPDATES AND REVISIONS OF THE GINA REPORT

GINA processes for the review of evidence and development of recommendations for GINA reports, including handling of conflict of interest, were reviewed by the Science Committee and approved by the Board in September 2018, and are described below.

Literature search

For each meeting of the GINA Science Committee, a rolling PubMed search is performed covering approximately 18 months, using filters established by the Committee: 1) asthma, all fields, all ages, only items with abstracts, clinical trial, human; and 2) asthma and meta-analysis, all fields, all ages, only items with abstracts, human. The ‘clinical trial’ publication type includes not only conventional randomized controlled trials, but also pragmatic, real-life and observational studies. The respiratory community is also invited to submit to the Program Director any other peer-reviewed publications that they believe should be considered, providing an abstract and the full paper are submitted in (or translated into) English; however, because of the comprehensive process for literature review, such *ad hoc* submissions have rarely resulted in substantial changes to the report.

Screening and review

After initial screening of articles identified by a cumulative search of the literature by the Editorial Assistant and Chair of the Science Committee, each publication identified by the above search is reviewed for relevance and quality by members of the Science Committee. Each publication is allocated to at least two Committee members, neither of whom may be an author (including co-author) or declare a conflict of interest in relation to the publication. All members receive a copy of all of the abstracts and non-conflicted members have the opportunity to provide comments during the pre-meeting review period. Members evaluate the abstract and, by his/her judgment, the full publication, and answer written questions about whether the scientific data impact on GINA recommendations, and if so, what specific changes should be made. A list of all publications reviewed by the Committee is posted on the GINA website.

Discussion and decisions during Science Committee meetings

During Committee meetings, each publication that was assessed by at least one member to potentially impact on the GINA report is discussed. This process comprises three parts: (1) evaluation of the quality and relevance of the publication; (2) a decision about inclusion of the publication in the report; and (3) (if relevant) discussion about related changes to the report. First, the Committee considers the quality of the study, the reliability of the findings, the interpretation of the results, and the relevance of the study to the GINA report, based on the responses from reviewers and discussion among members of the Committee. During this discussion, an author may be requested to provide clarification or respond to questions relating to the study, but they may not take part in the second phase, during which the Committee decides whether the publication should be included in the GINA report. These decisions to modify the report or its references are made by consensus by Committee members present. If the chair is an author on a publication being reviewed, an alternative chair is appointed to lead the discussion in part 1 and the decision in part 2 for that publication. If the committee resolves to include the publication in the report, the author is permitted to take part in

the third phase that involves discussions about and decisions on changes to the report, including the positioning of the study findings in the report and the way that they would be integrated with existing (or other new) components of the GINA management strategy. These discussions may take place immediately, or over the course of time as new evidence emerges or as other changes to the report are agreed and implemented. The above conflict of interest considerations also apply to members of the GINA Board who ex-officio attend GINA Science Committee meetings.

In 2009, after carrying out two sample reviews using the GRADE system,² GINA decided not to adopt this methodology for its general processes because of the major resource challenges that it would present. This decision also reflected that, unique among evidence based recommendations in asthma, and most other therapeutic areas, GINA conducts an ongoing twice-yearly update of the evidence base for its recommendations. As with all previous GINA reports, levels of evidence are assigned to management recommendations where appropriate. A description of the current criteria is found in Table A, which was developed by the National Heart Lung and Blood Institute. From 2019, GINA is also describing the values and preferences that contributed to major new recommendations.

New therapies and indications

For new therapies, the Committee makes recommendations after approval for asthma by at least one major regulatory agency, but decisions are based on the best available peer-reviewed evidence and not on labeling directives from government regulators. In May 2018, in the context of discussion about new evidence for use of long-term low dose macrolides to reduce exacerbations in moderate-severe asthma, the Science Committee and Board agreed that the Committee may, where relevant, consider making off-label recommendations for existing therapies, provided the Committee is satisfied with the available evidence around safety and efficacy/effectiveness.

Table A. Description of levels of evidence used in this report

Evidence level	Sources of evidence	Definition
A	Randomized controlled trials (RCTs) and meta-analyses. Rich body of data.	Evidence is from endpoints of well designed RCTs, meta-analyses of relevant studies, or strong observational evidence that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	Randomized controlled trials (RCTs) and meta-analyses. Limited body of data.	Evidence is from endpoints of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs or meta-analysis of such RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were under-taken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomized trials. Observational studies.	Evidence is from outcomes of uncontrolled or non-randomized trials or from observational studies.
D	Panel consensus judgment.	This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above listed criteria.

LITERATURE REVIEWED FOR GINA 2019 UPDATE

The GINA report has been updated in 2019 following the routine twice-yearly review of the literature by the GINA Science Committee. The literature searches for 'clinical trial' publication types (see above) and meta-analyses identified a total of 1137 publications, of which 906 were screened out for duplicates, relevance and/or quality. The remaining 231 publications (149 'clinical trials' and 82 meta-analyses) were reviewed by at least two members of the Science Committee; 123 were subsequently discussed at face-to-face meetings in May 2018 in San Diego, USA and in September 2018 in Paris, France. A list of key changes in GINA 2019 can be found starting on p.12, and a tracked changes copy of the 2018 report is archived on the GINA website.

FUTURE CHALLENGES

In spite of laudable efforts to improve asthma care over the past twenty years, many patients globally have not benefited from advances in asthma treatment and often lack even the rudiments of care. Many of the world's population live in areas with inadequate medical facilities and meager financial resources. The GINA Board of Directors recognizes that 'fixed' international guidelines and 'rigid' scientific protocols will not work in many locations. Thus, the recommendations found in this Report must be adapted to fit local practices and the availability of health care resources.

At the most fundamental level, patients in many areas may not have access even to low dose inhaled corticosteroids, which are the cornerstone of care for asthma patients of all severity. More broadly, medications remain the major contributor to the overall costs of asthma management, so the pricing of asthma medications continues to be an issue of urgent need and a growing area of research interest. With budesonide-formoterol now on the World Health Organization essential medicines list, the changes to treatment of mild asthma included in the 2019 report may provide a feasible solution to reduce the risk of severe exacerbations with very low dose treatment.

A challenge for the GINA Board of Directors for the next several years is to continue working with primary health care providers, public health officials and patient support organizations to design, implement, and evaluate asthma care programs to meet local needs in various countries. The Board continues to examine barriers to implementation of asthma management recommendations, especially in primary care settings and in developing countries, and to examine new and innovative approaches that will ensure the delivery of the best possible asthma care. GINA is a partner organization in a program launched in March 2006 by the World Health Organization, the Global Alliance against Chronic Respiratory Diseases (GARD). Through the work of the GINA Board of Directors, and in cooperation with GARD, substantial progress toward better care for all patients with asthma should be achieved in the next decade.

What's new in GINA 2019?

The GINA report has been updated in 2019 following the routine twice-yearly cumulative review of the literature by the GINA Scientific Committee, and major work by GINA members and others over the past 12 years to obtain evidence for feasible and efficacious treatment options for mild asthma. Full details of the changes can be found in the tracked version archived on the GINA website. In summary, the key changes are:

- SABA-only treatment is no longer recommended for treatment of asthma in adults and adolescents. This change was based on strong evidence that SABA-only treatment increases the risk of severe exacerbations and asthma-related death, and that adding any ICS significantly reduces the risk. The rationale is explained on p.49.
- GINA now recommends that all adults and adolescents with asthma should receive either symptom-driven (in mild asthma) or daily inhaled corticosteroid (ICS)-containing controller treatment, to reduce the risk of severe exacerbations and asthma-related death. Evidence-based options are provided for as-needed controller treatment in mild asthma, with a preferred controller for Step 1 (p.49) and Step 2 (p.50) being low dose ICS-formoterol taken as needed for relief of symptoms and before exercise if needed. The evidence and rationale are provided in the text. This population-level risk reduction strategy can be incorporated into personalized asthma management, as seen in the updated main treatment figure (Box 3-5A, p.46). Additional options are provided, including for clinical contexts where ICS-formoterol is not available or affordable.
- Off-label recommendations: the recommendations for long-term azithromycin in moderate-severe asthma, in mild asthma, for as-needed ICS-formoterol or ICS taken whenever SABA is taken (as combination or separate inhalers), are off-label in most countries. Azithromycin does not currently have an indication for long-term use in asthma, but the recommendation was made on the basis of published evidence, and the extensive experience with use of long-term macrolides in other clinical contexts such as bronchiectasis. ICS-formoterol and ICS are currently indicated in most countries only for maintenance treatment or for maintenance and reliever treatment. The new recommendations for mild asthma were made on the basis of the safety concerns about SABA-only treatment, and the fact that ICS and ICS-LABA already have an extensive safety record, and in the case of budesonide-formoterol, no new safety signals were seen in the large new clinical trials in mild asthma. For new medications, GINA still requires a regulatory approval, as well as two good-quality studies in suitable populations, before making a recommendation.
- Recommendations for initial asthma treatment (see Box 3-4, p.45), for stepping down treatment (Box 3-7, p.56) and for prevention of exercise-induced bronchoconstriction (p.79) have been updated, in line with the evidence available with as-needed ICS-formoterol.
- Tiotropium is now approved as add-on therapy for ages 6 years and older. In Step 5 (p.53), add-on tiotropium is one of the 'preferred' controller options, and is shown ahead of consideration of biologics because of the different cost implications. In Step 4 (p.52), add-on tiotropium is positioned as an 'other' controller option rather than a 'preferred' controller option, because there is insufficient evidence for equivalence to ICS-LABA.
- Add-on low dose azithromycin (off-label, as above) is recommended as an option for patients with symptomatic asthma despite moderate-high dose ICS-LABA, after consideration of potential adverse effects (p.53).
- High dose ICS-LABA treatment is now recommended only in Step 5 (previously, Step 4 treatment included moderate-high dose ICS-LABA). Where possible, high ICS doses should be prescribed for only a few months, and the potential for adverse effects should be taken into account.
- Dupilumab (anti-IL4 receptor α) is now recommended as an additional treatment option for patients ≥ 12 years with severe Type 2 asthma or OCS-dependent asthma (p.53, with additional details in Chapter 3E, p.84).
- Maintenance oral corticosteroids (OCS) are not a 'preferred' treatment in Step 5 (p.53), because of the high risk of adverse outcomes.
- The main GINA treatment figure (Box 3-5A, p.46) has been updated to reflect the above changes. It has also been reformatted in landscape orientation so that the arrowed circle describing personalized asthma treatment will always be seen along with the treatment steps. The figure emphasizes that all patients should receive controller treatment, either symptom-driven (in mild asthma) or daily.

- Children 6-11 years: a separate treatment figure is now provided for children ages 6-11 years (Box 3-5B, p.47). The preferred treatment options at Step 3 are medium dose ICS or low dose ICS-LABA, with as-needed SABA. Adherence, inhaler technique and comorbidities should be considered for children who fail to respond. Children should be referred if they have difficult-to-treat or severe asthma, or if the diagnosis is uncertain.
- ICS doses (Box 3-6, p.48): additional explanation of the meaning of low, medium and high doses has been added.
- Difficult-to-treat and severe asthma: previous material has been replaced with Chapter 3E of the report (p.84) which includes the content of the GINA 2019 Pocket Guide and decision tree for the diagnosis and management of difficult-to-treat and severe asthma in adults and adolescents. The Pocket Guide itself, which includes space for writing the eligibility criteria for biologics in your own clinical practice, can be downloaded free for personal use, or purchased in hard or soft copy, from the GINA website.
- Combination medications: in GINA resources, combinations are now referred to as, for example, “ICS-LABA” rather than “ICS/LABA”. This change was made because the meaning of a forward slash (“/”) in common English usage is “or”, and we became aware that “ICS/LABA” was being misinterpreted in some contexts as “ICS OR LABA”. Such an interpretation would obviously be very dangerous.
- SLIT: The description of the population included in a randomized controlled trial of sublingual allergen immunotherapy by Virchow et al has been corrected to align with the study design (p.58).
- Non-pharmacologic interventions: for clinical utility, this material has been moved from the Appendix to the main report (p.60).
- Breathing exercises: a large new study is available, confirming that, although breathing exercises are associated with improved quality of life, there is no improvement in symptom control or exacerbations (p.65). Websites containing videos of breathing exercises that have been used in asthma studies cited in the GINA report are included.
- Allergic bronchopulmonary aspergillosis (ABPA): a new section has been added (p.82).
- Written asthma action plans: additional evidence is now available for the ‘yellow zone’ of written asthma action plans, based on new studies in community patients and in highly adherent children (p.104).
- Severe exacerbations: Follow-up is now recommended to occur within 2 days after an ED visit or hospitalization (p.117).
- For pre-school asthma, additional suggestions are provided for investigating a history of wheezing episodes (p.133)
- In pre-school children, recent studies suggest that clinical and/or inflammatory features may predict better short-term response to ICS, but more studies are needed (p.139). Early referral is recommended if the child fails to respond to controller treatment.
- For exacerbations in pre-school children, OCS are not generally recommended except in emergency department and hospital settings (p.147). Follow-up after ED or hospital admission is recommended within 1-2 working days, and again 3-4 weeks later (p.152).
- For all ages, the importance of confirming the diagnosis of asthma at initial presentation is emphasized, with new data finding that the diagnosis cannot be confirmed in around 30% of people with asthma in the community.
- The asthma APGAR tool for assessment of children, adolescents and adults in primary care is described
- The terms ‘upper airway dysfunction’ and ‘vocal cord dysfunction’ have been replaced with ‘inducible laryngeal obstruction’, consistent with new international taxonomy.
- The term ‘fixed airflow limitation’ has been changed to ‘persistent airflow limitation’, to reflect the fact that such patients may still have some bronchodilator reversibility.
- Vitamin D: Additional evidence is available about the timing of vitamin D in pregnancy and effects on asthma outcomes (p.155).

Peer-reviewed publications about the GINA report

The following articles about the GINA report have been published in peer-reviewed journals since 2014.

Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, Buhl R, Cruz AA, Fleming L, Inoue H, Ko FW-s, Krishnan JA, Levy ML, Lin J, Pedersen SE, Sheikh A, Yorgancioglu A, Boulet L-P. GINA 2019: a fundamental change in asthma management. Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J* 2019; (in press).

Boulet LP, Reddel HK, Bateman EB, Pedersen S, FitzGerald JM and O'Byrne PM. The Global Initiative for Asthma (GINA): 25 years later. *Eur Respir J* 2019 (in press).

Reddel HK. The impact of the Global Initiative for Asthma (GINA): compass, concepts, controversies and challenges. *BRN Rev* 2019; 5: 4-18

Reddel, H. K., Bateman, E. D., Becker, A., Boulet, L. P., Cruz, A. A., Drazen, J. M., Haahtela, T., Hurd, S. S., Inoue, H., de Jongste, J. C., Lemanske, R. F., Jr., Levy, M. L., O'Byrne, P. M., Paggiaro, P., Pedersen, S. E., Pizzichini, E., Soto-Quiroz, M., Szefler, S. J., Wong, G. W., FitzGerald, J. M. A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015; 46: 622-39 (open access; doi 10.1183/13993003.00853-2015).

Reddel HK, Hurd SS, FitzGerald JM. World Asthma Day. GINA 2014: a global asthma strategy for a global problem. *Int J Tuberc Lung Dis* 2014; 18: 505-6 (open access: doi.org/10.5588/ijtld.14.0246)

Boulet LP, FitzGerald JM, Reddel HK. The revised 2014 GINA strategy report: opportunities for change. *Curr Opin Pulm Med* 2015; 21: 1-7

Reddel HK, Levy ML. The GINA asthma strategy report: what's new for primary care? *NPJ Prim Care Respir Med* 2015; 25: 15050 (open access: doi 10.1038/npjpcrm.2015.50)

Chapter 1.

Definition, description, and diagnosis of asthma

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE

KEY POINTS

What is asthma?

- Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. Airflow limitation may later become persistent.
- Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called ‘asthma phenotypes’; however, these do not correlate strongly with specific pathological processes or treatment responses.
- Asthma is usually associated with airway hyperresponsiveness and airway inflammation, but these are not necessary or sufficient to make the diagnosis.

How is asthma diagnosed?

- The diagnosis of asthma is based on the history of characteristic symptom patterns and evidence of variable airflow limitation. This should be documented from bronchodilator reversibility testing or other tests.
- Test before treating, wherever possible, i.e. document the evidence for the diagnosis of asthma before starting controller treatment, as it is often more difficult to confirm the diagnosis afterwards.
- Additional strategies may be needed to confirm the diagnosis of asthma in particular populations, including patients already on controller treatment, the elderly, and those in low-resource settings.

DEFINITION OF ASTHMA

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

This definition was reached by consensus, based on consideration of the characteristics that are typical of asthma before controller treatment is commenced, and that distinguish it from other respiratory conditions. However, airflow limitation may become persistent later in the course of the disease.

DESCRIPTION OF ASTHMA

Asthma is a common, chronic respiratory disease affecting 1–18% of the population in different countries (Appendix Chapter 1). Asthma is characterized by variable symptoms of wheeze, shortness of breath, chest tightness and/or cough, and by variable expiratory airflow limitation. Both symptoms and airflow limitation characteristically vary over time and in intensity. These variations are often triggered by factors such as exercise, allergen or irritant exposure, change in weather, or viral respiratory infections.

Symptoms and airflow limitation may resolve spontaneously or in response to medication, and may sometimes be absent for weeks or months at a time. On the other hand, patients can experience episodic flare-ups (exacerbations) of asthma that may be life-threatening and carry a significant burden to patients and the community (Appendix Chapter 1). Asthma is usually associated with airway hyperresponsiveness to direct or indirect stimuli, and with chronic airway inflammation. These features usually persist, even when symptoms are absent or lung function is normal, but may normalize with treatment.

Asthma phenotypes

Asthma is a heterogeneous disease, with different underlying disease processes. Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called ‘asthma phenotypes’.^{3–5} In patients with more severe asthma, some phenotype-guided treatments are available. However, to date, no strong relationship has

been found between specific pathological features and particular clinical patterns or treatment responses.⁶ More research is needed to understand the clinical utility of phenotypic classification in asthma.

Many clinical phenotypes of asthma have been identified.³⁻⁵ Some of the most common include:

- **Allergic asthma:** this is the most easily recognized asthma phenotype, which often commences in childhood and is associated with a past and/or family history of allergic disease such as eczema, allergic rhinitis, or food or drug allergy. Examination of the induced sputum of these patients before treatment often reveals eosinophilic airway inflammation. Patients with this asthma phenotype usually respond well to inhaled corticosteroid (ICS) treatment.
- **Non-allergic asthma:** some patients have asthma that is not associated with allergy. The cellular profile of the sputum of these patients may be neutrophilic, eosinophilic or contain only a few inflammatory cells (paucigranulocytic). Patients with non-allergic asthma often demonstrate less short-term response to ICS.
- **Adult-onset (late-onset) asthma:** some adults, particularly women, present with asthma for the first time in adult life. These patients tend to be non-allergic, and often require higher doses of ICS or are relatively refractory to corticosteroid treatment. Occupational asthma (i.e. asthma due to exposures at work) should be ruled out in patients presenting with adult-onset asthma.
- **Asthma with persistent airflow limitation:** some patients with long-standing asthma develop airflow limitation that is persistent or incompletely reversible. This is thought to be due to airway wall remodeling.
- **Asthma with obesity:** some obese patients with asthma have prominent respiratory symptoms and little eosinophilic airway inflammation.

Additional information can be found in Appendix Chapter 2 about factors predisposing to the development of asthma, and in Appendix Chapter 3 about pathophysiological and cellular mechanisms of asthma.

MAKING THE INITIAL DIAGNOSIS

Making the diagnosis of asthma,⁷ as shown in Box 1-1 (p18) is based on identifying both a characteristic pattern of respiratory symptoms such as wheezing, shortness of breath (dyspnea), chest tightness or cough, and variable expiratory airflow limitation. The pattern of symptoms is important, as respiratory symptoms may be due to acute or chronic conditions other than asthma. If possible, the evidence supporting a diagnosis of asthma (Box 1-2, p5) should be documented when the patient first presents, as the features that are characteristic of asthma may improve spontaneously or with treatment; as a result, it is often more difficult to confirm a diagnosis of asthma once the patient has been started on controller treatment.

Patterns of respiratory symptoms that are characteristic of asthma

The following features are typical of asthma and, if present, *increase* the probability that the patient has asthma:⁷

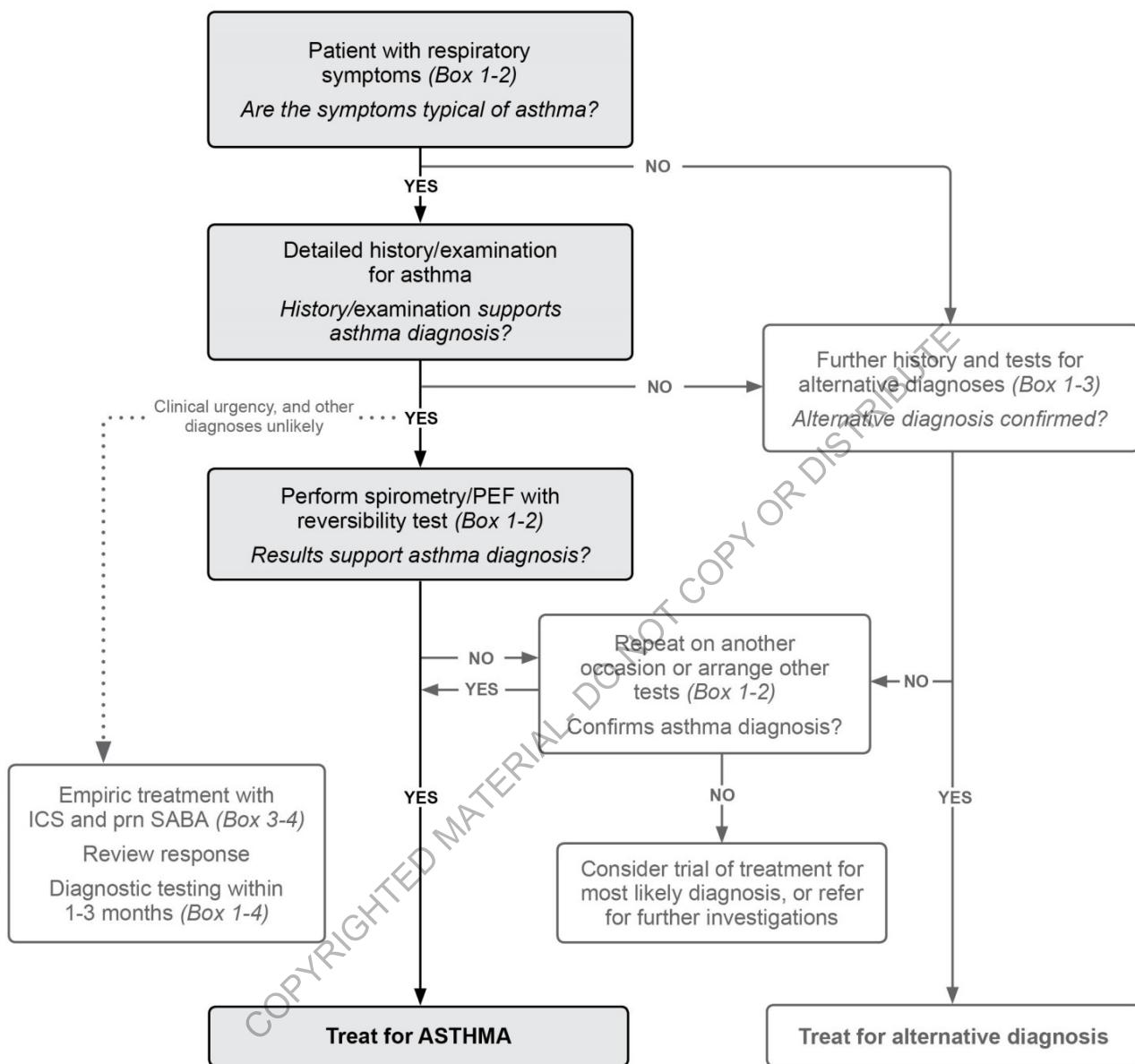
More than one symptom (wheeze, shortness of breath, cough, chest tightness), especially in adults

- Symptoms often worse at night or in the early morning
- Symptoms vary over time and in intensity
- Symptoms are triggered by viral infections (colds), exercise, allergen exposure, changes in weather, laughter, or irritants such as car exhaust fumes, smoke or strong smells.

The following features *decrease* the probability that respiratory symptoms are due to asthma:

- Isolated cough with no other respiratory symptoms (see p.25)
- Chronic production of sputum
- Shortness of breath associated with dizziness, light-headedness or peripheral tingling (paresthesia)
- Chest pain
- Exercise-induced dyspnea with noisy inspiration.

Box 1-1. Diagnostic flowchart for clinical practice – initial presentation



ICS: inhaled corticosteroids; PEF: peak expiratory flow (highest of three readings). When measuring PEF, use the same meter each time as the value may vary by up to 20% between different meters; prn: as-needed; SABA: short-acting beta₂-agonist.

Bronchodilator reversibility may be lost during severe exacerbations or viral infections, and in long-standing asthma. If bronchodilator reversibility is not found at initial presentation, the next step depends on the availability of tests and the clinical urgency of need for treatment. See Box 1-4 for diagnosis of asthma in patients already taking controller treatment.

Box 1-2. Diagnostic criteria for asthma in adults, adolescents, and children 6–11 years

DIAGNOSTIC FEATURE	CRITERIA FOR MAKING THE DIAGNOSIS OF ASTHMA
1. History of variable respiratory symptoms	
Wheeze, shortness of breath, chest tightness and cough Descriptors may vary between cultures and by age, e.g. children may be described as having heavy breathing	<ul style="list-style-type: none"> Generally more than one type of respiratory symptom (in adults, isolated cough is seldom due to asthma) Symptoms occur variably over time and vary in intensity Symptoms are often worse at night or on waking Symptoms are often triggered by exercise, laughter, allergens, cold air Symptoms often appear or worsen with viral infections
2. Confirmed variable expiratory airflow limitation	
Documented excessive variability in lung function* (one or more of the tests below) AND documented expiratory airflow limitation*	<p>The greater the variations, or the more occasions excess variation is seen, the more confident the diagnosis</p> <p>At a time when FEV₁ is reduced, confirm that FEV₁/FVC is reduced (it is usually >0.75–0.80 in adults, >0.90 in children⁸)</p>
Positive bronchodilator (BD) reversibility test* (more likely to be positive if BD medication is withheld before test: SABA ≥4 hours, LABA ≥15 hours)	<p>Adults: increase in FEV₁ of >12% and >200 mL from baseline, 10–15 minutes after 200–400 mcg albuterol or equivalent (greater confidence if increase is ≥15% and >400 mL).</p> <p>Children: increase in FEV₁ of >12% predicted</p>
Excessive variability in twice-daily PEF over 2 weeks*	<p>Adults: average daily diurnal PEF variability >10%**</p> <p>Children: average daily diurnal PEF variability >13%**</p>
Significant increase in lung function after 4 weeks of anti-inflammatory treatment	<p>Adults: increase in FEV₁ by >12% and >200 mL (or PEF[†] by >20%) from baseline after 4 weeks of treatment, outside respiratory infections</p>
Positive exercise challenge test*	<p>Adults: fall in FEV₁ of >10% and >200 mL from baseline</p> <p>Children: fall in FEV₁ of >12% predicted, or PEF >15%</p>
Positive bronchial challenge test (usually only performed in adults)	<p>Fall in FEV₁ from baseline of ≥20% with standard doses of methacholine or histamine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge</p>
Excessive variation in lung function between visits* (less reliable)	<p>Adults: variation in FEV₁ of >12% and >200 mL between visits, outside of respiratory infections</p> <p>Children: variation in FEV₁ of >12% in FEV₁ or >15% in PEF[†] between visits (may include respiratory infections)</p>

BD: bronchodilator (short-acting SABA or rapid-acting LABA); FEV₁: forced expiratory volume in 1 second; LABA: long-acting beta₂-agonist; PEF: peak expiratory flow (highest of three readings); SABA: short-acting beta₂-agonist. See Box 1-4 for diagnosis in patients already taking controller treatment.

*These tests can be repeated during symptoms or in the early morning. **Daily diurnal PEF variability is calculated from twice daily PEF as ([day's highest minus day's lowest] / mean of day's highest and lowest), and averaged over one week. [†]For PEF, use the same meter each time, as PEF may vary by up to 20% between different meters. BD reversibility may be lost during severe exacerbations or viral infections,⁹ and airflow limitation may become persistent over time. If bronchodilator reversibility is not present at initial presentation, the next step depends on the availability of other tests and the urgency of the need for treatment. In a situation of clinical urgency, asthma treatment may be commenced and diagnostic testing arranged within the next few weeks (Box 1-4, p.23), but other conditions that can mimic asthma (Box 1-3) should be considered, and the diagnosis of asthma confirmed as soon as possible.

Why is it important to confirm the diagnosis of asthma?

This is important to avoid unnecessary over-treatment, and to avoid missing other important diagnoses. In adults with an asthma diagnosis in the last 5 years, one-third could not be confirmed as having asthma after repeated testing over 12 months and staged withdrawal of controller treatment. The diagnosis of asthma was less likely to be confirmed in patients who had not had lung function testing performed at the time of initial diagnosis. Some patients (2%) had serious cardiorespiratory conditions that had been misdiagnosed as asthma.¹⁰

History and family history

Commencement of respiratory symptoms in childhood, a history of allergic rhinitis or eczema, or a family history of asthma or allergy, increases the probability that the respiratory symptoms are due to asthma. However, these features are not specific for asthma and are not seen in all asthma phenotypes. Patients with allergic rhinitis or atopic dermatitis should be asked specifically about respiratory symptoms.

Physical examination

Physical examination in people with asthma is often normal. The most frequent abnormality is expiratory wheezing (rhonchi) on auscultation, but this may be absent or only heard on forced expiration. Wheezing may also be absent during severe asthma exacerbations, due to severely reduced airflow (so called ‘silent chest’), but at such times, other physical signs of respiratory failure are usually present. Wheezing may also be heard with inducible laryngeal obstruction, chronic obstructive pulmonary disease (COPD), respiratory infections, tracheomalacia, or inhaled foreign body. Crackles (crepitations) and inspiratory wheezing are not features of asthma. Examination of the nose may reveal signs of allergic rhinitis or nasal polyposis.

Lung function testing to document variable expiratory airflow limitation

Asthma is characterized by variable expiratory airflow limitation, i.e. expiratory lung function varies over time and in magnitude to a greater extent than in healthy populations. In asthma, lung function may vary between completely normal and severely obstructed in the same patient. Poorly controlled asthma is associated with greater variability in lung function than well-controlled asthma.⁹

Lung function testing should be carried out by well-trained operators with well-maintained and regularly calibrated equipment.^{7,11} Forced expiratory volume in 1 second (FEV₁) from spirometry is more reliable than peak expiratory flow (PEF). If PEF is used, the same meter should be used each time, as measurements may differ from meter to meter by up to 20%.¹¹

A reduced FEV₁ may be found with many other lung diseases (or poor spirometric technique), but a reduced ratio of FEV₁ to FVC indicates airflow limitation. From population studies,⁸ the FEV₁/FVC ratio is usually greater than 0.75 to 0.80 in adults, and usually greater than 0.90 in children. Any values less than these suggest airflow limitation. Many spirometers now include multi-ethnic age-specific predicted values.⁸

In clinical practice, once an obstructive defect has been confirmed, variation in airflow limitation is generally assessed from variation in FEV₁ or PEF. ‘Variability’ refers to improvement and/or deterioration in symptoms and lung function. Excessive variability may be identified over the course of one day (diurnal variability), from day to day, from visit to visit, or seasonally, or from a reversibility test. ‘Reversibility’ generally refers to rapid improvements in FEV₁ (or PEF), measured within minutes after inhalation of a rapid-acting bronchodilator such as 200–400 mcg salbutamol,¹² or more sustained improvement over days or weeks after the introduction of effective controller treatment such as ICS.¹²

In a patient with typical respiratory symptoms, obtaining evidence of excessive variability in expiratory lung function is an essential component of the diagnosis of asthma. Some specific examples are:

- An increase in lung function after administration of a bronchodilator, or after a trial of controller treatment.
- A decrease in lung function after exercise or during a bronchial provocation test.
- Variation in lung function beyond the normal range when it is repeated over time, either on separate visits, or on home monitoring over at least 1–2 weeks.

Specific criteria for demonstrating excessive variability in expiratory lung function are listed in Box 1-2 (p.19). A decrease in lung function during a respiratory infection, while commonly seen in asthma, does not necessarily indicate that a person has asthma, as it may also be seen in otherwise healthy individuals or people with COPD.

Additional information about tests for diagnosis of asthma can be found in Appendix Chapter 4.

How much variation in expiratory airflow is consistent with asthma?

There is overlap in bronchodilator reversibility and other measures of variation between health and disease.¹³ In a patient with respiratory symptoms, the greater the variations in their lung function, or the more times excess variation is seen, the more likely the diagnosis is to be asthma (Box 1-2, p.19). Generally, in adults with respiratory symptoms typical of asthma, an increase or decrease in FEV₁ of >12% and >200 mL from baseline, or (if spirometry is not available) a change in PEF of at least 20%, is accepted as being consistent with asthma.

Diurnal PEF variability is calculated from twice daily readings as the daily amplitude percent mean, i.e. ([Day's highest – day's lowest]/mean of day's highest and lowest) x 100, then the average of each day's value is calculated over 1–2 weeks. The upper 95% confidence limit of diurnal variability (amplitude percent mean) from twice daily readings is 9% in healthy adults,¹⁴ and 12.3% in healthy children,¹⁵ so in general, diurnal variability >10% for adults and >13% for children is regarded as excessive.

If FEV₁ is within the predicted normal range when the patient is experiencing symptoms, this reduces the probability that the symptoms are due to asthma. However, patients whose baseline FEV₁ is >80% predicted can have a clinically important increase in lung function with bronchodilator or controller treatment. Predicted normal ranges (especially for PEF) have limitations, so the patient's own best reading ('personal best') is recommended as their 'normal' value.

When can variable airflow limitation be documented?

If possible, evidence of variable airflow limitation should be documented before treatment is started. This is because variability usually decreases with treatment as lung function improves. In addition, any increase in lung function after initiating controller treatment can help to confirm the diagnosis of asthma. Bronchodilator reversibility may not be present between symptoms, during viral infections or if the patient has used a beta₂-agonist within the previous few hours; and in some patients airflow limitation may become persistent or irreversible over time.

If spirometry is not available, or variable airflow limitation is not documented, a decision about whether to investigate further or start controller treatment immediately depends on clinical urgency and access to other tests. Box 1-4 (p.23) describes how to confirm the diagnosis of asthma in a patient already taking controller treatment.

Other tests

Bronchial provocation tests

One option for documenting variable airflow limitation is to refer the patient for bronchial provocation testing to assess airway hyperresponsiveness. Challenge agents include inhaled methacholine, histamine, exercise,¹⁶ eucapnic voluntary hyperventilation or inhaled mannitol. These tests are moderately sensitive for a diagnosis of asthma but have limited specificity;^{17,18} for example, airway hyperresponsiveness to inhaled methacholine has been described in patients with allergic rhinitis,¹⁹ cystic fibrosis,²⁰ bronchopulmonary dysplasia²¹ and COPD.²² This means that a negative test in a patient not taking ICS can help to exclude asthma, but a positive test does not always mean that a patient has asthma – the pattern of symptoms (Box 1-2, p.19) and other clinical features (Box 1-3, p.23) must also be taken into account.

Allergy tests

The presence of atopy increases the probability that a patient with respiratory symptoms has allergic asthma, but this is not specific for asthma nor is it present in all asthma phenotypes. Atopic status can be identified by skin prick testing or by measuring the level of specific immunoglobulin E (sIgE) in serum. Skin prick testing with common environmental allergens is simple and rapid to perform and, when performed by an experienced tester with standardized extracts, is inexpensive and has a high sensitivity. Measurement of sIgE is no more reliable than skin tests and is more expensive, but may be preferred for uncooperative patients, those with widespread skin disease, or if the history suggests a risk of

anaphylaxis.²³ The presence of a positive skin test or positive sIgE, however, does not mean that the allergen is causing symptoms - the relevance of allergen exposure and its relation to symptoms must be confirmed by the patient's history.

Does exhaled nitric oxide have a role in the diagnosis of asthma?

The fractional concentration of exhaled nitric oxide (FENO) is modestly associated with levels of sputum and blood eosinophils.²⁴ FENO has not been established as useful for ruling in or ruling out a diagnosis of asthma, as defined on p.16. FENO is higher in asthma that is characterized by Type 2 airway inflammation²⁵ but it is also elevated in non-asthma conditions (e.g. eosinophilic bronchitis, atopy, allergic rhinitis, eczema), and it is not elevated in some asthma phenotypes (e.g. neutrophilic asthma). FENO is lower in smokers and during bronchoconstriction²⁶ and the early phases of allergic response;²⁷ it may be increased or decreased during viral respiratory infections.²⁶

Although in adult steroid-naïve patients (mainly non-smokers) with non-specific respiratory symptoms, a finding of FENO >50 parts per billion (ppb) was associated with a good short-term response to ICS,²⁸ There are no long-term studies examining the safety (with regard to risk of exacerbations) of withholding ICS in patients with low initial FENO. Consequently, in patients with a diagnosis or suspected diagnosis of asthma, FENO cannot be recommended at present for deciding against treatment with ICS.

CONFIRMING THE DIAGNOSIS OF ASTHMA IN PATIENTS ALREADY TAKING CONTROLLER TREATMENT

If the basis of a patient's diagnosis of asthma has not previously been documented, confirmation with objective testing should be sought. Many patients (25–35%) with a diagnosis of asthma in primary care cannot be confirmed as having asthma.^{10,29-32}

The process for confirming the diagnosis in patients already on controller treatment depends on the patient's symptoms and lung function (Box 1-4). In some patients, this may include a trial of either a lower or a higher dose of controller treatment. If the diagnosis of asthma cannot be confirmed, refer the patient for expert investigation and diagnosis.

For some patients, it may be necessary to step down the controller treatment in order to confirm the diagnosis of asthma. The process is described in Box 1-5.

Box 1-3. Steps for confirming the diagnosis of asthma in a patient already taking controller treatment

Current status	Steps to confirm the diagnosis of asthma
Variable respiratory symptoms and variable airflow limitation	Diagnosis of asthma is confirmed. Assess the level of asthma control (Box 2-2, p.31) and review controller treatment (Box 3-5, p.46).
Variable respiratory symptoms but no variable airflow limitation	Repeat BD reversibility test again after withholding BD (SABA: 4 hours; LABA: 12 or 24 hours*) or during symptoms. If normal, consider alternative diagnoses (Box 1-3, p.23). <i>If FEV₁ is >70% predicted:</i> consider a bronchial provocation test. If negative, consider stepping down controller treatment (see Box 1-5) and reassess in 2–4 weeks <i>If FEV₁ is <70% predicted:</i> consider stepping up controller treatment for 3 months (Box 3-5), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation
Few respiratory symptoms, normal lung function, and no variable airflow limitation	Repeat BD reversibility test again after withholding BD (SABA: 4 hours; LABA: 12 or 24 hours*) or during symptoms. If normal, consider alternative diagnoses (Box 1-3). Consider stepping down controller treatment (see Box 1-5): <ul style="list-style-type: none">• <i>If symptoms emerge and lung function falls:</i> asthma is confirmed. Step up controller treatment to previous lowest effective dose.• <i>If no change in symptoms or lung function at lowest controller step:</i> consider ceasing controller, and monitor patient closely for at least 12 months (Box 3-7).
Persistent shortness of breath and persistent airflow limitation	Consider stepping up controller treatment for 3 months (Box 3-5, p.46), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation. Consider asthma–COPD overlap (Chapter 5, p.119).

BD: bronchodilator; LABA: long-acting beta₂-agonist; SABA: short-acting beta₂-agonist. * Depending on duration of action of the LABA

Box 1-4. How to step down controller treatment to help confirm the diagnosis of asthma

1. ASSESS
<ul style="list-style-type: none"> • Document the patient's current status including asthma control (Box 2-2, p.31) and lung function. If the patient has risk factors for asthma exacerbations (Box 2-2B), do not step down treatment without close supervision. • Choose a suitable time (e.g. no respiratory infection, not going away on vacation, not pregnant). • Provide a written asthma action plan (Box 4-2, p.107) so the patient knows how to recognize and respond if symptoms worsen. Ensure they have enough medication to resume their previous dose if their asthma worsens.
2. ADJUST
<ul style="list-style-type: none"> • Show the patient how to reduce their ICS dose by 25–50%, or stop extra controller (e.g. LABA, leukotriene receptor antagonist) if being used (Box 3-7, p.56). Schedule a review visit for 2–4 weeks.
3. REVIEW RESPONSE
<ul style="list-style-type: none"> • Repeat assessment of asthma control and lung function tests in 2–4 weeks (Box 1-2, p.19). • If symptoms increase and variable airflow limitation is confirmed after stepping down treatment, the diagnosis of asthma is confirmed. The controller dose should be returned to the lowest previous effective dose. • If, after stepping down to a low dose controller treatment, symptoms do not worsen and there is still no evidence of variable airflow limitation, consider ceasing controller treatment and repeating asthma control assessment and lung function tests in 2–3 weeks, but follow the patient for at least 12 months

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in a patient with suspected asthma varies with age (Box 1-3). Any of these alternative diagnoses may also be found *together with* asthma.

Box 1-5. Differential diagnosis of asthma in adults, adolescents and children 6–11 years

Age	Symptoms	Condition
6–11 years	Sneezing, itching, blocked nose, throat-clearing Sudden onset of symptoms, unilateral wheeze Recurrent infections, productive cough Recurrent infections, productive cough, sinusitis Cardiac murmurs Pre-term delivery, symptoms since birth Excessive cough and mucus production, gastrointestinal symptoms	Chronic upper airway cough syndrome Inhaled foreign body Bronchiectasis Primary ciliary dyskinesia Congenital heart disease Bronchopulmonary dysplasia Cystic fibrosis
12–39 years	Sneezing, itching, blocked nose, throat-clearing Dyspnea, inspiratory wheezing (stridor) Dizziness, paresthesia, sighing Productive cough, recurrent infections Excessive cough and mucus production Cardiac murmurs Shortness of breath, family history of early emphysema Sudden onset of symptoms	Chronic upper airway cough syndrome Inducible laryngeal obstruction Hyperventilation, dysfunctional breathing Bronchiectasis Cystic fibrosis Congenital heart disease Alpha ₁ -antitrypsin deficiency Inhaled foreign body
40+ years	Dyspnea, inspiratory wheezing (stridor) Dizziness, paresthesia, sighing Cough, sputum, dyspnea on exertion, smoking or noxious exposure Productive cough, recurrent infections Dyspnea with exertion, nocturnal symptoms Treatment with angiotensin converting enzyme (ACE) inhibitor Dyspnea with exertion, non-productive cough, finger clubbing Sudden onset of dyspnea, chest pain Dyspnea, unresponsive to bronchodilators	Inducible laryngeal obstruction Hyperventilation, dysfunctional breathing COPD* Bronchiectasis Cardiac failure Medication-related cough Parenchymal lung disease Pulmonary embolism Central airway obstruction
All ages	Chronic cough, hemoptysis, dyspnea; and/or fatigue, fever, (night) sweats, anorexia, weight loss	Tuberculosis

*For more detail, see Chapter 5 (p.119). Any of the above conditions may also contribute to respiratory symptoms in patients with confirmed asthma.

HOW TO MAKE THE DIAGNOSIS OF ASTHMA IN OTHER CONTEXTS

Patients presenting with non-productive cough as the only respiratory symptom

Diagnoses to be considered are so-called 'cough variant asthma', cough induced by angiotensin converting enzyme (ACE) inhibitors, gastroesophageal reflux, chronic upper airway cough syndrome (often called 'postnasal drip'), chronic sinusitis, and inducible laryngeal obstruction.^{33,34} Patients with cough-variant asthma have chronic cough as their principal, if not only, symptom, associated with airway hyperresponsiveness. It is often more problematic at night. Lung function may be normal, and for these patients, documentation of variability in lung function (Box 1-2, p.19) is important.³⁵ Cough-variant asthma must be distinguished from eosinophilic bronchitis in which patients have cough and sputum eosinophils but normal spirometry and airway responsiveness.³⁵

Occupational asthma and work-aggravated asthma

Asthma acquired in the workplace is frequently missed. Asthma may be induced or (more commonly) aggravated by exposure to allergens or other sensitizing agents at work, or sometimes from a single, massive exposure. Occupational rhinitis may precede asthma by up to a year and early diagnosis is essential, as persistent exposure is associated with worse outcomes.³⁶

An estimated 5–20% of new cases of adult-onset asthma can be attributed to occupational exposure.³⁶ Adult-onset asthma requires a systematic inquiry about work history and exposures, including hobbies.³⁷ Asking patients whether their symptoms improve when they are away from work (weekends or vacation) is an essential screening question.³⁸ It is important to confirm the diagnosis of occupational asthma objectively as it may lead to the patient changing their occupation, which may have legal and socioeconomic implications. Specialist referral is usually necessary, and frequent PEF monitoring at and away from work is often used to help confirm the diagnosis. Further information about occupational asthma is found in Chapter 3 (p.81) and in specific guidelines.³⁶

Athletes

The diagnosis of asthma in athletes should be confirmed by lung function tests, usually with bronchial provocation testing.¹⁶ Conditions that may either mimic or be associated with asthma, such as rhinitis, laryngeal disorders (e.g. inducible laryngeal obstruction³⁴), dysfunctional breathing, cardiac conditions and over-training, must be excluded.³⁹

Pregnant women

Pregnant women and women planning a pregnancy should be asked whether they have asthma so that appropriate advice about asthma management and medications can be given (see Chapter 3: *Managing asthma in special populations or settings*, p.79).⁴⁰ If objective confirmation of the diagnosis is needed, it would not be advisable to carry out a bronchial provocation test or to step down controller treatment until after delivery.

The elderly

Asthma is frequently undiagnosed in the elderly,⁴¹ due to poor perception of airflow limitation; acceptance of dyspnea as being 'normal' in old age; lack of fitness; and reduced physical activity. The presence of comorbid diseases also complicates the diagnosis. In a large population based survey of asthma patients older than 65 years, factors associated with a history of asthma hospitalization included co-diagnosis of COPD, coronary artery disease, depression, diabetes mellitus, and difficulty accessing medications or clinical care because of cost.⁴² Symptoms of wheezing, breathlessness and cough that are worse on exercise or at night can also be caused by cardiovascular disease or left ventricular failure, which are common in this age group. A careful history and physical examination, combined with an electrocardiogram and chest X-ray, will assist in the diagnosis.⁴³ Measurement of plasma brain natriuretic polypeptide (BNP) and assessment of cardiac function with echocardiography may also be helpful.⁴⁴ In older people with a history of smoking or biomass fuel exposure, COPD and overlapping asthma and COPD (asthma–COPD overlap) should be considered (Chapter 5, p.119).

Smokers and ex-smokers

Asthma and COPD may be difficult to distinguish in clinical practice, particularly in older patients and smokers and ex-smokers, and these conditions may overlap (asthma-COPD overlap). The *Global Strategy for Diagnosis, Management and Prevention of COPD (GOLD)*⁴⁵ defines COPD on the basis of chronic respiratory symptoms, exposure to a risk factor such as smoking, and post-bronchodilator FEV₁/FVC <0.7. Clinically important bronchodilator reversibility (>12% and >200 mL) is often found in COPD.⁴⁶ Low diffusion capacity is more common in COPD than asthma. The history and pattern of symptoms and past records can help to distinguish these patients from those with long-standing asthma who have developed persistent airflow limitation (see Chapter 5, p.119). Uncertainty in the diagnosis should prompt early referral for specialized investigation and treatment recommendations, as patients with asthma-COPD overlap have worse outcomes than those with asthma or COPD alone.⁴⁷

Obese patients

While asthma is more common in obese than non-obese people,⁴⁸ respiratory symptoms associated with obesity can mimic asthma. In obese patients with dyspnea on exertion, it is important to confirm the diagnosis of asthma with objective measurement of variable airflow limitation. One study found that non-obese patients were just as likely to be over-diagnosed with asthma as obese patients (around 30% in each group).²⁹ Another study found both over- and under-diagnosis of asthma in obese patients.⁴⁹

Low resource settings

Communities with limited resources are found not only in low and middle income countries (LMIC), but also in affluent nations. In low resource settings, diagnosis of respiratory symptoms commences with a symptom-based or syndromic approach. Questions about duration of symptoms and about fever, chills, sweats, weight loss, pain on breathing and hemoptysis help to distinguish chronic respiratory infections such as tuberculosis, HIV/AIDS and parasitic or fungal lung diseases from asthma and COPD.^{50,51} Variable airflow limitation can be confirmed using PEF meters; these have been proposed by the World Health Organization as essential tools in the Package of Essential Non-communicable Diseases Interventions.⁵² In low resource settings, documentation of symptoms and PEF before and after a therapeutic trial with as-needed SABA and regular ICS, often together with a 1 week course of oral corticosteroids, can help to confirm the diagnosis of asthma before long-term treatment is commenced.⁵³

In low and middle-income countries, a comparison between the prevalence of asthma symptoms and of a doctor's diagnosis of asthma among adolescents and young adults suggests that, at the population level, as many as 50% of cases may be undiagnosed.^{54,55} In a recent review, it has been reported that, among doctors working in primary care health services, the precision of the diagnosis of asthma is far from ideal, varying from 54% under-diagnosis to 34% over-diagnosis.⁵⁶ Poverty is commonly associated with restrictive spirometry, so where possible, both FEV₁ and FVC should be recorded.⁵⁷ These observations demonstrate how important it is to build capacity of primary care physicians for asthma diagnosis and management.

Chapter 2.
Assessment of
asthma

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE

KEY POINTS

About asthma control and severity

- The level of asthma control is the extent to which the features of asthma can be observed in the patient, or have been reduced or removed by treatment.
- Asthma control is assessed in two domains: *symptom control* and *future risk* of adverse outcomes. Poor symptom control is burdensome to patients and increases the risk of exacerbations, but patients with apparently mild asthma, i.e. with few or no symptoms, can still have severe exacerbations.
- Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations. It is important to distinguish between severe asthma and asthma that is uncontrolled, e.g. due to incorrect inhaler technique and/or poor adherence.

How to assess a patient with asthma

- Assess symptom control from the frequency of daytime and night-time asthma symptoms and reliever use, and from activity limitation. Symptom control tools include Asthma Control Test and Asthma Control Questionnaire.
- Assess the patient's future risk for exacerbations, even when symptom control is good. Identified risk factors for exacerbations that are independent of symptom control include a history of ≥ 1 exacerbations in the previous year, poor adherence, incorrect inhaler technique, low lung function, smoking, and blood eosinophilia.
- Also assess risk factors for persistent airflow limitation and medication side-effects, treatment issues such as inhaler technique and adherence, and comorbidities, and ask the patient about their asthma goals
- Once the diagnosis of asthma has been made, lung function is most useful as an indicator of future risk. It should be recorded at diagnosis, 3–6 months after starting treatment, and periodically thereafter. Discordance between symptoms and lung function should prompt further investigation.

OVERVIEW

For every patient, assessment of asthma should include the assessment of asthma control (both symptom control and future risk of adverse outcomes), treatment issues particularly inhaler technique and adherence, and any comorbidities that could contribute to symptom burden and poor quality of life (Box 2-1, p29). Lung function, particularly forced expiratory volume in 1 second (FEV₁) as a percentage of predicted, is an important part of the assessment of future risk.

What is meant by 'asthma control'?

The level of asthma control is the extent to which the manifestations of asthma can be observed in the patient, or have been reduced or removed by treatment.^{14,58} It is determined by the interaction between the patient's genetic background, underlying disease processes, the treatment that they are taking, environment, and psychosocial factors.⁵⁸

Asthma control has two domains: symptom control (previously called 'current clinical control') and future risk of adverse outcomes (Box 2-2, p.31). Both should always be assessed. Lung function is an important part of the assessment of future risk; it should be measured at the start of treatment, after 3–6 months of treatment (to identify the patient's personal best), and periodically thereafter for ongoing risk assessment.

How to describe a patient's asthma control

Asthma control should be described in terms of both symptom control and future risk domains, for example:

Ms X has good asthma symptom control, but she is at increased risk of future exacerbations because she has had a severe exacerbation within the last year.

Mr Y has poor asthma symptom control. He also has several additional risk factors for future exacerbations including low lung function, current smoking, and poor medication adherence.

What does the term ‘asthma control’ mean to patients?

Many studies describe discordance between the patient’s and health provider’s assessment of the patient’s level of asthma control. This does not necessarily mean that patients ‘over-estimate’ their level of control or ‘under-estimate’ its severity, but that patients understand and use the word ‘control’ differently from health professionals, e.g. based on how quickly their symptoms resolve when they take reliever medication.^{58,59} If the term ‘asthma control’ is used with patients, the meaning should always be explained.

Box 2-1. Assessment of asthma in adults, adolescents, and children 6–11 years

1. Assess asthma control = symptom control and future risk of adverse outcomes

- Assess symptom control over the last 4 weeks (Box 2-2A)
- Identify any other risk factors for exacerbations, persistent airflow limitation or side-effects (Box 2-2B)
- Measure lung function at diagnosis/start of treatment, 3–6 months after starting controller treatment, then periodically

2. Assess treatment issues

- Document the patient’s current treatment step (Box 3-5, p.46)
 - Watch inhaler technique, assess adherence and side-effects
 - Check that the patient has a written asthma action plan
 - Ask about the patient’s attitudes and goals for their asthma and medications

3. Assess comorbidities

- Rhinitis, rhinosinusitis, gastroesophageal reflux, obesity, obstructive sleep apnea, depression and anxiety can contribute to symptoms and poor quality of life, and sometimes to poor asthma control

ASSESSING ASTHMA SYMPTOM CONTROL

Asthma symptoms such as wheeze, chest tightness, shortness of breath and cough typically vary in frequency and intensity, and contribute to the burden of asthma for the patient. Poor symptom control is also strongly associated with an increased risk of asthma exacerbations.^{60–62}

Asthma symptom control should be assessed at every opportunity, including during routine prescribing or dispensing. Directed questioning is important, as the frequency or severity of symptoms that patients regard as unacceptable or bothersome may vary from current recommendations about the goals of asthma treatment, and differs from patient to patient. For example, despite having low lung function, a person with a sedentary lifestyle may not experience bothersome symptoms and so may appear to have good symptom control.

To assess symptom control (Box 2-2A) ask about the following in the past four weeks: frequency of asthma symptoms (days per week), any night waking due to asthma or limitation of activity, and frequency of short-acting b₂-agonist (SABA) reliever use for relief of symptoms. In general, do not include reliever taken before exercise, since this is often routine.

Asthma symptom control tools for adults and adolescents

Simple screening tools: these can be used in primary care to quickly identify patients who need more detailed assessment. Examples include the consensus-based GINA symptom control tool (Part A, Box 2-2A). This classification correlates with assessments made using numerical asthma control scores.^{63,64} It can be used, together with a risk assessment (Box 2-2B), to guide treatment decisions (Box 3-5, p.46). Other examples are the Primary Care Asthma Control Screening Tool (PACS),⁶⁵ and the 30-second Asthma Test, which also includes time off work/school.⁶⁶

Categorical symptom control tools: examples include the consensus-based ‘Royal College of Physicians (RCP) Three Questions’ tool,⁶⁷ which asks about difficulty sleeping, daytime symptoms and activity limitation due to asthma in the previous month. Another example is the Asthma APGAR tool which includes a patient-completed asthma control assessment covering 5 domains: activity limitations, daytime and nighttime symptom frequency (based on US criteria for frequency of night waking), triggers, adherence, and patient-perceived response to treatment. This assessment is linked to a care algorithm for identifying problems and adjusting treatment up or down. A study in the US showed that introduction of the Asthma APGAR tools for patients aged 5–45 in primary care improved rates of asthma control; reduced asthma-related urgent care, and hospital visits; and increased practices’ adherence to asthma management guidelines.⁶⁸

Numerical ‘asthma control’ tools: these tools provide scores and cut points to distinguish different levels of symptom control, validated against health care provider assessment. Many translations are available. These scores may be useful for assessing patient progress; they are commonly used in clinical research, but may be subject to copyright restrictions. Numerical asthma control tools are more sensitive to change in symptom control than categorical tools.⁶³

Examples of numerical asthma control tools for assessing symptom control are:

- *Asthma Control Questionnaire (ACQ).*^{69,70} Scores range from 0–6 (higher is worse). A score of 0.0–0.75 is classified as well-controlled asthma; 0.75–1.5 as a ‘grey zone’; and >1.5 as poorly controlled asthma. The ACQ score is calculated as the average of 5, 6 or 7 items: all versions of the ACQ include five symptom questions; ACQ-6 includes reliever use; and in ACQ-7, a score for pre-bronchodilator FEV₁ is averaged with symptom and reliever items. The minimum clinically important difference is 0.5.⁷¹
- *Asthma Control Test (ACT).*^{64,72,73} Scores range from 5–25 (higher is better). Scores of 20–25 are classified as well-controlled asthma; 16–19 as not well-controlled; and 5–15 as very poorly controlled asthma. The ACT includes four symptom/reliever questions plus a patient self-assessed level of control. The minimum clinically important difference is 3 points.⁷³

When different systems are used for assessing asthma symptom control, the results correlate broadly with each other, but are not identical. Respiratory symptoms may be non-specific so, when assessing changes in symptom control, it is important to clarify that symptoms are due to asthma.

Asthma symptom control tools for children 6–11 years of age

In children, as in adults, assessment of asthma symptom control is based on symptoms, limitation of activities and use of rescue medication. Careful review of the impact of asthma on a child’s daily activities, including sports, play and social life, and on school absenteeism, is important. Many children with poorly controlled asthma avoid strenuous exercise so their asthma may appear to be well controlled. This may lead to poor fitness and a higher risk of obesity.

Children vary considerably in the degree of airflow limitation observed before they complain of dyspnea or use their reliever therapy, and marked reduction in lung function is often seen before it is recognized by the parents. Parents may report irritability, tiredness, and changes in mood in their child as the main problems when the child’s asthma is not controlled. Parents have a longer recall period than children, who may recall only the last few days; therefore, it is important to include both the parent’s and child’s information when the level of symptom control is being assessed.

Several numeric asthma control scores have been developed for children. These include:

- *Childhood Asthma Control Test (c-ACT)*⁷⁴ with separate sections for parent and child to complete
- *Asthma Control Questionnaire (ACQ)*^{75,76}

Some asthma control scores for children include exacerbations with symptoms. These include:

- *Test for Respiratory and Asthma Control in Kids (TRACK)*^{77–79}
- *Composite Asthma Severity Index (CASI)*⁸⁰

The results of these various tests correlate to some extent with each other and with the GINA classification of symptom control. Box 2-3 provides more details about assessing asthma control in children.

Box 2-2. GINA assessment of asthma control in adults, adolescents and children 6–11 years

A. Asthma symptom control	Level of asthma symptom control			
In the past 4 weeks, has the patient had:	Well controlled	Partly controlled	Uncontrolled	
<ul style="list-style-type: none"> Daytime asthma symptoms more than twice/week? Any night waking due to asthma? Reliever needed for symptoms* more than twice/week? Any activity limitation due to asthma? 	Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/>	None of these	1–2 of these	3–4 of these
B. Risk factors for poor asthma outcomes				
<p>Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations.</p> <p>Measure FEV₁ at start of treatment, after 3–6 months of controller treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment.</p>				
<p>Having uncontrolled asthma symptoms is an important risk factor for exacerbations.⁸¹</p> <p>Additional potentially modifiable risk factors for flare-ups (exacerbations), even in patients with few symptoms,[†] include:</p> <ul style="list-style-type: none"> Medications: High SABA use⁸² (with increased mortality if >1 x 200-dose canister/month⁸³); inadequate ICS: not prescribed ICS; poor adherence;⁸⁴ incorrect inhaler technique⁸⁵ Comorbidities: obesity;^{86,87} chronic rhinosinusitis;^{87,88} GERD;⁸⁷ confirmed food allergy;⁸⁹ pregnancy⁹⁰ Exposures: smoking;⁹¹ allergen exposure if sensitized;⁹¹ air pollution.^{92–94} Context: Major psychological or socioeconomic problems⁹⁵ Lung function: low FEV₁, especially <60% predicted^{91,96}; high bronchodilator reversibility^{87,97,98} Other tests in patients with Type 2 inflammation: blood eosinophils;^{87,97,99} elevated FENO (in adults with allergic asthma taking ICS)¹⁰⁰ <p>Other major independent risk factors for flare-ups (exacerbations)</p> <ul style="list-style-type: none"> Ever intubated or in intensive care unit for asthma¹⁰¹ ≥1 severe exacerbation in last 12 months¹⁰² <p>Risk factors for developing persistent airflow limitation</p> <ul style="list-style-type: none"> History: preterm birth, low birth weight and greater infant weight gain;¹⁰³ chronic mucus hypersecretion^{104,105} Medications: lack of ICS treatment¹⁰⁶ Exposures: tobacco smoke;¹⁰⁴ noxious chemicals; occupational exposures³⁶ Investigations: low initial FEV₁;¹⁰⁵ sputum or blood eosinophilia¹⁰⁵ <p>Risk factors for medication side-effects</p> <ul style="list-style-type: none"> Systemic: frequent OCS; long-term, high dose and/or potent ICS; also taking P450 inhibitors¹⁰⁷ Local: high-dose or potent ICS;^{107,108} poor inhaler technique¹⁰⁹ 				

FEV₁: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; OCS: oral corticosteroid; P450 inhibitors: cytochrome P450 inhibitors such as ritonavir, ketoconazole, itraconazole; SABA: short-acting beta₂-agonist. *Based on SABA reliever. Excludes reliever taken before exercise.

For children 6–11 years, also refer to Box 2-3, p.32. See Box 3-8, p.57 for specific risk reduction strategies.

[†]'Independent' risk factors are those that are significant after adjustment for the level of symptom control. Poor symptom control and exacerbation risk should not be simply combined numerically, as they may have different causes and may need different treatment strategies.

Box 2-3. Specific questions for assessment of asthma in children 6–11 years

Asthma symptom control	
Day symptoms	How often does the child have cough, wheeze, dyspnea or heavy breathing (number of times per week or day)? What triggers the symptoms? How are they handled?
Night symptoms	Cough, awakenings, tiredness during the day? (If the only symptom is cough, consider rhinitis or gastroesophageal reflux disease).
Reliever use	How often is reliever medication used? (check date on inhaler or last prescription) Distinguish between pre-exercise use (sports) and use for relief of symptoms.
Level of activity	What sports/hobbies/interests does the child have, at school and in their spare time? How does the child's level of activity compare with their peers or siblings? How many days is the child absent from school? Try to get an accurate picture of the child's day from the child without interruption from the parent/carer.
Risk factors for adverse outcomes	
Exacerbations	How do viral infections affect the child's asthma? Do symptoms interfere with school or sports? How long do the symptoms last? How many episodes have occurred since their last medical review? Any urgent doctor/emergency department visits? Is there a written action plan? Persistent bronchodilator reversibility is a risk factor for exacerbations, even if the child has few symptoms. ⁹⁸
Lung function	Check curves and technique. Main focus is on FEV ₁ and FEV ₁ /FVC ratio. Plot these values as percent predicted to see trends over time.
Side-effects	Check the child's height at least yearly, as poorly-controlled asthma can affect growth, ¹¹⁰ and growth velocity may be lower in the first 1–2 years of ICS treatment. ¹¹¹ Ask about frequency and dose of ICS and OCS.
Treatment factors	
Inhaler technique	Ask the child to show how they use their inhaler. Compare with a device-specific checklist.
Adherence	On how many days does the child use their controller in a week (e.g. 0, 2, 4, 7 days)? Is it easier to remember to use it in the morning or evening? Where is inhaler kept – is it in plain view to reduce forgetting? Check date on inhaler.
Goals/concerns	Does the child or their parent/carer have any concerns about their asthma (e.g. fear of medication, side-effects, interference with activity)? What are the child's/parent's/carer's goals for treatment?
Comorbidities	
Allergic rhinitis	Itching, sneezing, nasal obstruction? Can the child breathe through their nose? What medications are being taken for nasal symptoms?
Eczema	Sleep disturbance, topical corticosteroids?
Food allergy	Is the child allergic to any foods? (confirmed food allergy is a risk factor for asthma-related death ⁸⁹)
Obesity	Check age-adjusted BMI. Ask about diet and physical activity.
Other investigations (if needed)	
2-week diary	If no clear assessment can be made based on the above questions, ask the child or parent/carer to keep a daily diary of asthma symptoms, reliever use and peak expiratory flow (best of three) for 2 weeks (Appendix Chapter 4).
Exercise challenge (laboratory)	Provides information about airway hyperresponsiveness and fitness (Box 1-2, p.19). Only undertake a challenge if it is otherwise difficult to assess asthma control.

FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; ICS: inhaled corticosteroids; OCS: oral corticosteroids.

ASSESSING FUTURE RISK OF ADVERSE OUTCOMES

The second component of assessing asthma control (Box 2-2B, p.31) is to identify whether the patient is at risk of adverse asthma outcomes, particularly exacerbations, persistent airflow limitation, and side-effects of medications (Box 2-2B). Asthma symptoms, although an important outcome for patients, and themselves a strong predictor of future risk of exacerbations, are not sufficient on their own for assessing asthma because:

Asthma symptoms can be controlled by placebo or sham treatments^{112,113} or by inappropriate use of long-acting beta₂-agonist (LABA) alone,¹¹⁴ which leaves airway inflammation untreated.

- Respiratory symptoms may be due to other conditions such as lack of fitness, or comorbidities such as inducible laryngeal obstruction.³⁴
- Anxiety or depression may contribute to symptom reporting.
- Some patients have few symptoms despite low lung function.

Asthma symptom control and exacerbation risk should not be simply combined numerically, as poor control of symptoms and of exacerbations may have different causes and may need different treatment approaches.

Risk factors for exacerbations

Poor asthma symptom control itself substantially increases the risk of exacerbations.⁶⁰⁻⁶² However, several additional independent risk factors have been identified, i.e. factors, that, when present, increase the patient's risk of exacerbations even if symptoms are few. These risk factors (Box 2-2B) include a history of ≥ 1 exacerbations in the previous year, poor adherence, incorrect inhaler technique, chronic sinusitis and smoking, all of which can be assessed in primary care.¹¹⁵

Risk factors for development of persistent airflow limitation

The average rate of decline in FEV₁ in non-smoking healthy adults is 15–20 mL/year.¹¹⁶ People with asthma may have an accelerated decline in lung function and develop airflow limitation that is not fully reversible. This is often associated with more persistent dyspnea. Independent risk factors that have been identified for persistent airflow limitation include exposure to cigarette smoke or noxious agents, chronic mucus hypersecretion, and asthma exacerbations in patients not taking ICS¹⁰⁶ (see Box 2-2B). Children with persistent asthma may have reduced growth in lung function, and some are at risk of accelerated decline in lung function in early adult life.¹¹⁷

Risk factors for medication side-effects

Choices with any medication are based on the balance of benefit and risk. Most people using asthma medications do not experience any side-effects. The risk of side-effects increases with higher doses of medications, but these are needed in few patients. Systemic side-effects that may be seen with long-term, high-dose ICS include easy bruising; an increase beyond the usual age-related risk of osteoporosis, cataracts and glaucoma; and adrenal suppression. Local side effects of ICS include oral thrush and dysphonia. Patients are at greater risk of ICS side-effects with higher doses or more potent formulations,^{107,108} and, for local side-effects, with incorrect inhaler technique.¹⁰⁹

ROLE OF LUNG FUNCTION IN ASSESSING ASTHMA CONTROL

Does lung function relate to other asthma control measures?

Lung function does not correlate strongly with asthma symptoms in adults¹¹⁸ or children.¹¹⁹ In some asthma control tools, lung function is numerically averaged or added with symptoms,^{69,120} but if the tool includes several symptom items, these can outweigh clinically important differences in lung function.¹²¹ In addition, low FEV₁ is a strong independent predictor of risk of exacerbations, even after adjustment for symptom frequency.

Lung function should be assessed at diagnosis or start of treatment; after 3–6 months of controller treatment to assess the patient's personal best FEV₁; and periodically thereafter. For example, in most adult patients, lung function should be recorded at least every 1–2 years, but more frequently in higher risk patients including those with exacerbations and

those at risk of decline in lung function (see Box 2-2B). Lung function should also be recorded more frequently in children based on asthma severity and clinical course (Evidence D).

Once the diagnosis of asthma has been confirmed, it is not generally necessary to ask patients to withhold their regular or as-needed medications before visits,¹⁴ but preferably the same conditions should apply at each visit.

How to interpret lung function test results in asthma

A low FEV₁ percent predicted:

- Identifies patients at risk of asthma exacerbations, independent of symptom levels, especially if FEV₁ is <60% predicted.^{91,96,122,123}
- Is a risk factor for lung function decline, independent of symptom levels.¹⁰⁵
- If symptoms are few, suggests limitation of lifestyle, or poor perception of airflow limitation,¹²⁴ which may be due to untreated airway inflammation.¹²⁵

A ‘normal’ or high FEV₁ in a patient with frequent respiratory symptoms (especially when symptomatic):

- Prompts consideration of alternative causes for the symptoms; e.g. cardiac disease, or cough due to post-nasal drip or gastroesophageal reflux disease (Box 1-3, p.23).

Persistent bronchodilator reversibility:

- Finding significant bronchodilator reversibility (increase in FEV₁ >12% and >200 mL from baseline¹²) in a patient taking controller treatment, or who has taken a short-acting beta₂-agonist within 4 hours, or a LABA within 12 hours, suggests uncontrolled asthma.

In children, spirometry cannot be reliably obtained until age 5 years or more, and it is less useful than in adults. Many children with uncontrolled asthma have normal lung function between flare-ups (exacerbations).

How to interpret changes in lung function in clinical practice

With regular ICS treatment, FEV₁ starts to improve within days, and reaches a plateau after around 2 months.¹²⁶ The patient's highest FEV₁ reading (personal best) should be documented, as this provides a more useful comparison for clinical practice than FEV₁ percent predicted. If predicted values are used in children, measure their height at each visit.

Some patients may have a faster than average decrease in lung function, and develop ‘fixed’ (incompletely reversible) airflow limitation. While a trial of higher-dose ICS-LABA and/or systemic corticosteroids may be appropriate to see if FEV₁ can be improved, high doses should not be continued if there is no response.

The between-visit variability of FEV₁ (<12% week to week or 15% year to year in healthy individuals¹²) limits its use in adjusting asthma treatment in clinical practice. The minimal important difference for improvement and worsening in FEV₁ based on patient perception of change has been reported to be about 10%.^{127,128}

The role of short-term and long-term PEF monitoring

Once the diagnosis of asthma is made, short-term PEF monitoring may be used to assess response to treatment, to evaluate triggers (including at work) for worsening symptoms, or to establish a baseline for action plans. After starting ICS, personal best PEF (from twice daily readings) is reached on average within 2 weeks.¹²⁹ Average PEF continues to increase, and diurnal PEF variability to decrease, for about 3 months.^{118,129} Excessive variation in PEF suggests sub-optimal asthma control, and increases the risk of exacerbations.¹³⁰

Long-term peak expiratory flow (PEF) monitoring is now generally only recommended for patients with severe asthma, or those with impaired perception of airflow limitation^{125,131-134} (Appendix Chapter 4). For clinical practice, displaying PEF results on a standardized chart may improve accuracy of interpretation.¹³⁵

ASSESSING ASTHMA SEVERITY

How to assess asthma severity in clinical practice

Currently, asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations.^{14,58,136} It can be assessed once the patient has been on controller treatment for several months and, if appropriate, treatment step down has been attempted to find the patient's minimum effective level of treatment. Asthma severity is not a static feature and may change over months or years.

Asthma severity can be assessed when the patient has been on regular controller treatment for several months:^{14,136}

- *Mild asthma* is asthma that is well controlled with Step 1 or Step 2 treatment (Box 3-5, p.46), i.e. with as-needed controller medication alone, or with low-intensity maintenance controller treatment such as low dose ICS, leukotriene receptor antagonists or chromones.
- *Moderate asthma* is asthma that is well controlled with Step 3 treatment e.g. low dose ICS-LABA.
- *Severe asthma* is asthma that requires Step 4 or 5 treatment (Box 3-5, p.46), e.g. high-dose ICS-LABA, to prevent it from becoming 'uncontrolled', or asthma that remains 'uncontrolled' despite this treatment. While many patients with uncontrolled asthma may be difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, the European Respiratory Society/American Thoracic Society Task Force on Severe Asthma considered that the definition of severe asthma should be reserved for patients with refractory asthma and those in whom response to treatment of comorbidities is incomplete.¹³⁶ See Chapter 3E (p.84) for more detail about the assessment of patients with difficult to treat or severe asthma,

How to classify asthma severity in epidemiologic studies and clinical trials

For descriptions of participants in epidemiological studies and clinical trials, classification of asthma severity has often been based on prescribed treatment step (Box 3-5, p.46). For example, patients prescribed Step 1 or 2 treatments are often described as having mild asthma; those prescribed Step 3–4 as having moderate asthma; and those prescribed Step 4–5 as having moderate-to-severe asthma. This approach is based on the assumption that patients are receiving appropriate treatment, and that those prescribed more intense treatment are likely to have more severe underlying disease. However, this is only a surrogate measure, and it causes confusion since most studies also require participants to have uncontrolled symptoms at entry. For epidemiological studies or clinical trials, it is preferable to categorize patients by the type of treatment that they are prescribed, without inferring severity. In particular, to avoid confusion, SABA-only treatment should not be described as 'Step 1' treatment.

For low resource countries that do not currently have access to medications such as ICS, the World Health Organization definition of severe asthma¹³⁷ includes a category of 'untreated severe asthma'. This category corresponds to other classifications of uncontrolled asthma in patients not taking controller treatment.

'Severe' is often also used to describe the intensity of asthma symptoms, the magnitude of airflow limitation, or the nature of an exacerbation. In older asthma literature, many different severity classifications have been used; many of these were similar to current concepts of asthma control.⁵⁸

The patient's view of asthma severity

Patients may perceive their asthma as severe if they have intense or frequent symptoms, but this does not necessarily indicate underlying severe disease, as symptoms may rapidly become well controlled with ICS. It is important that health professionals communicate clearly to patients what they mean by the word 'severe'.

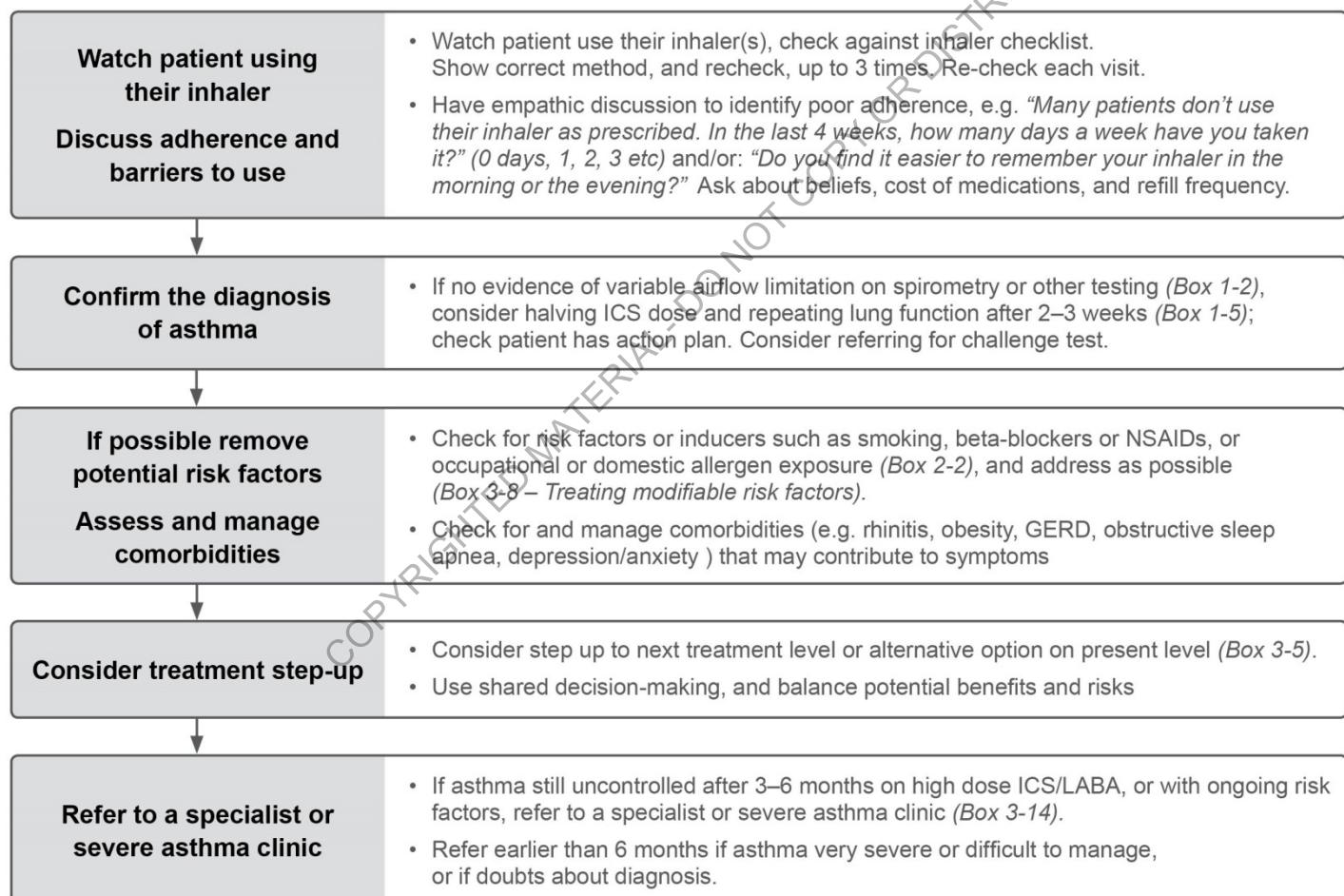
How to distinguish between uncontrolled and severe asthma

Although most asthma patients can achieve good symptom control and minimal exacerbations with regular controller treatment, some patients will not achieve one or both of these goals even with maximal therapy.¹²⁰ In some patients this is due to truly refractory severe asthma, but in many others, it is due to comorbidities, persistent environmental exposures, or psychosocial factors.

It is important to distinguish between severe asthma and uncontrolled asthma, as the latter is a much more common reason for persistent symptoms and exacerbations, and may be more easily improved. Box 2-4 shows the initial steps that can be carried out to identify common causes of uncontrolled asthma. More details are given in Section 3E about difficult-to-treat and severe asthma. The most common problems that need to be excluded before a diagnosis of severe asthma can be made are:

- Poor inhaler technique (up to 80% of community patients)⁸⁵ (Box 3-12, p.70)
- Poor medication adherence¹³⁸ (Box 3-13, p.71)
- Incorrect diagnosis of asthma, with symptoms due to alternative conditions such as inducible laryngeal obstruction, cardiac failure or lack of fitness (Box 1-3, p.23)
- Comorbidities and complicating conditions such as rhinosinusitis, gastroesophageal reflux, obesity and obstructive sleep apnea (Chapter 3, Part D, p.75)⁸⁷
- Ongoing exposure to sensitizing or irritant agents in the home or work environment.

Box 2-4. Investigating a patient with poor symptom control and/or exacerbations despite treatment



GERD: gastro-esophageal reflux disease; ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; NSAID: non-steroidal anti-inflammatory drugs.

For clinical efficiency, this flow-chart starts with the most common reasons for uncontrolled asthma (i.e. incorrect inhaler technique and poor adherence), as these can be identified in clinical practice – and often remedied – without any special resources. If symptoms and/or lung function improve when inhaler technique or adherence are addressed, this can provide confirmation of the diagnosis of asthma. However, the various steps may be carried out in a different order depending on the clinical context, and available resources.

Chapter 3.

**Treating asthma to
control symptoms
and minimize risk**

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE

This chapter is divided into five parts:

- Part A. General principles of asthma management
- Part B. Medications and strategies for asthma symptom control and risk reduction
 - Medications
 - Treating modifiable risk factors
 - Non-pharmacological therapies and strategies
- Part C. Guided asthma self-management education and skills training
 - Information, inhaler skills, adherence, written asthma action plan, self-monitoring, regular review
- Part D. Managing asthma with comorbidities and in special populations
- Part E. Difficult-to-treat and severe asthma in adults and adolescents (including decision tree)

Management of worsening and acute asthma is described in Chapter 4 (p.101).

PART A. GENERAL PRINCIPLES OF ASTHMA MANAGEMENT

KEY POINTS

Goals of asthma management

- The long-term goals of asthma management are to achieve good symptom control, and to minimize future risk of asthma-related mortality, exacerbations, persistent airflow limitation and side-effects of treatment. The patient's own goals regarding their asthma and its treatment should also be identified.

The patient-health professional partnership

- Effective asthma management requires a partnership between the person with asthma (or the parent/carer) and their health care providers.
- Teaching communication skills to health care providers may lead to increased patient satisfaction, better health outcomes, and reduced use of health care resources.
- The patient's 'health literacy' – that is, the patient's ability to obtain, process and understand basic health information to make appropriate health decisions – should be taken into account.

Making decisions about asthma treatment

- Control-based management means that treatment is adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk (of exacerbations and side-effects)
- For population-level decisions about asthma treatment, the 'preferred option' at each step represents the best treatment for most patients, based on group mean data for efficacy, effectiveness and safety from randomized controlled trials, meta-analyses and observational studies, and net cost.
- For individual patients, treatment decisions should also take into account any patient characteristics or phenotype that predict the patient's likely response to treatment, together with the patient's preferences and practical issues (inhaler technique, adherence, and cost to the patient).

LONG-TERM GOALS OF ASTHMA MANAGEMENT

The long-term goals of asthma management are:

- To achieve good control of symptoms and maintain normal activity levels
- To minimize the risk of asthma-related death, exacerbations, persistent airflow limitation and side-effects.

It is also important to elicit the patient's own goals regarding their asthma, as these may differ from conventional medical goals. Shared goals for asthma management can be achieved in various ways, taking into account differing health care systems, medication availability, and cultural and personal preferences.

THE PATIENT-HEALTH CARE PROVIDER PARTNERSHIP

Effective asthma management requires the development of a partnership between the person with asthma (or the parent/carer) and health care providers.¹³⁹ This should enable the person with asthma to gain the knowledge, confidence and skills to assume a major role in the management of their asthma. Self-management education reduces asthma morbidity in both adults¹⁴⁰ (Evidence A) and children¹⁴¹ (Evidence A).

There is emerging evidence that a shared-care approach is associated with improved outcomes.¹⁴² Patients should be encouraged to participate in decisions about their treatment, and given the opportunity to express their expectations and concerns. This partnership needs to be individualized to each patient. A person's willingness and ability to engage in self-management may vary depending on factors such as ethnicity, literacy, understanding of health concepts (health literacy), numeracy, beliefs about asthma and medications, desire for autonomy, and the health care system.

Good communication

Good communication by health care providers is essential as the basis for good outcomes¹⁴³⁻¹⁴⁵ (Evidence B). Teaching health care providers to improve their communication skills (Box 3-1) can result in increased patient satisfaction, better health outcomes, and reduced use of health care resources¹⁴³⁻¹⁴⁵ without lengthening consultation times.¹⁴⁶ It can also enhance patient adherence.¹⁴⁶ Training patients to give information clearly, seek information, and check their understanding of information provided is also associated with improved adherence with treatment recommendations.¹⁴⁶

Health literacy and asthma

There is increasing recognition of the impact of low health literacy on health outcomes, including in asthma.^{147,148} Health literacy means much more than the ability to read: it is defined as 'the degree to which individuals have the capacity to obtain, process and understand basic health information and services to make appropriate health decisions'.¹⁴⁷ Low health literacy is associated with reduced knowledge and worse asthma control.¹⁴⁹ In one study, low numeracy among parents of children with asthma was associated with higher risk of exacerbations.¹⁴⁸ Interventions adapted for cultural and ethnicity perspectives have been associated with improved knowledge and significant improvements in inhaler technique.¹⁵⁰ Suggested communication strategies for reducing the impact of low health literacy are shown in Box 3-1.

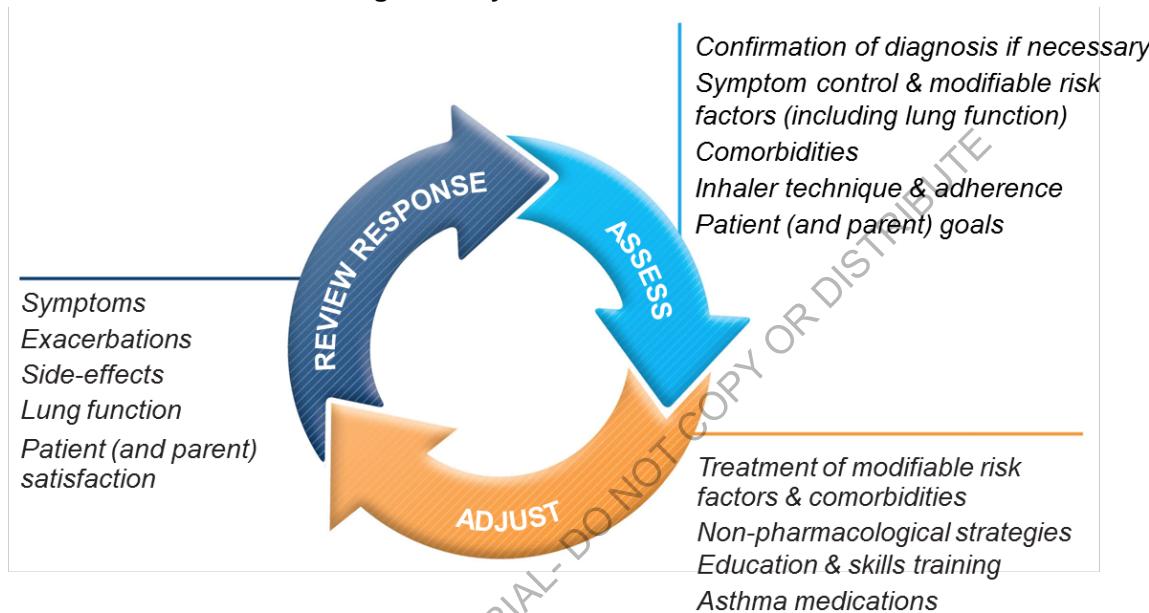
Box 3-1. Communication strategies for health care providers

Key strategies to facilitate good communication ^{144,145}
<ul style="list-style-type: none">• A congenial demeanor (friendliness, humor and attentiveness)• Allowing the patient to express their goals, beliefs and concerns• Empathy, reassurance, and prompt handling of any concerns• Giving encouragement and praise• Giving appropriate (personalized) information• Providing feedback and review
How to reduce the impact of low health literacy ¹⁴⁷
<ul style="list-style-type: none">• Order information from most to least important• Speak slowly and use simple words (avoid medical language, if possible)• Simplify numeric concepts (e.g. use numbers instead of percentages)• Frame instructions effectively (use illustrative anecdotes, drawings, pictures, table or graphs)• Confirm understanding by using the 'teach-back' method (ask patients to repeat instructions)• Ask a second person (e.g. nurse, family member) to repeat the main messages• Pay attention to non-verbal communication by the patient (e.g. poor eye contact)• Make patients feel comfortable about asking questions

CONTROL-BASED ASTHMA MANAGEMENT

In control-based asthma management, pharmacological and non-pharmacological treatment is adjusted in a continuous cycle that involves assessment, treatment and review (Box 3-2). Asthma outcomes have been shown to improve after the introduction of control-based guidelines^{151,152} or practical tools for implementation of control-based management strategies.^{142,153} The concept of control-based management is also supported by the design of most randomized controlled medication trials, with patients identified for a change in asthma treatment on the basis of features of poor symptom control with or without other risk factors such as low lung function or a history of exacerbations.

Box 3-2. The control-based asthma management cycle



For many patients in primary care, symptom control is a good guide to a reduced risk of exacerbations.¹⁵⁴ When inhaled corticosteroids (ICS) were introduced into asthma management, large improvements were observed in symptom control and lung function, and exacerbations and asthma-related mortality decreased.

However, with other asthma therapies (including ICS-long-acting beta₂-agonists (LABA)^{155,156}) or different treatment regimens (such as ICS-formoterol maintenance and reliever therapy¹⁵⁷), and in patients with severe asthma, there may be discordance between responses for symptom control and exacerbations. In addition, some patients continue to have exacerbations despite well-controlled symptoms, and for patients with ongoing symptoms, side-effects may be an issue if ICS doses continue to be stepped up.

Therefore, in control-based management, *both* domains of asthma control (symptom control and future risk – see Box 2-2, p.31) should be taken into account when choosing asthma treatment and reviewing the response.^{14,58}

Alternative strategies for adjusting asthma treatment

Some alternative strategies have been evaluated for adjusting asthma treatment.

- *Treatment guided by sputum eosinophil count:* in adults, this approach, when compared with guidelines-based treatment, leads to a reduced risk of exacerbations and similar levels of symptom control and lung function.¹⁵⁸ The benefits have primarily been seen in patients requiring secondary care.¹⁵⁴ However, only a limited number of centers have routine access to induced sputum analysis.
- *Treatment guided by fractional concentration of exhaled nitric oxide (FENO):* In several studies of FENO-guided treatment, problems with the design of the intervention and/or control algorithms make comparisons and conclusions difficult.¹⁵⁹ Results of FENO measurement at a single point in time should be interpreted with caution

(see p.22).^{26,28} In children and young adults with asthma, FENO-guided treatment was associated with a significant reduction in the number of patients with ≥ 1 exacerbation (OR 0.67 [95% CI 0.51-0.90]) and in exacerbation rate (mean difference -0.27 [-0.49- -0.06] per year) compared with guidelines-based treatment (Evidence A); similar differences were seen in comparisons between FENO-guided treatment and non-guidelines-based algorithms.¹⁶⁰ However, in non-smoking adults with asthma, no significant reduction in risk of exacerbations and in exacerbation rates was observed when compared to guideline-based treatment; a difference was only seen in studies with other (non-standard) comparator approaches.¹⁶¹ No significant differences were seen in symptoms or ICS dose with FENO-guided treatment compared with other strategies.^{160,161}

At present, neither sputum- nor FENO-guided treatment is recommended for the general asthma population. Sputum-guided treatment is recommended for adult patients with moderate or severe asthma who are managed in (or can be referred to) centers experienced in this technique¹³⁶ (Evidence A). FeNO-guided treatment significantly reduces exacerbation rates compared with guidelines-based treatment, at least in children (Evidence A).¹⁶⁰ However, further studies are needed to identify the populations most likely to benefit from sputum-guided or FENO-guided treatment, and the optimal frequency of FENO monitoring.

Choosing between asthma treatment options

At each treatment step in asthma management, different medication options are available that, although not of identical efficacy, may be alternatives for controlling asthma. Different considerations apply to recommendations or choices made for broad populations compared with those for individual patients (Box 3-3, p. 42), as follows:

- *Population-level medication choices*, e.g. for national formularies or managed care organizations. These aim to represent the best option for most patients in the population. For each treatment step, a 'preferred' controller medication is recommended that provides the best benefit to risk ratio (including cost) for both symptom control and risk reduction. Choice of the preferred controller is based on group mean data from efficacy studies (highly controlled studies in well-characterized populations) and effectiveness studies (from pragmatically controlled studies, or studies in broader populations, or strong observational data),¹⁶² as well as on safety data and cost.
- *Patient-level medication choices*: choices at this level also take into account any patient characteristics or phenotype that may predict a clinically important difference in their response compared with other patients, together with the patient's preferences and practical issues (cost, ability to use the medication and adherence).

The extent to which asthma treatment can be individualized according to patient characteristics or phenotypes depends on the health system, the clinical context, the potential magnitude of difference in outcomes, cost and available resources. At present, most research activity about individualized treatment is focused on severe asthma^{163,164} (see Chapter 3E, p.84).

Box 3-3. Population level versus patient level decisions about asthma treatment

Choosing between treatment options at a population level

(e.g. national formularies, health maintenance organizations, national guidelines)

The 'preferred' medication at each step is the best treatment for most patients, based on:

- Efficacy
 - Effectiveness
 - Safety
 - Availability and cost at the population level
- } Based on group mean data for symptoms, exacerbations and lung function
(from randomized controlled trials, pragmatic studies and observational data)

Choosing between controller options for individual patients

Use shared decision-making with the patient/parent/carer to discuss the following:

1. *Preferred treatment* (as above) for symptom control and risk reduction
2. *Patient characteristics or phenotype*
 - Does the patient have any features that predict differences in their future risk or treatment response compared with other patients (e.g. smoker; history of exacerbations, blood eosinophilia)?
 - Are there any modifiable risk factors or comorbidities that may affect outcomes?
3. *Patient preference*
 - What are the patient's goals, beliefs and concerns about asthma and medications?
4. *Practical issues*
 - Inhaler technique – can the patient use the inhaler correctly after training?
 - Adherence – how often is the patient likely to take the medication?
 - Cost to patient – can the patient afford the medication?

PART B. MEDICATIONS AND STRATEGIES FOR SYMPTOM CONTROL AND RISK REDUCTION

KEY POINTS

- For safety, GINA no longer recommends treatment of asthma in adults and adolescents with SABA alone
- GINA recommends that all adults and adolescents with asthma should receive ICS-containing controller treatment, either as-needed (in mild asthma) or daily, to reduce their risk of serious exacerbations and to control symptoms

Mild asthma

- Treatment with regular daily low dose ICS is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization and death
- In adults and adolescents with mild asthma, treatment with as-needed low dose ICS-formoterol reduces the risk of severe exacerbations by about two-thirds compared with SABA-only treatment, and is non-inferior to daily low dose ICS

Stepping up if asthma remains uncontrolled despite good adherence and inhaler technique

- For patients with persistent symptoms and/or exacerbations despite low dose ICS, consider step up but first check for common problems such as inhaler technique, adherence, persistent allergen exposure and comorbidities
 - For adults and adolescents, the preferred step-up treatment is combination low dose ICS-long-acting beta₂-agonist (LABA).
 - For adults and adolescents with exacerbations despite other therapies, the risk of exacerbations is reduced with combination low dose ICS-formoterol (with beclometasone or budesonide) as both maintenance and reliever, compared with maintenance controller treatment plus as-needed SABA.
 - For children 6–11 years, Step 3 options include medium dose ICS and combination low dose ICS-LABA, as maintenance therapy with as-needed SABA.

Stepping down to find the minimum effective dose

- Consider step down once good asthma control has been achieved and maintained for about 3 months, to find the patient's lowest treatment that controls both symptoms and exacerbations
 - Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit
 - Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma.

For all patients with asthma

- Provide inhaler skills training; this is essential for medications to be effective, but technique is often incorrect
- Encourage adherence with controller medication, even when symptoms are infrequent
- Provide training in asthma self-management (self-monitoring of symptoms and/or PEF, written asthma action plan and regular medical review) to control symptoms and minimize the risk of exacerbations and need for health care utilization.
- For patients with one or more risk factors for exacerbations:
 - Prescribe regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients
 - Identify and address modifiable risk factors, (e.g. smoking, low lung function)
 - Consider non-pharmacological strategies and interventions to assist with symptom control and risk reduction, (e.g. smoking cessation advice, breathing exercises, some avoidance strategies)

Difficult-to-treat and severe asthma (see section 3E)

- Patients with poor symptom control and/or exacerbations despite Step 4-5 treatment should be assessed for contributing factors, and asthma treatment optimized. If the problems continue, refer to a specialist center for phenotypic assessment and consideration of add-on therapy including biologics

ASTHMA MEDICATIONS

Categories of asthma medications

When compared with medications used for other chronic diseases, most of the medications used for treatment of asthma have very favorable therapeutic ratios (Appendix Chapter 5). The pharmacological options for long-term treatment of asthma fall into the following three main categories.

- *Controller medications*: these are used to reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and decline in lung function. In patients with mild asthma, controller treatment may be delivered through as-needed low dose ICS-formoterol, taken when symptoms occur and before exercise.
- *Reliever (rescue) medications*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment.
- *Add-on therapies for patients with severe asthma* (Section 3E, p.84): these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications (usually a high dose ICS and a LABA) and treatment of modifiable risk factors (see Box 3-8, p.57).

Initial controller treatment

For the best outcomes, ICS-containing controller treatment should be initiated as soon as possible after the diagnosis of asthma is made, as the evidence suggests that:

- Early initiation of low dose ICS in patients with asthma leads to a greater improvement in lung function than if symptoms have been present for more than 2–4 years.^{165,166} One study showed that after this time, higher ICS doses were required, and lower lung function was achieved.¹⁶⁷
- Patients not taking ICS who experience a severe exacerbation have a greater long-term decline in lung function than those who have already started ICS.¹⁰⁶
- For patients with occupational asthma, early removal from exposure to the sensitizing agent and early controller treatment increase the probability of recovery.³⁶

Recommended options for initial controller treatment in adults and adolescents, based on evidence (where available) and consensus, are listed in Box 3-4. The patient's response should be reviewed, and treatment stepped down once good control is achieved. Recommendations for a stepwise approach to ongoing treatment are found in Box 3-5 (p.46).

In studies mainly limited to non-smoking patients, FENO >50 parts per billion (ppb) has been associated with a good short-term response to ICS.²⁸ However, there are no studies examining the long-term safety with regard to exacerbations of withholding ICS in patients with low initial FENO. Consequently, in patients with a diagnosis or suspected diagnosis of asthma, FENO can support the decision to start ICS, but cannot safely be recommended at present for deciding against treatment with ICS. Based on current evidence,^{168–171} GINA recommends treatment with daily low-dose ICS for most patients with asthma, or as-needed low dose ICS-formoterol for those with infrequent symptoms (Box 3-2),¹⁷² to reduce the risk of serious exacerbations.

Stepwise approach for adjusting asthma treatment in adults, adolescents and children 6–11 years old

Once asthma treatment has been commenced (Box 3-4), ongoing treatment decisions are based on a personalized cycle of assessment, adjustment of treatment, and review of the response. For each patient, in addition to treatment of modifiable risk factors, controller medication can be adjusted up or down in a stepwise approach (Box 3-5) to achieve good symptom control and minimize future risk of exacerbations, persistent airflow limitation and medication side-effects. Once good asthma control has been maintained for 2–3 months, treatment may be stepped down in order to find the patient's minimum effective treatment (Box 3-7, p.56).

If a patient has persisting uncontrolled symptoms and/or exacerbations despite 2–3 months of controller treatment, assess and correct the following common problems *before considering any step up in treatment*:

- Incorrect inhaler technique
- Poor adherence
- Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as beta-blockers or (in some patients) non-steroidal anti-inflammatory drugs (NSAIDs)
- Comorbidities that may contribute to respiratory symptoms and poor quality of life
- Incorrect diagnosis.

Box 3-4. Initial asthma treatment - recommended options for adults and adolescents

Presenting symptoms	Preferred INITIAL treatment
All patients	SABA-only treatment (without ICS) is not recommended
Infrequent asthma symptoms, e.g. less than twice a month	<ul style="list-style-type: none"> • As-needed low dose ICS-formoterol (Evidence B) <p>Other options include taking ICS whenever SABA is taken, in combination or separate inhalers (Evidence B)</p>
Asthma symptoms or need for reliever twice a month or more	<ul style="list-style-type: none"> • Low dose ICS** with as-needed SABA (Evidence A), or • As-needed low dose ICS-formoterol (Evidence A) <p>Other options include LTRA (less effective than ICS, Evidence A), or taking ICS whenever SABA is taken either in combination or separate inhalers (Evidence B). Consider likely adherence with controller if reliever is SABA.</p>
Troublesome asthma symptoms most days; or waking due to asthma once a week or more, especially if any risk factors exist (Box 2-2B)	<ul style="list-style-type: none"> • Low dose ICS-LABA[†] as maintenance and reliever therapy with ICS-formoterol[#] (Evidence A) or as conventional maintenance treatment with as-needed SABA (Evidence A), OR • Medium dose ICS[†] with as-needed SABA (Evidence A)
Initial asthma presentation is with severely uncontrolled asthma, or with an acute exacerbation	<ul style="list-style-type: none"> • Short course of oral corticosteroids AND start regular controller treatment with high-dose ICS (Evidence A), or medium-dose ICS-LABA[#] (Evidence D)

Before starting initial controller treatment

- Record evidence for the diagnosis of asthma, if possible
- Record the patient's level of symptom control and risk factors, including lung function (Box 2-2, p17)
- Consider factors influencing choice between available treatment options (Box 3-3, p27)
- Ensure that the patient can use the inhaler correctly
- Schedule an appointment for a follow-up visit

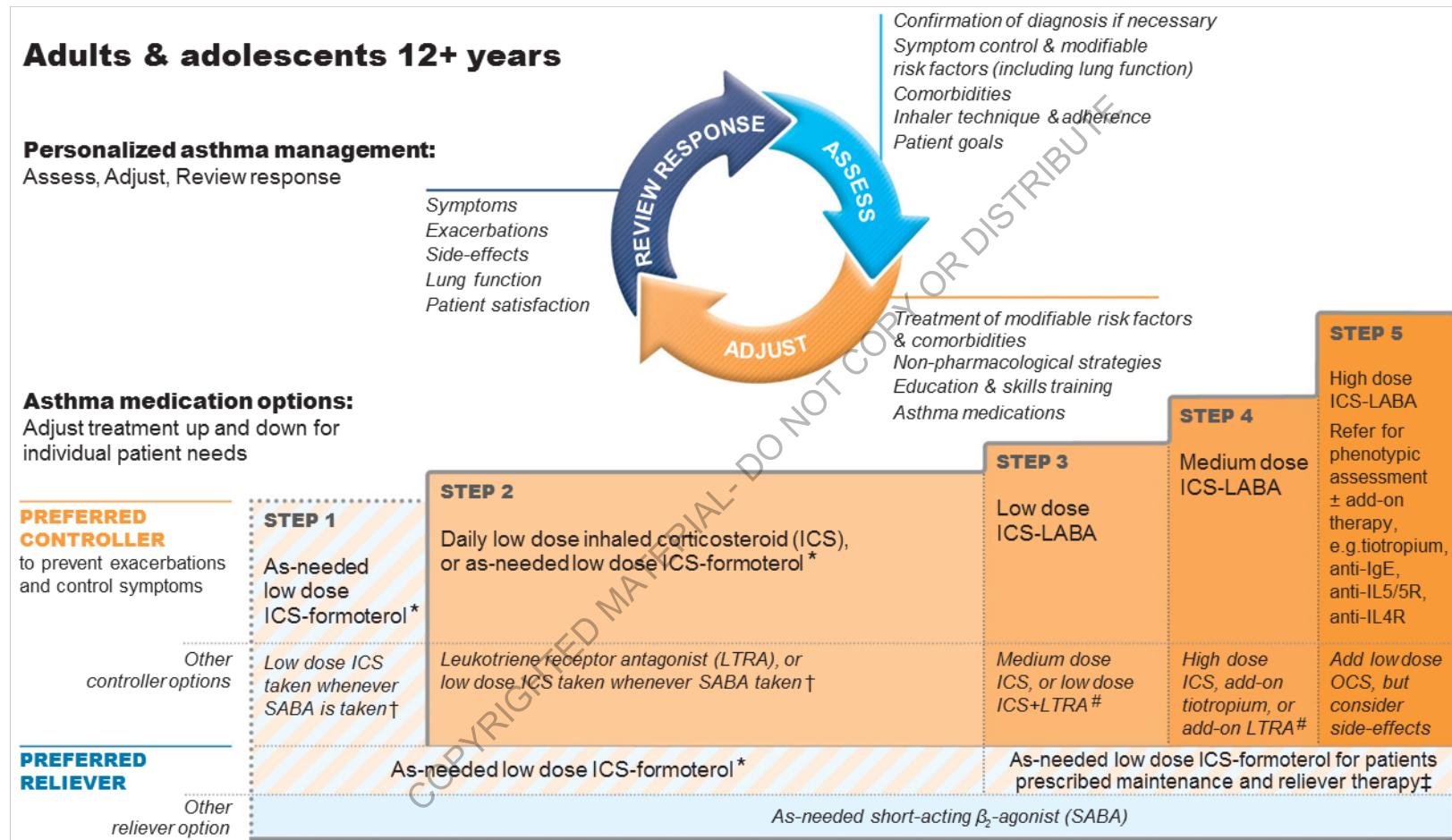
After starting initial controller treatment

- Review patient's response (Box 2-2, p.31) after 2–3 months, or earlier depending on clinical urgency
- See Box 3-5 for recommendations for ongoing treatment and other key management issues
- Step down treatment once good control has been maintained for 3 months (Box 3-7, p.56).

ICS: inhaled corticosteroids; LABA: long-acting beta₂-agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting beta₂-agonist . This table is based on evidence from available studies and consensus, including considerations of cost.

**Corresponds to starting at Step 2 in Box 3-5. [†] Corresponds to starting at Step 3 in Box 3-5. [#] Not recommended for initial treatment in children 6–11 years.

Box 3-5A. Personalized management for adults and adolescents to control symptoms and minimize future risk



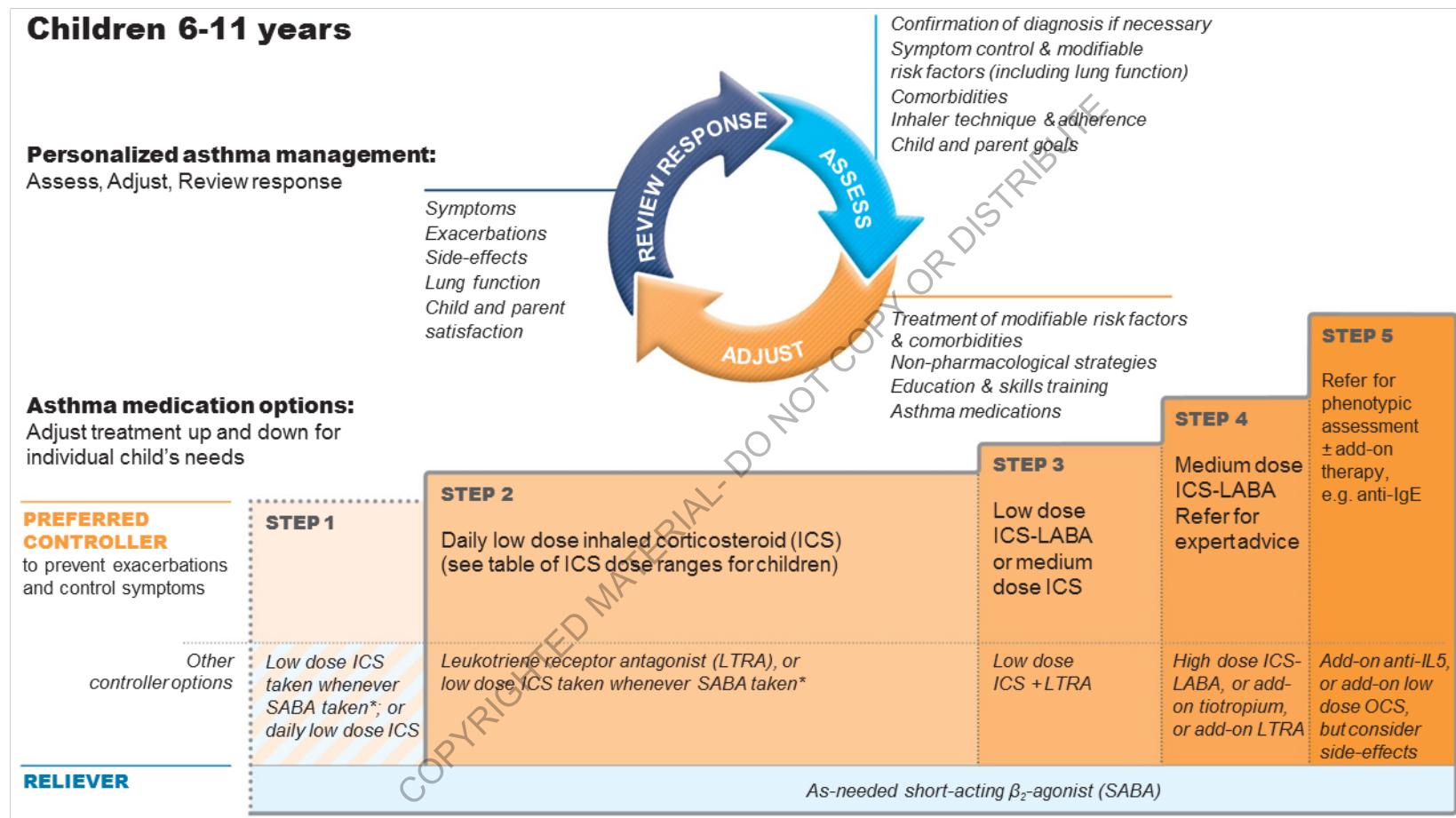
* Off-label; data only with budesonide-formoterol (bud-form)

† Off-label; separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy

Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1 >70% predicted

Box 3-5B. Personalized management for children 6-11 years to control symptoms and minimize future risk



Box 3-6. Low, medium and high daily doses of inhaled corticosteroids

Low dose ICS provides most of the clinical benefit of ICS for most patients with asthma. However, ICS responsiveness varies between patients, so some patients may need **medium dose ICS** if their asthma is uncontrolled despite good adherence and correct technique with low dose ICS (with or without LABA). **High dose ICS** (in combination with LABA or separately) is needed by very few patients, and its long-term use is associated with an increased risk of local and systemic side-effects, which must be balanced against the potential benefits.

This is not a table of equivalence, but of estimated clinical comparability, based on available studies and product information.

Adults and adolescents (12 years and older)

Drug	Daily dose (mcg) – see notes above		
	Low	Medium	High
Beclometasone dipropionate (CFC)*	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate(DPI)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

Children 6–11 years – see notes above (for children 5 years and younger, see Box 6-6, p.144)

CFC: chlorofluorocarbon propellant; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; n.a. not applicable *Beclometasone dipropionate CFC is included for comparison with older literature.	100–200	>200–400	>400
	50–100	>100–200	>200
	100–200	>200–400	>400
	250–500	>500–1000	>1000
	80	>80–160	>160
	n.a.	n.a.	n.a.
	100–200	>200–400	>400
	100–200	>200–500	>500
	110	≥220–<440	≥440
	400–800	>800–1200	>1200

CFC: chlorofluorocarbon propellant; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; n.a. not applicable

*Beclometasone dipropionate CFC is included for comparison with older literature.

Box 3-6 is not a table of equivalence, but of estimated clinical comparability. Categories of ‘low’, ‘medium’, and ‘high’ doses are based on published information and available studies, including direct comparisons where available. Doses may be country-specific depending on labelling requirements. Most of the clinical benefit from ICS is seen at low doses, and clear evidence of dose-response relationships is seldom available within the dose ranges evaluated for regulatory purposes. ‘High’ doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects.

For new preparations, manufacturer’s information should be reviewed carefully; products containing the same molecule may not be clinically equivalent. For more detailed discussion see Raissy et al.¹⁰⁷

Choice of medication, device and dose

In clinical practice, the choice of medication, device and dose should be based for each individual patient on assessment of symptom control, risk factors, patient preference, and practical issues (cost, ability to use the device, and adherence) (Box 3-3, p.42). It is important to monitor the response to treatment and any side-effects, and to adjust the dose accordingly (Box 3-5, p.46). Once good symptom control has been maintained for 3 months, the ICS dose should be carefully titrated to the minimum dose that will maintain good symptom control and minimize exacerbation risk, while reducing the potential for side-effects (Box 3-7). Patients who are being considered for a high daily dose of ICS (except for short periods) should be referred for expert assessment and advice, where possible (Chapter 3E, p.84). There is currently insufficient good quality evidence to support use of extra-fine particle ICS aerosols over others.¹⁷³ More detail about asthma medications is provided in Appendix Chapter 5 (adults: Part A; children 6–11 years: Part B).

Below is more detail about the evidence for each of the treatments shown in Box 3-5A and 3-5B. Clinicians should check local eligibility and payer criteria before prescribing. As shown in these figures, GINA recommends that all patients should receive as-needed (in mild asthma) or regular ICS-containing controller, incorporated as part of the patient's personalized asthma management. Box 3-6 lists ICS doses that are considered to be low, medium and high.

STEP 1: Preferred controller: as-needed low dose combination ICS-formoterol (adults and adolescents)

Preferred Step 1 controller for adults and adolescents: low dose combination ICS-formoterol taken as needed for relief of symptoms, and if needed before exercise.

GINA Step 1 recommendations are for patients with symptoms less than twice a month, and no exacerbation risk factors, a group that is rarely studied. Use of low dose ICS-formoterol as needed for symptom relief in Step 1 for adults and adolescents (Evidence B) is supported by *indirect* evidence from a large double-blind study comparing this regimen with SABA-only treatment and with regular low dose ICS plus as-needed SABA in patients with mild asthma eligible for Step 2 therapy (see below).¹⁷⁴ At present, as-needed ICS-formoterol is off-label in most countries.

The most important considerations for GINA in recommending as-needed low dose ICS-formoterol were:

- the evidence that patients with few interval asthma symptoms can still have severe or fatal exacerbations.¹⁷⁵ GINA recommends assessing risk factors for exacerbations as well as symptom control (Box 2-2)
- the two-thirds reduction in severe exacerbation rate in the Step 2 study of as-needed low dose budesonide-formoterol compared with SABA-only therapy, and the fact that this was achieved with <20% of the average ICS dose compared with daily ICS¹⁷⁴
- the evidence that in patients with infrequent symptoms, adherence with prescribed daily ICS is very poor,¹⁷⁶ exposing them to risks of SABA-only treatment
- the priority to avoid conflicting messages in asthma education. Previously, at the start of asthma treatment, patients were provided with SABA to use for symptom relief, but later, despite this treatment being effective from the patient's perspective, they were told that they needed to reduce their SABA use by taking a daily controller even when they had no symptoms. Recommending that all patients should be provided with a controller (as-needed in mild asthma) from the start of therapy allows consistent messaging about the need for both symptom relief and risk reduction, and may avoid establishing patient reliance on SABA as their main asthma treatment.

So far, all evidence for as-needed ICS-formoterol in mild asthma is with low dose budesonide-formoterol, but BDP-formoterol may also be suitable. These medications are well-established for as-needed use within maintenance and reliever therapy in GINA Steps 3-5,¹⁷⁷ and no new safety signals were seen in the large studies with as-needed budesonide-formoterol in mild asthma.^{168,178}

For pre-exercise use in patients with mild asthma, one 6-week study showed that use of low dose budesonide-formoterol for symptom relief and before exercise reduced exercise-induced bronchoconstriction to a similar extent as regular daily low dose ICS with SABA for symptom relief and before exercise¹⁷⁹ (Evidence B).

Other Step 1 controller options for adults and adolescents

Low dose ICS taken whenever SABA is taken (Evidence B): In Step 1, the evidence for this strategy is indirect, from studies with separate or combination ICS and SABA inhalers in patients eligible for Step 2 treatment (see below).¹⁸⁰⁻¹⁸² In making this recommendation, the most important considerations were reducing the risk of severe exacerbations, and the difficulty of achieving good adherence with regularly-prescribed ICS in patients with infrequent symptoms. The as-needed use of ICS whenever SABA is taken may be an option in countries where ICS-formoterol is not available or affordable. As-needed use of separate or combination ICS inhalers is currently off-label.

Regular daily low dose ICS has been suggested by GINA since 2014 for consideration in Step 1, to reduce the risk of exacerbations. This was based on indirect evidence from studies in patients eligible for Step 2 treatment^{168,169,172} (Evidence B). However, patients with symptoms less than twice a month are extremely unlikely to take ICS regularly even if prescribed, leaving them exposed to the risks of SABA-only treatment, so for feasibility reasons, this regimen is no longer recommended for general use in such patients.

Step 1 controller options for children 6-11 years

Possible controller options for this age-group include taking ICS whenever SABA is taken, based on indirect evidence from a single Step 2 study with separate inhalers that showed substantially fewer exacerbations compared with SABA-only treatment.(Evidence B).¹⁸¹ Regular ICS with as-needed SABA is also a possible option for this age-group (Evidence B), but the likelihood of poor adherence in children with infrequent symptoms should be taken into account.

Not recommended

GINA no longer recommends SABA-only treatment of asthma in adults or adolescents. Although SABAs are highly effective for the quick relief of asthma symptoms¹⁸³ (Evidence A), patients whose asthma is treated with SABA alone are at risk of asthma-related death (Evidence A)¹⁷⁰ and urgent asthma-related healthcare (Evidence A),¹⁷¹ even if they have good symptom control.¹⁸⁴ One long-term study of regular SABA in patients with newly-diagnosed asthma showed worse outcomes and lower lung function than in patients who were treated with daily low dose ICS from the start.¹⁸⁵

In adults, inhaled anticholinergic agents like ipratropium, oral SABA or short-acting theophylline are potential alternatives to SABA for relief of asthma symptoms; however, these agents have a slower onset of action than inhaled SABA (Evidence A), and oral SABA and theophylline have a higher risk of side-effects. No long-term safety studies have been performed to assess the risk of severe exacerbations with these reliever medications in patients not also taking ICS.

The rapid-onset LABA, formoterol, is as effective as SABA as a reliever medication in adults and children,¹⁸⁶ but use of regular or frequent LABA without ICS is strongly discouraged because of the risk of exacerbations (Evidence A).

STEP 2: Preferred controller options: Daily low dose ICS plus as-needed SABA (adults, adolescents and children), OR as-needed low dose ICS-formoterol (adults and adolescents)

Preferred Step 2 controller (adults, adolescents and children): regular daily low dose ICS plus as-needed SABA

There is a large body of evidence from RCTs and observational studies showing that the risks of severe exacerbations, hospitalizations and mortality are substantially reduced with regular low dose ICS; symptoms and exercise-induced bronchoconstriction are also reduced^{168-170,187} (Evidence A). Severe exacerbations are halved with low dose ICS even in patients with symptoms 0-1 days a week.¹⁷²

For this recommendation, the most important consideration was to reduce the risk of severe exacerbations. When prescribing daily ICS for patients with mild asthma, clinicians should be aware of the likelihood of poor adherence, exposing patients to SABA-only treatment.

Preferred Step 2 controller (adults and adolescents): low dose ICS-formoterol, taken as-needed for relief of symptoms and, if needed, before exercise.

The evidence for this controller option to date is with low dose budesonide-formoterol. A large study in mild asthma found a 64% reduction in severe exacerbations compared with SABA-only treatment (Evidence B),¹⁷⁴ and two large studies in mild asthma showed non-inferiority for severe exacerbations compared with regular ICS (Evidence A).^{174,178}

In making this recommendation, the most important considerations for GINA were to prevent severe exacerbations and to avoid the need for daily ICS in patients with mild asthma. The small differences compared with regular ICS in FEV₁, (~30-50mL), symptom control (difference in ACQ-5 of ~0.15 vs minimal clinically important difference 0.5), and symptom-free days (mean difference 10.6 days per year)^{174,178} were considered to be less important. In patients with mild asthma, one study showed that budesonide-formoterol taken as-needed and before exercise had similar benefit in reducing exercise-induced bronchoconstriction as daily ICS with SABA as-needed and pre-exercise.¹⁷⁹

Other Step 2 controller options for adults and adolescents

Leukotriene receptor antagonists (LTRA) are less effective than ICS,¹⁸⁸ particularly for exacerbation reduction (Evidence A). They may be appropriate for initial controller treatment for some patients who are unable or unwilling to use ICS; for patients who experience intolerable side-effects from ICS; or for patients with concomitant allergic rhinitis^{189,190} (Evidence B).

For adult or adolescent patients not previously using controller treatment, regular daily combination low dose ICS-LABA as the initial maintenance controller treatment reduces symptoms and improves lung function compared with low dose ICS alone. However, it is more expensive and does not further reduce the risk of exacerbations compared with ICS alone¹⁹¹ (Evidence A).

For patients with purely seasonal allergic asthma, e.g. with birch pollen, with no interval asthma symptoms, regular daily ICS or as-needed ICS-formoterol should be started immediately symptoms commence, and continued for four weeks after the relevant pollen season ends (Evidence D).

Step 2 controller options for children 6-11 years

The preferred controller option for children at Step 2 is regular low dose ICS (see Box 3-6, p.48 for ICS dose ranges in children). Other controller options for children are daily LTRA, which is less effective than ICS,¹⁸⁸ or taking low dose ICS whenever SABA is taken, based on the results of one study with separate ICS and SABA inhalers in patients aged 5-18 years.¹⁸¹

Options not recommended for routine use

Sustained-release theophylline has only weak efficacy in asthma¹⁹²⁻¹⁹⁴ (Evidence B) and side-effects are common, and may be life-threatening at higher doses.¹⁹⁵ Chromones (nedocromil sodium and sodium cromoglycate) have a favorable safety profile but low efficacy^{196,197} (Evidence A), and their inhalers require burdensome daily washing to avoid blockage.

STEP 3: Preferred controller options: Low dose ICS-LABA maintenance plus as-needed SABA, OR low dose ICS-formoterol maintenance and reliever therapy (adults and adolescents); medium dose ICS plus as-needed SABA OR low-dose combination ICS-LABA plus as-needed SABA (children 6-11 years)

Before considering a step up, check for common problems such as incorrect inhaler technique, poor adherence, and environmental exposures, and confirm that the symptoms are due to asthma (Box 2-4, p22).

Preferred Step 3 controller options for adults and adolescents

For adults and adolescents, there are two 'preferred' Step 3 options: combination low dose ICS-LABA as maintenance treatment with as-needed SABA as reliever, and low dose ICS-formoterol as both maintenance and reliever treatment. For patients receiving maintenance ICS treatment with as-needed SABA, adding LABA in a combination inhaler provides additional improvements in symptoms and lung function with a reduced risk of exacerbations compared with the same dose of ICS,¹⁹⁸⁻²⁰⁰ (Evidence A) but there is only a small reduction in reliever use.^{199,200} Currently approved

combination ICS-LABA inhalers for Step 3 maintenance treatment of asthma include low doses of fluticasone propionate-formoterol, fluticasone furoate-vilanterol, fluticasone propionate-salmeterol, beclometasone-formoterol, budesonide-formoterol and mometasone-formoterol (see Box 3-6, p.48). Effectiveness of fluticasone furoate-vilanterol over usual care was demonstrated for asthma symptom control in a large real-world study, but there was no difference in exacerbations.^{68,201}

The ICS-formoterol maintenance and reliever regimen can be prescribed with low dose beclometasone-formoterol or budesonide-formoterol. In adult and adolescent patients with ≥ 1 exacerbation in the previous year, the ICS-formoterol maintenance and reliever regimen significantly reduces exacerbations and provides similar levels of asthma control at relatively low doses of ICS, compared with a fixed dose of ICS-LABA as maintenance treatment or a higher dose of ICS, both with as-needed SABA²⁰²⁻²⁰⁷ (Evidence A). Low dose ICS-formoterol is the preferred reliever for patients prescribed the maintenance and reliever treatment regimen. It should not be used as the reliever for patients taking combination ICS-LABA medications with a different LABA.

Other Step 3 controller options for adults and adolescents

For adult patients with allergic rhinitis and sensitized to house dust mite, with suboptimally controlled asthma despite low to high dose ICS, consider adding sublingual allergen immunotherapy (SLIT), provided FEV₁ is $>70\%$ predicted.^{208,209} (see p.58).

Another option for adults and adolescents is to increase ICS to medium dose (see Box 3-6, p.48), but at a group level this is less effective than adding a LABA^{128,210,211} (Evidence A). Other less efficacious options are low dose ICS plus either LTRA²¹² (Evidence A) or low dose, sustained-release theophylline²¹³ (Evidence B).

Step 3 controller options for children 6-11 years

In children, after checking inhaler technique and adherence, and treating modifiable risk factors, the preferred options at a population level are to increase ICS to medium dose (see Box 3-6, p.48), (Evidence A)²¹⁴ or change to combination low dose ICS-LABA (Evidence A).²¹⁵ In a large study of children aged 4-11 years with a history of an exacerbation in the previous year, combination ICS-LABA was non-inferior to the same dose of ICS alone for severe exacerbations, with no difference in symptom control or reliever use.²¹⁶ There has been one study of maintenance and reliever therapy with low dose budesonide-formoterol in children; it showed a large reduction in exacerbations compared with the same dose of budesonide-formoterol with SABA reliever, or compared with higher dose ICS.²¹⁷ This regimen is not approved for children <12 years.

STEP 4: Preferred controller: Low dose ICS-formoterol as maintenance and reliever therapy (adults and adolescents), OR medium dose ICS-LABA maintenance plus as-needed SABA (adults, adolescents and children).

Although at a group level most benefit from ICS is obtained at low dose, individual ICS responsiveness varies, and some patients whose asthma is uncontrolled on low dose ICS-LABA despite good adherence and correct technique may benefit from increasing the maintenance dose to medium. High dose ICS is no longer recommended at Step 4.

Preferred Step 4 controller options for adults and adolescents

The selection of Step 4 treatment depends on the prior selection at Step 3. Before stepping up, check for common problems such as incorrect inhaler technique, poor adherence, and environmental exposures, and confirm that the symptoms are due to asthma (Box 2-4, p.36).

For adult and adolescent patients with ≥ 1 exacerbations in the previous year, combination low dose ICS-formoterol as maintenance and reliever treatment is more effective in reducing exacerbations than the same dose of maintenance ICS-LABA or higher doses of ICS²⁰⁶ (Evidence A). This regimen can be prescribed with low dose budesonide-formoterol or beclometasone-formoterol as in Step 3; the maintenance dose may be increased to medium if necessary. For patients taking low dose maintenance ICS-LABA with as-needed SABA, whose asthma is not adequately controlled, treatment may be increased to medium dose ICS-LABA¹⁵⁶ (Evidence B); combination ICS-LABA medications are as for Step 3.

Other Step 4 controller options for adults and adolescents

Tiotropium (long-acting muscarinic antagonist) by mist inhaler may be used as add-on therapy in patients aged 6 years and older; it modestly improves lung function^{218,219} (Evidence A) and modestly reduces exacerbations.²¹⁸⁻²²⁰ In Step 4, there is insufficient evidence to support ICS+tiotropium over ICS-LABA combination.²²⁰

For adult patients with allergic rhinitis and sensitization to house dust mite, with suboptimally controlled asthma despite low-high dose ICS, consider adding sublingual allergen immunotherapy (SLIT), provided FEV₁ is >70% predicted.^{208,209} (see p.58).

Theophylline should not be used in children. For medium or high dose budesonide, efficacy may be improved with dosing four times daily^{221,222} (Evidence B), but adherence may be an issue. For other ICS, twice-daily dosing is appropriate (Evidence D). Other options for adults or adolescents that can be added to a medium- or high-dose ICS but that are less efficacious than adding LABA, include LTRA²²³⁻²²⁷ (Evidence A), or low dose sustained-release theophylline¹⁹³ (Evidence B).

Step 4 options for children 6-11 years

For children 6–11 years, if asthma is not well controlled on moderate dose ICS (see Box 3-6, p.48), the recommendation is to refer the child for expert assessment and advice.

Tiotropium (long-acting muscarinic antagonist) by mist inhaler may be used as add-on therapy in children aged 6 years and older; it modestly improves lung function and reduces exacerbations²¹⁸ (Evidence A).

STEP 5: Preferred option: Refer for phenotypic assessment and consideration of add-on treatment

Patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered, should be referred to a specialist with expertise in investigation and management of severe asthma¹³⁶ (Evidence D).

The GINA Pocket Guide and decision tree on Diagnosis and Management of difficult-to-treat and severe asthma in adolescent and adult patients are included in Chapter 3E (p.84). Treatment options that may be considered after optimization of existing therapy may include the following. **Always check local eligibility and payer criteria.**

- **Combination high dose ICS-LABA:** this may be considered in adults and adolescents, but the increase in ICS dose generally provides little additional benefit^{120,128,211,228} (Evidence A), and there is an increased risk of side-effects, including adrenal suppression.²²⁹ A high dose is recommended only on a trial basis for 3–6 months when good asthma control cannot be achieved with medium dose ICS plus LABA and/or a third controller (e.g. LTRA or sustained-release theophylline^{193,226} Evidence B).
- **Add-on tiotropium** (long-acting muscarinic antagonist) in patients aged ≥6 years whose asthma is not well-controlled with ICS-LABA. Add-on tiotropium (mostly 5µg once daily by mist inhaler) modestly improves lung function (Evidence A) and modestly increases the time to severe exacerbation requiring oral corticosteroids (Evidence B).^{219,220} There is no evidence with other LAMA preparations.²¹⁹
- **Add-on azithromycin** (three times a week, off-label) for adult patients with persistent symptomatic asthma despite moderate-high dose ICS and LABA reduced asthma exacerbations in eosinophilic²³⁰ and non-eosinophilic asthma^{230,231} (Evidence B) and improved asthma-related quality of life^{230,231} (Evidence B). Diarrhea was more common.²³⁰ Since macrolides such as azithromycin can cause ototoxicity and cardiac arrhythmia, asthma patients with hearing impairment²³⁰ or abnormal prolongation of the corrected QT interval^{230,231} were excluded from the studies. Before considering add-on off-label therapy with azithromycin in adult patients with uncontrolled or severe asthma, sputum should be checked for atypical mycobacteria, and the risk of increasing antimicrobial resistance at the patient and the population level should be taken into account.
- **Add-on anti-immunoglobulin E** (anti-IgE) (omalizumab) treatment: for patients aged ≥6 years with moderate or severe allergic asthma that is uncontrolled on Step 4-5 treatment^{232,233} (Evidence A).

- **Add-on anti-interleukin-5/5R** treatment (subcutaneous mepolizumab for patients aged ≥12 years; intravenous reslizumab for ages ≥18 years) or anti-interleukin 5 receptor treatment (subcutaneous benralizumab for ages ≥12 years), with severe eosinophilic asthma that is uncontrolled on Step 4-5 treatment (Evidence A).²³⁴⁻²³⁸
- **Add-on anti-interleukin-4R α** treatment (subcutaneous dupilumab) for patients aged ≥12 years with severe Type 2 asthma, or requiring treatment with maintenance OCS (Evidence A).^{239,240}
- **Sputum-guided treatment:** for adults with persisting symptoms and/or exacerbations despite high-dose ICS or ICS-LABA, treatment may be adjusted based on eosinophilia (>3%) in induced sputum. In severe asthma, this strategy leads to reduced exacerbations and/or lower doses of ICS¹⁵⁸ (Evidence A).
- **Add-on treatment with bronchial thermoplasty:** may be considered for some adult patients with severe asthma^{136,241} (Evidence B). Evidence is limited and in selected patients (see p.59). The long term effects compared with control patients, including for lung function, are not known.
- **Add-on low dose oral corticosteroids** (≤ 7.5 mg/day prednisone equivalent): may be effective for some adults with severe asthma¹³⁶ (Evidence D), but are often associated with substantial side effects^{242,243} (Evidence B). They should only be considered for adults with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence with Step 4 treatment, and after exclusion of other contributory factors and other add-on treatments. Patients should be counseled about potential side-effects (Evidence D).²⁴³ They should be assessed and monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥ 3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).²⁴⁴

REVIEWING RESPONSE AND ADJUSTING TREATMENT

How often should asthma be reviewed?

Patients with asthma should be reviewed regularly to monitor their symptom control, risk factors and occurrence of exacerbations, as well as to document the response to any treatment changes. For most controller medications, improvement begins within days of initiating treatment, but the full benefit may only be evident after 3–4 months.²⁴⁵ In severe and chronically under-treated disease, it may take longer.²⁴⁶

All health care providers should be encouraged to assess asthma control, adherence and inhaler technique at every visit, not just when the patient presents because of their asthma.²⁴⁷ The frequency of visits depends upon the patient's initial level of control, their response to treatment, and their level of engagement in self-management. Ideally, patients should be seen 1–3 months after starting treatment and every 3–12 months thereafter. After an exacerbation, a review visit within 1 week should be scheduled²⁴⁸ (Evidence D).

Stepping up asthma treatment

Asthma is a variable condition, and periodic treatment adjustments by the clinician and/or the patient may be needed.²⁴⁹

- *Sustained step up (for at least 2–3 months):* although at a group level most benefit from ICS is obtained at low dose, individual ICS responsiveness varies, and some patients whose asthma is uncontrolled on low dose ICS-LABA despite good adherence and correct technique may benefit from increasing the maintenance dose to medium. A step up in treatment may be recommended (Box 3-5, p31) if the symptoms are confirmed to be due to asthma; inhaler technique and adherence are satisfactory; and modifiable risk factors such as smoking have been addressed (Box 3-8, p38). Any step-up should be regarded as a therapeutic trial, and the response reviewed after 2–3 months. If there is no response, treatment should be reduced to the previous level, and alternative treatment options or referral considered.
- *Short-term step up (for 1–2 weeks):* an occasional short-term increase in maintenance ICS dose for 1–2 weeks may be necessary; for example, during viral infections or seasonal allergen exposure. This may be initiated by the patient according to their written asthma action plan (Box 4-2, p61), or by the health care provider.

- *Day-to-day adjustment:* for patients prescribed combination budesonide-formoterol or beclometasone-formoterol as maintenance and reliever treatment, the patient adjusts the number of as-needed doses of ICS-formoterol from day to day according to their symptoms, while continuing the maintenance dosage.

Stepping down treatment when asthma is well controlled

Once good asthma control has been achieved and maintained for 3 months and lung function has reached a plateau, treatment can often be successfully reduced, without loss of asthma control. The aims of stepping down are:

- To find the patient's minimum effective treatment, i.e. to maintain good control of symptoms and exacerbations, and to minimize the costs of treatment and potential for side-effects
- To encourage the patient to continue controller treatment. Patients often experiment with intermittent treatment through concern about the risks or costs of daily treatment,²⁵⁰ but this leaves them exposed to the risks of SABA-only treatment. For patients prescribed maintenance ICS-containing treatment with SABA reliever, it may be helpful to inform them that lower doses can be achieved if controller treatment is taken every day. For patients whose asthma is well-controlled on low dose ICS or LTRA, controller treatment can be continued at a very low average daily ICS dose by prescription of as-needed ICS-formoterol.^{174,178}

Before stepping down

The approach to stepping down will differ from patient to patient depending on their current treatment, risk factors and preferences. There are few experimental data on the optimal timing, sequence and magnitude of treatment reductions in asthma.

Predictors of loss of control during dose reduction include airway hyperresponsiveness and sputum eosinophilia,²⁵¹ but these tests are not readily available in primary care. In one study, a history of exacerbations in the previous 12 months was associated with greater risk of exacerbation after step-down.²⁵²

Any step-down of asthma treatment should be considered as a therapeutic trial, with the response evaluated in terms of both symptom control and exacerbation frequency. Prior to stepping down treatment, the patient should be provided with a written asthma action plan and instructions for how and when to resume their previous treatment if their symptoms worsen.

How to step down treatment

Decisions about treatment step-down should be made on an individual patient level. In one study of patients with well-controlled asthma on medium dose ICS-LABA, reducing the ICS dose and removing the LABA had similar effects on a composite treatment failure outcome. However, stopping LABA was associated with lower lung function and more hospitalizations; and decreasing the ICS dose was inferior to maintaining a stable dose of ICS-LABA.²⁵³ If treatment is stepped down too far or too quickly, exacerbation risk may increase even if symptoms remain reasonably controlled²⁵⁴ (Evidence B). Complete cessation of ICS is associated with a significant risk of exacerbations²⁵⁵ (Evidence A).

Step-down strategies for different controller treatments are summarized in Box 3-7, p.56; these are based on current evidence, but more research is needed. Only a small number of step-down studies have been performed in children.

Box 3-7. Options for stepping down treatment once asthma is well controlled

General principles of stepping down asthma treatment

- Consider stepping down when asthma symptoms have been well controlled and lung function has been stable for 3 or more months (Evidence D). If the patient has risk factors for exacerbations (Box 2-2, p17), for example a history of exacerbations in the past year,²⁵² or persistent airflow limitation, do not step down without close supervision.
- Choose an appropriate time (no respiratory infection, patient not travelling, not pregnant).
- Approach each step as a therapeutic trial. Engage the patient in the process; document their asthma status (symptom control, lung function and risk factors, Box 2-2); provide clear instructions; provide a written asthma action plan (Box 4-2, p61) and ensure the patient has sufficient medication to resume their previous dose if necessary; monitor symptoms and/or PEF; and schedule a follow-up visit (Evidence D).
- Stepping down ICS doses by 25-50% at 3 month intervals is feasible and safe for most patients²⁵⁶ (Evidence A).

Current step	Current medication and dose	Options for stepping down	Evidence
Step 5	High dose ICS-LABA plus oral corticosteroids (OCS)	<ul style="list-style-type: none"> Continue high dose ICS-LABA and reduce OCS dose Use sputum-guided approach to reducing OCS Alternate-day OCS treatment Replace OCS with high dose ICS 	D B D D
	High dose ICS-LABA plus other add-on agents	<ul style="list-style-type: none"> Refer for expert advice 	D
Step 4	Moderate to high dose ICS-LABA maintenance treatment	<ul style="list-style-type: none"> Continue combination ICS-LABA with 50% reduction in ICS component, by using available formulations Discontinuing LABA may lead to deterioration²⁵⁷ 	B A
	Medium dose ICS-formoterol* as maintenance and reliever	<ul style="list-style-type: none"> Reduce maintenance ICS-formoterol* to low dose, and continue as-needed low dose ICS-formoterol* reliever 	D
	High dose ICS plus second controller	<ul style="list-style-type: none"> Reduce ICS dose by 50% and continue second controller²⁵⁶ 	B
Step 3	Low dose ICS-LABA maintenance	<ul style="list-style-type: none"> Reduce ICS-LABA to once daily Discontinuing LABA may lead to deterioration²⁵⁷ 	D A
	Low dose ICS-formoterol* as maintenance and reliever	<ul style="list-style-type: none"> Reduce maintenance ICS-formoterol* dose to once daily and continue as-needed low dose ICS-formoterol* reliever 	C
	Moderate- or high-dose ICS	<ul style="list-style-type: none"> Reduce ICS dose by 50%²⁵⁶ 	A
Step 2	Low dose ICS	<ul style="list-style-type: none"> Once-daily dosing (budesonide, ciclesonide, mometasone)^{258,259} Switch to as-needed low dose ICS-formoterol^{174,178} Adding LTRA may allow ICS dose to be stepped down²⁶⁰ Insufficient evidence to support step-down to as-needed ICS with SABA²⁶¹ 	A A B -
	Low dose ICS or LTRA	<ul style="list-style-type: none"> Switch to as-needed low dose ICS formoterol^{174,178} Complete cessation of ICS in adults and adolescents is not advised as the risk of exacerbations is increased with SABA-only treatment²⁵⁵ 	A A

BDP: beclometasone dipropionate; ICS: inhaled corticosteroids; LABA: long-acting beta₂-agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids.

*ICS-formoterol maintenance and reliever treatment can be prescribed with low dose budesonide-formoterol or BDP-formoterol.

TREATING OTHER MODIFIABLE RISK FACTORS

Some patients continue to experience exacerbations even with maximal doses of current treatment. Having even one exacerbation increases the risk that a patient will have another within the next 12 months.¹⁰² There is increasing research interest in identifying at-risk patients (Box 2-2B, p.31), and in investigating new strategies to further reduce exacerbation risk.

In clinical practice, exacerbation risk can be reduced both by optimizing asthma medications, and by identifying and treating modifiable risk factors (Box 3-8). Not all risk factors require or respond to a step up in controller treatment.

Box 3-8. Treating modifiable risk factors to reduce exacerbations

Risk factor	Treatment strategy	Evidence
Any patient with ≥1 risk factor for exacerbations (including poor symptom control)	<ul style="list-style-type: none"> Ensure patient is prescribed an ICS-containing controller Ensure patient has a written action plan appropriate for their health literacy Review patient more frequently than low-risk patients Check inhaler technique and adherence frequently Identify any modifiable risk factors (Box 2-2, p17) 	A A A A D
≥1 severe exacerbation in last year	<ul style="list-style-type: none"> Consider alternative controller regimens to reduce exacerbation risk, e.g. ICS-formoterol maintenance and reliever regimen Consider stepping up treatment if no modifiable risk factors Identify any avoidable triggers for exacerbations 	A A C
Exposure to tobacco smoke	<ul style="list-style-type: none"> Encourage smoking cessation by patient/family; provide advice and resources Consider higher dose of ICS if asthma poorly-controlled 	A B
Low FEV ₁ , especially if <60% predicted	<ul style="list-style-type: none"> Consider trial of 3 months' treatment with high-dose ICS and/or 2 weeks' OCS Exclude other lung disease, e.g. COPD Refer for expert advice if no improvement 	B D D
Obesity	<ul style="list-style-type: none"> Strategies for weight reduction Distinguish asthma symptoms from symptoms due to deconditioning, mechanical restriction, and/or sleep apnea 	B D
Major psychological problems	<ul style="list-style-type: none"> Arrange mental health assessment Help patient to distinguish between symptoms of anxiety and asthma; provide advice about management of panic attacks 	D D
Major socioeconomic problems	<ul style="list-style-type: none"> Identify most cost-effective ICS-based regimen 	D
Confirmed food allergy	<ul style="list-style-type: none"> Appropriate food avoidance; injectable epinephrine 	A
Allergen exposure if sensitized	<ul style="list-style-type: none"> Consider trial of simple avoidance strategies; consider cost Consider step up of controller treatment Consider adding SLIT in symptomatic adult HDM-sensitive patients with allergic rhinitis despite ICS, provided FEV₁ is >70% predicted 	C D B
Sputum eosinophilia (limited centers)	<ul style="list-style-type: none"> Increase ICS dose independent of level of symptom control 	A*

FEV₁: forced expiratory volume in 1 second; HDM: house dust mite; ICS: inhaled corticosteroids; OCS: oral corticosteroids; SLIT: sublingual immunotherapy.

* Based on evidence from relatively small studies in selected populations. Also see Box 3-9 and p.60 for more information about non-pharmacological interventions.

The potential for local and/or systemic side-effects of medications can be minimized by ensuring correct inhaler technique (Box 3-12, p.70), by reminding patients to rinse and spit out after using ICS, and, after good asthma control has been maintained for 3 months, by finding each patient's minimum effective dose (the lowest dose that will maintain good symptom control and minimize exacerbations, Box 3-7, p.37).

OTHER THERAPIES

Allergen immunotherapy

Allergen-specific immunotherapy may be a treatment option where allergy plays a prominent role, including asthma with allergic rhinoconjunctivitis.²⁶² There are currently two approaches: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). In the past, few studies in asthma have compared immunotherapy with pharmacological therapy, or used standardized outcomes such as exacerbations, and most studies have been in patients with mild asthma.

Subcutaneous immunotherapy (SCIT)

SCIT involves the identification and use of clinically relevant allergens, and administration of extracts in progressively higher doses to induce desensitization and/or tolerance. European physicians tend to favor single allergen immunotherapy whereas Northern American physicians often prescribe multiple allergens for treatment.²⁶³ In people with asthma and allergic sensitization, SCIT is associated with a reduction in symptom scores and medication requirements, and improved allergen-specific and non-specific airway hyperresponsiveness.²⁶³

For SCIT, local injection site reactions may range from a minimal immediate wheal and flare to a large, painful, delayed allergic response. Uncommon systemic effects include anaphylactic reactions, which may be life threatening, and severe asthma exacerbations. Deaths from SCIT, although rare, have occurred in people with asthma regardless of disease severity.

Advice

- Compared to pharmacological and avoidance options, potential benefits of SCIT must be weighed against the risk of adverse effects and the inconvenience and cost of the prolonged course of therapy, including the minimum half-hour wait required after each injection (Evidence D).

Sublingual immunotherapy (SLIT)

Modest effects were identified in a systematic review of SLIT for asthma in adults and children,²⁶⁴⁻²⁶⁶ but there was concern about the design of many of the studies.²⁶⁷ There are few studies comparing SLIT with pharmacological therapy for asthma.²⁶⁸ A recent trial of SLIT for house dust mites (HDM) in patients with asthma and HDM allergic rhinitis demonstrated a modest reduction of ICS with high dose SLIT.²⁰⁹ In another study in patients with asthma and HDM allergic rhinitis, SLIT added to low or moderate dose ICS showed increased time to exacerbation during ICS reduction in sub-optimally controlled asthma.²⁰⁸

Side effects²⁶⁹⁻²⁷¹ from SLIT for inhalant allergens are predominantly limited to oral and gastrointestinal symptoms.²⁶⁶

Advice

- For adult patients with allergic rhinitis and sensitized to house dust mite, with persisting asthma symptoms despite low-moderate dose ICS-containing therapy, consider adding sublingual allergen immunotherapy (SLIT), provided FEV₁ is >70% predicted (Evidence B)
- As for any treatment, potential benefits of SLIT for individual patients should be weighed against the risk of adverse effects, and the cost to the patient and health system.

Vaccinations

Influenza causes significant morbidity and mortality in the general population, and contributes to some acute asthma exacerbations. The risk of influenza infection itself can be reduced by annual vaccination. A systematic review of placebo-controlled randomized controlled trials of influenza vaccination showed no reduction in asthma exacerbations,²⁷² but no such studies had been performed since 2001. However, a recent systematic review and meta-

analysis that included observational studies with a wide range of study designs suggested that influenza vaccination reduced the risk of asthma exacerbations, although for most of the studies, bias could not be excluded.²⁷³ There is no evidence for an increase in asthma exacerbations after influenza vaccination compared to placebo.²⁷³ Limited evidence exists with respect to the safety and efficacy of live attenuated intranasal vaccination in children; most of the evidence that does exist is restricted to children 3 years and older.

People with asthma, particularly children and the elderly, are at higher risk of pneumococcal disease,²⁷⁴ but there is insufficient evidence to recommend routine pneumococcal vaccination in people with asthma.²⁷⁵

Advice

- Advise patients with moderate to severe asthma to receive an influenza vaccination every year, or at least when vaccination of the general population is advised (Evidence C).
- There is insufficient evidence to recommend routine pneumococcal vaccination in people with asthma (Evidence D).

Bronchial thermoplasty

Bronchial thermoplasty is a potential treatment option at Step 5 in some countries for adult patients whose asthma remains uncontrolled despite optimized therapeutic regimens and referral to an asthma specialty center (Evidence B). Bronchial thermoplasty involves treatment of the airways during three separate bronchoscopies with a localized radiofrequency pulse.¹¹³ The treatment is associated with a large placebo effect.¹¹³ In patients taking high-dose ICS-LABA, bronchial thermoplasty was associated with an increase in asthma exacerbations during the 3 month treatment period, and a subsequent decrease in exacerbations, but no beneficial effect on lung function or asthma symptoms compared with sham-controlled patients.¹¹³ Extended follow up of some treated patients reported a sustained reduction in exacerbations compared with pre-treatment.²⁷⁶ However, longer-term follow up of larger cohorts comparing effectiveness and safety, including for lung function, in both active and sham-treated patients is needed.

Advice

- For adult patients whose asthma remains uncontrolled despite optimization of asthma therapy and referral to a severe asthma specialty center, bronchial thermoplasty is a potential treatment option at Step 5 in some countries (Evidence B).
- Caution should be used in selecting patients for this procedure. The number of studies is small, people with chronic sinus disease, frequent chest infections or FEV₁ <60% predicted were excluded from the pivotal sham-controlled study, and patients did not have their asthma treatment optimized before bronchial thermoplasty was performed.
- Bronchial thermoplasty should be performed in adults with severe asthma only in the context of an independent Institutional Review Board-approved systematic registry or a clinical study, so that further evidence about effectiveness and safety of the procedure can be accumulated.^{136,277}

VITAMIN D

Several cross-sectional studies have shown that low serum levels of Vitamin D are linked to impaired lung function, higher exacerbation frequency and reduced corticosteroid response.²⁷⁸ Vitamin D supplementation may reduce the rate of asthma exacerbation requiring treatment with systemic corticosteroids in asthma patients with baseline 25(OH)D of less than 25 nmol/L.²⁷⁹ In a meta-analysis, benefit for asthma worsenings was seen in some studies, but to date, there is no good-quality evidence that Vitamin D supplementation leads to improvement in asthma control or reduction in exacerbations.²⁸⁰⁻²⁸² More studies are needed.

NON-PHARMACOLOGICAL STRATEGIES

In addition to pharmacological treatments, other strategies may be considered where relevant, to assist in improving symptom control and/or reducing future risk. The advice and evidence level are summarized in Box 3-9, with brief text on the following pages.

Box 3-9. Non-pharmacological interventions - summary

Intervention	Advice/recommendation (continued on next page)	Evidence
Cessation of smoking and ETS exposure	<ul style="list-style-type: none"> At every visit, strongly encourage people with asthma who smoke to quit. Provide access to counseling and smoking cessation programs (if available) Advise parents/carers of children with asthma not to smoke and not to allow smoking in rooms or cars that their children use Strongly encourage people with asthma to avoid environmental smoke exposure Assess smokers/ex-smokers for COPD or overlapping features of asthma and COPD (asthma–COPD overlap, ACO, Chapter 5, p.119), as additional treatment strategies may be required 	A A B D
Physical activity	<ul style="list-style-type: none"> Encourage people with asthma to engage in regular physical activity for its general health benefits Provide advice about prevention of exercise-induced bronchoconstriction with regular ICS Provide advice about prevention of breakthrough exercise-induced bronchoconstriction with <ul style="list-style-type: none"> warm-up before exercise SABA before exercise low dose ICS-formoterol before exercise Regular physical activity improves cardiopulmonary fitness, but confers no other specific benefit on lung function or asthma symptoms, with the exception of swimming in young people with asthma There is little evidence to recommend one form of physical activity over another 	A A A A B B D
Avoidance of occupational exposures	<ul style="list-style-type: none"> Ask all patients with adult-onset asthma about their work history and other exposures In management of occupational asthma, identify and eliminate occupational sensitizers as soon as possible, and remove sensitized patients from any further exposure to these agents Patients with suspected or confirmed occupational asthma should be referred for expert assessment and advice, if available 	A A A
Avoidance of medications that may make asthma worse	<ul style="list-style-type: none"> Always ask about asthma before prescribing NSAIDs, and advise patients to stop using them if asthma worsens Always ask people with asthma about concomitant medications Aspirin and NSAIDs (non-steroidal anti-inflammatory drugs) are not generally contraindicated unless there is a history of previous reactions to these agents (see p.82) Decide about prescription of oral or intra-ocular beta-blockers on a case-by-case basis. Initiate treatment under close medical supervision by a specialist If cardioselective beta-blockers are indicated for acute coronary events, asthma is not an absolute contra-indication, but the relative risks/benefits should be considered 	A D A D D
Healthy diet	<ul style="list-style-type: none"> Encourage patients with asthma to consume a diet high in fruit and vegetables for its general health benefits 	A

Box 3-9 (continued) Non-pharmacological interventions – Summary

Intervention	Advice/recommendation	Evidence
Avoidance of indoor allergens	<ul style="list-style-type: none"> Allergen avoidance is not recommended as a general strategy in asthma For sensitized patients, there is limited evidence of clinical benefit for asthma in most circumstances with single-strategy indoor allergen avoidance Remediation of dampness or mold in homes reduces asthma symptoms and medication use in adults For patients sensitized to house dust mite and/or pets, there is limited evidence of clinical benefit for asthma with avoidance strategies (only in children) Allergen avoidance strategies are often complicated and expensive, and there are no validated methods for identifying those who are likely to benefit 	A A A B D
Weight reduction	<ul style="list-style-type: none"> Include weight reduction in the treatment plan for obese patients with asthma For obese adults with asthma a weight reduction program plus twice-weekly aerobic and strength exercises is more effective for symptom control than weight reduction alone 	B B
Breathing exercises	<ul style="list-style-type: none"> Breathing exercises may be a useful supplement to asthma pharmacotherapy for symptoms and quality of life, but they do not improve lung function or reduce exacerbation risk 	A
Avoidance of indoor air pollution	<ul style="list-style-type: none"> Encourage people with asthma to use non-polluting heating and cooking sources, and for sources of pollutants to be vented outdoors where possible 	B
Avoidance of outdoor allergens	<ul style="list-style-type: none"> For sensitized patients, when pollen and mold counts are highest, closing windows and doors, remaining indoors, and using air conditioning may reduce exposure to outdoor allergens 	D
Dealing with emotional stress	<ul style="list-style-type: none"> Encourage patients to identify goals and strategies to deal with emotional stress if it makes their asthma worse There is insufficient evidence to support one stress-reduction strategy over another, but relaxation strategies and breathing exercises may be helpful Arrange a mental health assessment for patients with symptoms of anxiety or depression 	D B D
Avoidance of outdoor air pollutants/weather conditions	<ul style="list-style-type: none"> During unfavorable environmental conditions (very cold weather or high air pollution) it may be helpful to stay indoors in a climate-controlled environment, and to avoid strenuous outdoor physical activity; and to avoid polluted environments during viral infections, if feasible 	D
Avoidance of foods and food chemicals	<ul style="list-style-type: none"> Food avoidance should not be recommended unless an allergy or food chemical sensitivity has been clearly demonstrated, usually by carefully supervised oral challenges For confirmed food allergy, food allergen avoidance may reduce asthma exacerbations If food chemical sensitivity is confirmed, complete avoidance is not usually necessary, and sensitivity often decreases when asthma control improves 	D D D

NSAID: non-steroidal anti-inflammatory drugs; SABA: short-acting beta₂-agonist.

Interventions with highest level evidence are shown first..

Smoking cessation and avoidance of environmental tobacco smoke

Cigarette smoking has multiple deleterious effects in people with established asthma, in addition to its other well-known effects such as increased risk of lung cancer, COPD and cardiovascular disease; and, with exposure in pregnancy, increased risk of asthma and lower respiratory infections in children.

In people with asthma (children and adults), exposure to passive smoke increases the risk of hospitalization and poor asthma control. Active smoking is associated with increased risk of poor asthma control, hospital admissions and, in some studies, death from asthma; it increases the rate of decline of lung function and may lead to COPD; and it reduces the effectiveness of inhaled and oral corticosteroids.²⁸³ After smoking cessation, lung function improves and airway inflammation decreases.²⁸⁴ Reduction of passive smoke exposure improves asthma control and reduces hospital admissions in adults and children.²⁸⁵

Advice

- At every visit, strongly encourage people with asthma who smoke to quit. They should be provided with access to counseling and, if available, to smoking cessation programs (Evidence A).
- Strongly encourage people with asthma to avoid environmental smoke exposure (Evidence B).
- Advise parents/carers of children with asthma not to smoke and not to allow smoking in rooms or cars that their children use (Evidence A).
- Assess patients with a >10 pack-year smoking history for COPD or asthma–COPD overlap, as additional treatment strategies may be required (see *Global Strategy for Asthma Management and Prevention 2018*, Chapter 5).²⁸⁶

Physical activity

For people with asthma, as in the general population, regular moderate physical activity has important health benefits including reduced cardiovascular risk and improved quality of life. Overall, physical activity has no benefit on lung function or asthma symptoms,²⁸⁷ but improved cardiopulmonary fitness may reduce the risk of dyspnea unrelated to airflow limitation being mistakenly attributed to asthma. In one study of non-obese patients with asthma, high intensity interval training together with a diet with high protein and low glycemic index improved asthma symptom control, although no benefit on lung function was seen.²⁸⁸ In young people with asthma, swimming training is well tolerated and leads to increased lung function and cardio-pulmonary fitness;²⁸⁹ however, there are some concerns about chlorine exposure with indoor pools.

Exercise is an important cause of asthma symptoms for many asthma patients, but EIB can usually be reduced with maintenance ICS.¹⁶ Breakthrough exercise-related symptoms can be managed with warm-up before exercise,¹⁶ and/or by taking SABA¹⁶ or low-dose ICS-formoterol¹⁷⁹ before or during exercise.

Advice

- Encourage people with asthma to engage in regular physical activity because of its general health benefits (Evidence A). However, regular physical activity confers no specific benefit on lung function or asthma symptoms *per se*, with the exception of swimming in young people with asthma (Evidence B). There is insufficient evidence to recommend one form of physical activity over another (Evidence D).
- Provide patients with advice about prevention and management of exercise-induced bronchoconstriction including with daily treatment with ICS (Evidence A) plus SABA as-needed and pre-exercise (Evidence A), or with low dose ICS-formoterol as-needed and before exercise (Evidence B), with warm-up before exercise if needed (Evidence A).

Avoidance of occupational exposures

Occupational exposures to allergens or sensitizers account for a substantial proportion of the incidence of adult asthma.²⁹⁰ Once a patient has become sensitized to an occupational allergen, the level of exposure necessary to induce symptoms may be extremely low, and resulting exacerbations become increasingly severe. Attempts to reduce occupational exposure have been successful, especially in industrial settings.³⁶ Cost-effective minimization of latex sensitization can be achieved by using non-powdered low-allergen gloves instead of powdered latex gloves.³⁶

Advice

- Ask all patients with adult-onset asthma about their work history and other exposures (Evidence A).
- In management of occupational asthma, identify and eliminate occupational sensitizers as soon as possible, and remove sensitized patients from any further exposure to these agents (Evidence A).
- Patients with suspected or confirmed occupational asthma should be referred for expert assessment and advice, if available, because of the economic and legal implications of the diagnosis (Evidence A)

Avoidance of medications that may make asthma worse

Aspirin and other NSAIDs can cause severe exacerbations.²⁹¹ Beta-blocker drugs administered orally or intra-ocularly may cause bronchospasm²⁹² and have been implicated in some asthma deaths. However, beta-blockers have a proven benefit in the management of cardiovascular disease. People with asthma who have had an acute coronary event and received cardio-selective beta blockers within 24 hours of hospital admission have been found to have lower in-hospital mortality rates.²⁹³

Advice

- Always ask people with asthma about concomitant medications (Evidence A).
- Always ask about asthma and previous reactions before prescribing NSAIDs, and advise patients to stop using these medications if asthma worsens.
- Aspirin and NSAIDs are not generally contraindicated in asthma unless there is a history of previous reactions to these agents (Evidence A). (See '*Aspirin-exacerbated respiratory disease*', p.82)
- For people who may benefit from oral or intra-ocular beta-blocker treatment, a decision to prescribe these medications should be made on a case-by-case basis, and treatment should only be initiated under close medical supervision by a specialist (Evidence D).
- Asthma should not be regarded as an absolute contraindication to use cardioselective beta-blockers when they are indicated for acute coronary events, but the relative risks and benefits should be considered (Evidence D). The prescribing physician and patient should be aware of the risks and benefits of treatment.²⁹⁴

Avoidance of indoor allergens

Because many asthma patients react to multiple factors that are ubiquitous in the environment, avoiding these factors completely is usually impractical and very burdensome for the patient. Medications to maintain good asthma control have an important role because patients are often less affected by environmental factors when their asthma is well-controlled.

There is conflicting evidence about whether measures to reduce exposure to indoor allergens are effective at reducing asthma symptoms.^{295,296} The majority of single interventions have failed to achieve a sufficient reduction in allergen load to lead to clinical improvement.^{295,297,298} It is likely that no single intervention will achieve sufficient benefits to be cost effective (Box 3-10, p.64). One study of insecticidal bait in homes eradicated cockroaches for a year and led to a significant decrease in symptoms, improvement in pulmonary function, and less health care use for children with moderate to severe asthma.²⁹⁹

Domestic mites: these mites live and thrive in many sites throughout the house so they are difficult to reduce and impossible to eradicate. A systematic review of multi-component interventions to reduce allergens including house dust mite showed no benefit for asthma in adults and a small benefit for children.³⁰⁰ One study that used a rigorously applied integrated approach to dust mite control led to a significant decrease in symptoms, medication use and improvement in pulmonary function for children with dust mite sensitization and asthma.³⁰¹ However, this approach is complicated and expensive and is not generally recommended. A study in mite-sensitized children recruited after emergency department presentation showed a decrease in emergency department visits, but not oral corticosteroids, with the use of mite-impermeable encasement of the mattress, pillow and duvet.³⁰²

Furred animals: complete avoidance of pet allergens is impossible for sensitized patients as these allergens are ubiquitous outside the home³⁰³ in schools,³⁰⁴ public transport, and even cat-free buildings, probably transferred on

clothes.³⁰⁴ Although removal of such animals from the home of a sensitized patient is encouraged,³⁰⁵ it can be many months before allergen levels decrease,³⁰⁶ and the clinical effectiveness of this and other interventions remains unproven.³⁰⁷

Rodents: symptomatic patients suspected of domestic exposure to rodents should be evaluated with skin prick tests or specific IgE, as exposure may not be apparent unless there is an obvious infestation.³⁰⁸ High level evidence for the effectiveness of removing rodents is lacking, as most integrated pest management interventions also remove other allergen sources;³⁰⁸ one non-sham-controlled study showed comparable clinical improvement with pest reduction education and integrated pest management.³⁰⁹

Box 3-10. Effectiveness of avoidance measures for indoor allergens

Measure	Evidence of effect on allergen levels	Evidence of clinical benefit
House dust mites		
Encase bedding in impermeable covers	Some (A)	Adults - none (A) Children - some (A)
Wash bedding on hot cycle (55–60°C)	Some (C)	None (D)
Replace carpets with hard flooring	Some (B)	None (D)
Acaricides and/or tannic acid	Weak (C)	None (D)
Minimize objects that accumulate dust	None (D)	None (D)
Vacuum cleaners with integral HEPA filter and double-thickness bags	Weak (C)	None (D)
Remove, hot wash, or freeze soft toys	None (D)	None
Pets		
Remove cat/dog from the home	Weak (C)	None (D)
Keep pet from the main living areas/bedrooms	Weak (C)	None (D)
HEPA-filter air cleaners	Some (B)	None (A)
Wash pet	Weak (C)	None (D)
Replace carpets with hard flooring	None (D)	None (D)
Vacuum cleaners with integral HEPA filter and double-thickness bags	None (D)	None (D)
Cockroaches		
Bait plus professional extermination of cockroaches	Minimal (D)	None (D)
Baits placed in households	Some (B)	Some (B)
Rodents		
Integrated pest management strategies	Some (B)	Some (B)
Fungi		
Remediation of dampness or mold in homes	A	A
Air filters, air conditioning	Some (B)	None (D)

This table is adapted from Custovic et al³¹⁰

Cockroaches: avoidance measures for cockroaches are only partially effective in removing residual allergens³¹¹ and evidence of clinical benefit is lacking.

Fungi: fungal exposure has been associated with asthma exacerbations. The number of fungal spores can best be reduced by removing or cleaning mold-laden objects.³¹² Air conditioners and dehumidifiers may be used to reduce humidity to less than 50% and to filter large fungal spores. However, air conditioning and sealing of windows have also been associated with increases in fungal and house dust mite allergens.³¹³

Advice

- Allergen avoidance is not recommended as a general strategy for people with asthma (Evidence A).
- For sensitized patients, although it would seem logical to attempt to avoid allergen exposure in the home, there is some evidence for clinical benefit with single avoidance strategies (Evidence A) and only limited evidence for benefit with multi-component avoidance strategies (in children) (Evidence B).
- Although allergen avoidance strategies may be beneficial for some sensitized patients (Evidence B), they are often complicated and expensive, and there are no validated methods for identifying those who are likely to benefit (Evidence D).

Healthy diet

In the general population, a diet high in fresh fruit and vegetables has many health benefits, including prevention of many chronic diseases and forms of cancer. Many epidemiological studies report that a high fruit and vegetable diet is associated with a lower risk of asthma and lung function decline. There is some evidence that increasing fruit and vegetable intake leads to an improvement in asthma control and a reduced risk of exacerbations.³¹⁴

Advice

- Encourage patients with asthma to consume a diet high in fruit and vegetables for its general health benefits (Evidence A).

Weight reduction for obese patients

Asthma is more difficult to control in obese patients,³¹⁵⁻³¹⁷ and response to ICS may be reduced.³¹⁸ Weight loss improves asthma control, lung function and health status, and reduces medication needs in obese patients with asthma.^{319,320} The most striking results have been observed after bariatric surgery,^{321,322} but even 5–10% weight loss with diet, with or without exercise, can lead to improved asthma control and quality of life.³²³

In one study of obese patients with asthma, a weight loss program plus twice-weekly aerobic and strength exercises improved symptom control, lung function and inflammatory markers compared with weight loss alone (Evidence B). In this study, cases (n=28) received a weight loss program plus twice-weekly sessions of aerobic (50–75% of peak V_{O_2}) and resistance muscle training, and controls (n=27) received a weight loss program plus twice-weekly sham breathing and stretching exercises.³²⁴

Advice

- Include weight reduction in the treatment plan for obese patients with asthma (Evidence B). Increased exercise alone appears to be insufficient (Evidence B).

Breathing exercises

A systematic review of studies of breathing and/or relaxation exercises for asthma and/or dysfunctional breathing, including the Buteyko method and the Papworth method, reported improvements in symptoms, quality of life and/or psychological measures, but not in physiological outcomes or risk of exacerbations.³²⁵ A subsequent large pragmatic study of breathing training in patients with impaired asthma-related quality of life showed significant but small improvements in quality of life, but no difference in asthma symptom control or risk of exacerbations. Results with three face-to-face physiotherapy sessions and DVD-based training were similar.³²⁶ Breathing exercises used in some of these studies are available at www.breathestudy.co.uk³²⁶ and www.woolcock.org.au/moreinfo.

In order for studies of non-pharmacological strategies such as breathing exercises to be considered high quality, control groups should be appropriately matched for level of contact with health professionals and for asthma education. A study of two physiologically contrasting breathing exercises, which were matched for contact with health professionals and instructions about rescue inhaler use, showed similar improvements in reliever use and ICS dose after down-titration in both groups.³²⁷ This suggests that perceived improvement with breathing exercises may be largely due to factors such as relaxation, voluntary reduction in use of rescue medication, or engagement of the patient in their care. The cost of some programs may be a potential limitation.

Advice

- Breathing exercises may be considered as a supplement to conventional asthma management strategies for symptoms and quality of life, but they do not improve lung function or reduce exacerbation risk (Evidence A).

Avoidance of indoor air pollution

In addition to passive and active smoking, other major indoor air pollutants that are known to impact on respiratory health include nitric oxide, nitrogen oxides, carbon monoxide, carbon dioxide, sulfur dioxide, formaldehyde, and biologicals (endotoxin).³²⁸ Sources include cooking and heating devices, particularly if they are not externally flued (vented). Installation of non-polluting, more effective heating (heat pump, wood pellet burner, flued gas) in the homes of children with asthma does not significantly improve lung function but significantly reduces symptoms of asthma, days off school, healthcare utilization, and pharmacist visits.³²⁹

Advice

- Encourage people with asthma to use non-polluting heating and cooking sources, and for sources of pollutants to be vented outdoors where possible (Evidence B).

Strategies for dealing with emotional stress

Emotional stress may lead to asthma exacerbations in children³³⁰ and adults. Hyperventilation associated with laughing, crying, anger, or fear can cause airway narrowing.^{331,332} Panic attacks have a similar effect.^{333,334} However, it is important to note that asthma is not primarily a psychosomatic disorder. During stressful times, medication adherence may also decrease.

Advice

- Encourage patients to identify goals and strategies to deal with emotional stress if it makes their asthma worse (Evidence D).
- There is insufficient evidence to support one strategy over another, but relaxation strategies and breathing exercises may be helpful in reducing asthma symptoms (Evidence B).
- Arrange a mental health assessment for patients with symptoms of anxiety or depression (Evidence D).

Avoidance of outdoor allergens

For patients sensitized to outdoor allergens such as pollens and molds, these are impossible to avoid completely.

Advice

- For sensitized patients, closing windows and doors, remaining indoors when pollen and mold counts are highest, and using air conditioning may reduce exposure (Evidence D).
- The impact of providing information in the media about outdoor allergen levels is difficult to assess.

Avoidance of outdoor air pollution

Meta-analysis of epidemiological studies showed a significant association between air pollutants such as ozone, nitrogen oxides, acidic aerosols, and particulate matter and symptoms or exacerbations of asthma, including emergency room visits and hospitalizations.⁹³ Certain weather and atmospheric conditions like thunderstorms³³⁵ may trigger asthma exacerbations by a variety of mechanisms, including dust and pollution, by increasing the level of respirable allergens, and causing changes in temperature and/or humidity. Reduction of outdoor air pollutants usually requires national or local policy changes. For example, short-term traffic restrictions imposed in Beijing during the Olympics reduced pollution and was associated with a significant fall in asthma outpatient visits.³³⁶

Advice

- In general, when asthma is well-controlled, there is no need for patients to modify their lifestyle to avoid unfavorable outdoor conditions (air pollutants, weather).

- It may be helpful during unfavorable environmental conditions (very cold weather, low humidity or high air pollution) to avoid strenuous outdoor physical activity and stay indoors in a climate-controlled environment; and to avoid polluted environments during viral infections (Evidence D)

Avoidance of food and food chemicals

Food allergy as an exacerbating factor for asthma is uncommon and occurs primarily in young children. Confirmed food allergy is a risk factor for asthma-related mortality.⁸⁹

Food chemicals, either naturally occurring or added during processing, may also trigger asthma symptoms especially when asthma is poorly controlled. Sulfites (common food and drug preservatives found in such foods as processed potatoes, shrimp, dried fruits, beer, and wine) have often been implicated in causing severe asthma exacerbations.³³⁷ However, the likelihood of a reaction is dependent on the nature of the food, the level and form of residual sulfite, the sensitivity of the patient, and the mechanism of the sulfite-induced reaction.³³⁷ There is little evidence to support any general role for other dietary substances including benzoate, the yellow dye, tartrazine, and monosodium glutamate in worsening asthma.

Advice

- Ask people with asthma about symptoms associated with any specific foods (Evidence D).
- Food avoidance should not be recommended unless an allergy or food chemical sensitivity has been clearly demonstrated (Evidence D), usually by carefully supervised oral challenges.⁸⁹
- If food allergy is confirmed, food allergen avoidance can reduce asthma exacerbations (Evidence D).
- If food chemical sensitivity is confirmed, complete avoidance is not usually necessary, and sensitivity often decreases when overall asthma control improves (Evidence D).

INDICATIONS FOR REFERRAL FOR EXPERT ADVICE

While the majority of people with asthma can usually be managed in primary care, some clinical situations warrant referral for expert advice regarding diagnosis and/or management (Box 3-10). This list is based on consensus, and indications for referral may vary, as there is substantial variation between health systems in the delivery of the majority of asthma care: by primary health care providers in some countries, and by specialists in others.

Box 3-11. Indications for considering referral for expert advice, where available

Difficulty confirming the diagnosis of asthma

- Patient has symptoms of chronic infection, or features suggesting a cardiac or other non-pulmonary cause (Box 1-3, p.23) (immediate referral recommended)
- Diagnosis is unclear even after a trial of therapy with ICS or systemic corticosteroids
- Patients with features of both asthma and COPD, if there is doubt about priorities for treatment

Suspected occupational asthma

- Refer for confirmatory testing and identification of sensitizing or irritant agent, specific advice about eliminating exposure and pharmacological treatment. See specific guidelines (e.g. ³⁶) for details.

Persistent uncontrolled asthma or frequent exacerbations

- Patient's symptoms remain uncontrolled, or patient has ongoing exacerbations or low lung function despite correct inhaler technique and good adherence with Step 4 treatment (moderate dose ICS-LABA, Box 3-5, p.46). Before referral, depending on the clinical context, identify and treat modifiable risk factors (Box 2-2, p.31; Box 3-8, p.57) and comorbidities (p.75)
- Patient has frequent asthma-related health care utilization (e.g. multiple ED visits or urgent primary care visits)
- See Section 3E (p.84) on difficult to treat and severe asthma, including a decision tree

Any risk factors for asthma-related death (see Box 4-1, p.103)

- Near-fatal asthma attack (ICU admission, or mechanical ventilation for asthma) at any time in the past
- Anaphylaxis or confirmed food allergy in a patient with asthma

Evidence of, or risk of, significant treatment side-effects

- Patients with significant side-effects from treatment
- Need for long-term oral corticosteroid use
- Frequent courses of oral corticosteroids (e.g. two or more courses a year)

Symptoms suggesting complications or sub-types of asthma

- e.g. aspirin-exacerbated respiratory disease (p.82); allergic bronchopulmonary aspergillosis

Additional reasons for referral in children 6–11 years

- Doubts about diagnosis of asthma e.g. respiratory symptoms are not responding well to treatment in a child who was born prematurely
- Symptoms or exacerbations remain uncontrolled despite moderate dose ICS (Box 3-6B, p.48) with correct inhaler technique and good adherence
- Suspected side-effects of treatment (e.g. growth delay)
- Asthma and confirmed food allergy

ICS: inhaled corticosteroids; ICU: intensive care unit. For indications for referral in children 0–5 years, see p.135.

PART C. GUIDED ASTHMA SELF-MANAGEMENT EDUCATION AND SKILLS TRAINING

OVERVIEW

With a chronic disease such as asthma, it is important for patients to be provided with education and skills in order to effectively manage their asthma. This is most effectively achieved through a partnership between the patient and their health care providers. The essential components for this include:

- Skills training to use inhaler devices effectively
- Encouraging adherence with medications, appointments and other advice, within an agreed management strategy
- Asthma information
- Training in guided self-management, with self-monitoring of symptoms or peak flow; a written asthma action plan to show how to recognize and respond to worsening asthma; and regular review by a health care provider.

In developing, customizing and evaluating self-management interventions for different cultures, sociocultural factors should be taken into account.³³⁸

SKILLS TRAINING FOR EFFECTIVE USE OF INHALER DEVICES

Delivery of respiratory medications by inhalation achieves a high concentration in the airways, more rapid onset of action, and fewer systemic adverse effects than systemic delivery. However, using an inhaler is a skill that must be learnt and maintained in order for the medication to be delivered effectively.

Poor inhaler technique leads to poor asthma control, increased risk of exacerbations and increased adverse effects.⁸⁵ Most patients (up to 70–80%) are unable to use their inhaler correctly. Unfortunately, many health care providers are unable to correctly demonstrate how to use the inhalers they prescribe.³³⁹ Most people with incorrect technique are unaware that they have a problem. There is no ‘perfect’ inhaler – patients can have problems using any inhaler device.

Strategies for ensuring effective use of inhaler devices are summarized in Box 3-12, p.70.³⁴⁰

These principles apply to all types of inhaler devices. For patients prescribed pressurized metered dose inhalers (pMDIs), use of a spacer improves delivery and (for ICS) reduces the potential for local side-effects such as dysphonia and oral candidiasis.³⁴¹ With ICS, the risk of candidiasis can also be reduced by rinsing and spitting out after use.

Checking and correcting inhaler technique using a standardized checklist takes only 2–3 minutes and leads to improved asthma control in adults^{342,343} and older children³⁴⁰ (Evidence A). A physical demonstration is essential to improve inhaler technique.³⁴⁴ This is easiest if the health care provider has placebo inhalers and a spacer. After training, inhaler technique falls off with time, so checking and re-training must be repeated regularly. This is particularly important for patients with poor symptom control or a history of exacerbations. Pharmacists and nurses can provide highly effective inhaler skills training.^{340,345,346}

Some inhaler devices and techniques for their use are illustrated on the GINA website (www.ginasthma.org) and the ADMIT website (www.inhalers4u.org).

Box 3-12. Strategies to ensure effective use of inhaler devices

CHEOOSE
<ul style="list-style-type: none">• Choose the most appropriate inhaler device for the patient before prescribing. Consider the medication options (Box 3-5, p.46), the available devices, patient skills and cost.• If different options are available, encourage the patient to participate in the choice• For pMDIs, use of a spacer improves delivery and (with ICS) reduces the potential for side-effects• Ensure that there are no physical barriers, e.g. arthritis, that limit use of the inhaler• Avoid use of multiple different inhaler types where possible, to avoid confusion
CHECK
<ul style="list-style-type: none">• Check inhaler technique at every opportunity• Ask the patient to show you how they use their inhaler (don't just ask if they know how to use it)• Identify any errors using a device-specific checklist
CORRECT
<ul style="list-style-type: none">• Show the patient how to use the device correctly with a physical demonstration, e.g. using a placebo inhaler• Check technique again, paying attention to problematic steps. You may need to repeat this process 2–3 times.³⁴²• Only consider an alternative device if the patient cannot use the inhaler correctly after several repeats of training• Re-check inhaler technique frequently. After initial training, errors often recur within 4–6 weeks.³⁴⁷
CONFIRM
<ul style="list-style-type: none">• Clinicians should be able to demonstrate correct technique for each of the inhalers they prescribe• Pharmacists and nurses can provide highly effective inhaler skills training^{345,346}

ADHERENCE WITH MEDICATIONS AND OTHER ADVICE

Identifying poor adherence

Poor adherence is defined as the failure of treatment to be taken as agreed upon by the patient and the health care provider. There is increasing awareness of the importance of poor adherence in chronic diseases, and of the potential to develop interventions to improve adherence.³⁴⁸ Approximately 50% of adults and children on long-term therapy for asthma fail to take medications as directed at least part of the time.¹³⁸

In clinical practice, poor adherence may be identified by an empathic question that acknowledges the likelihood of incomplete adherence and encourages an open discussion. See Box 3-13, p.71 for examples.

Checking the date of the last prescription or the date on the inhaler may assist in identifying poor adherence. In some health systems, pharmacists can assist in identifying poorly adherent patients by monitoring dispensing records. In clinical studies, poor adherence may be identified by short adherence behavior questionnaires, or from dispensing records; dose or pill counting; electronic inhaler monitoring,³⁴⁹ and drug assay such as for prednisolone.³⁵⁰

Factors contributing to poor adherence

It is important to elicit patients' beliefs and concerns about asthma and asthma medications in order to understand the reasons behind their medication-taking behavior. Specific drug and non-drug factors involved in poor adherence are listed in Box 3-13, p.71. They include both intentional and unintentional factors. Issues such as ethnicity,³⁵¹ health literacy,^{352,353} and numeracy¹⁴⁸ are often overlooked. Patients' concerns about side-effects may be either real or perceived.^{250,354}

Interventions that improve adherence in asthma

Few adherence interventions have been studied comprehensively in asthma. Some examples of successful interventions are:

- Shared decision-making for medication/dose choice improved adherence and asthma outcomes.^{139,142}
- Inhaler reminders, either proactively or for missed doses, improved adherence and reduced exacerbations and oral corticosteroid use.³⁵⁵⁻³⁵⁷
- In a difficult inner-city environment, home visits for a comprehensive asthma program by an asthma nurse led to improved adherence and reduced prednisone courses over the following several months.³⁵⁸
- Providing adherence information to clinicians did not improve ICS use among patients with asthma unless clinicians chose to view the details of their patients' medication use.³⁵⁹
- In a health maintenance organization, an automated voice recognition program with messages triggered when refills were due or overdue led to improved ICS adherence relative to usual care, but no difference in urgent care visits.³⁶⁰
- In one study, directly observed controller medication administration at school, combined with telemedicine oversight, was associated with more symptom-free days and fewer urgent visits than usual care.³⁶¹

Improving adherence to controller medications may not necessarily translate to improved clinical outcomes.³⁶² Further studies are needed of adherence strategies that are feasible for implementation in primary care.

Box 3-13. Poor medication adherence in asthma

Factors contributing to poor adherence	How to identify poor adherence in clinical practice
Medication/regimen factors <ul style="list-style-type: none">• Difficulties using inhaler device (e.g. arthritis)• Burdensome regimen (e.g. multiple times per day)• Multiple different inhalers Unintentional poor adherence <ul style="list-style-type: none">• Misunderstanding about instructions• Forgetfulness• Absence of a daily routine• Cost Intentional poor adherence <ul style="list-style-type: none">• Perception that treatment is not necessary• Denial or anger about asthma or its treatment• Inappropriate expectations• Concerns about side-effects (real or perceived)• Dissatisfaction with health care providers• Stigmatization• Cultural or religious issues• Cost	Ask an empathic question <ul style="list-style-type: none">• Acknowledge the likelihood of incomplete adherence and encourage an open non-judgmental discussion. <p>Examples are:</p> <ul style="list-style-type: none">○ ‘Many patients don’t use their inhaler as prescribed. In the last 4 weeks, how many days a week have you been taking it – not at all, 1, 2, 3 or more days a week?’³⁶³○ ‘Do you find it easier to remember your inhaler in the morning or the evening?’ Check medication usage <ul style="list-style-type: none">• Check the date of the last controller prescription• Check the date and dose counter on the inhaler• In some health systems, prescribing and dispensing frequency can be monitored electronically by clinicians and/or pharmacists• See review articles for more detail.^{138,364}
Examples of successful adherence interventions <ul style="list-style-type: none">• Shared decision-making for medication/dose choice^{139,142}• Inhaler reminders, either proactively or for missed doses³⁵⁵⁻³⁵⁷• Prescribing low-dose ICS once-daily versus twice-daily³⁶⁵• Home visits for a comprehensive asthma program by an asthma nurse³⁵⁸	

ASTHMA INFORMATION

While education is relevant to asthma patients of all ages, the information and skills training required by each person may vary, as will their ability or willingness to take responsibility. All individuals will require certain core information and skills but most education must be personalized and provided in a number of steps.

For young children, the focus of asthma education will be on the parent/carer, but young children can be taught simple asthma management skills. Adolescents may have unique difficulties regarding adherence, and peer support group education may help in addition to education provided by the health care provider.³⁶⁶ These are complex interventions, and there have been few studies. Regional issues and the adolescent's developmental stage may affect the outcomes of such programs.³⁶⁷

The key features and components of an asthma education program are provided in Box 3-14. Information alone improves knowledge but does not improve asthma outcomes.³⁶⁸ Social and psychological support may also be required to maintain positive behavioral change, and skills are required for effective medication delivery. At the initial consultation, verbal information should be supplemented with written or pictorial^{369,370} information about asthma and its treatment. The GINA website (www.ginasthma.org) contains patient educational materials as well as links to several asthma websites. Patients and their families should be encouraged to make a note of any questions that arise from reading this information or as a result of the consultation, and should be given time to address these during the next consultation.

Asthma education and training can be delivered effectively by a range of health care providers including pharmacists and nurses^{345,346,371} (Evidence A). Trained lay health educators (also known as community health workers) can deliver discrete areas of respiratory care such as asthma self-management education, with, in one study, increased symptom-free days and reduced healthcare utilization compared with usual care³⁷² and in another, comparable outcomes to those achieved by practice nurses based in primary care³⁷³ (Evidence B). These findings suggest the need for additional studies to assess applicability in other settings and populations.

Box 3-14. Asthma information

Goal: To provide the person with asthma, their family and other carers with suitable information and training to manage their asthma in partnership with their health care providers

Approach	Content
<ul style="list-style-type: none">• Focus on the development of the partnership• Accept that this is a continuing process• Share information• Adapt the approach to the patient's level of health literacy (Box 3-1, p.39)• Fully discuss expectations, fears and concerns• Develop shared goals	<ul style="list-style-type: none">• Asthma diagnosis• Rationale for treatment, and differences between 'relievers' and 'controllers'• Potential side-effects of medications• Prevention of symptoms and flare-ups• How to recognize worsening asthma and what actions to take; how and when to seek medical attention• Management of comorbidities

TRAINING IN GUIDED ASTHMA SELF-MANAGEMENT

Guided self-management may involve varying degrees of independence, ranging broadly from patient-directed self-management to doctor-directed self-management. With patient-directed self-management patients make changes in accordance with a prior written action plan without needing to first contact their health care provider. With doctor-directed self-management, patients still have a written action plan, but refer most major treatment decisions to their physician at the time of a planned or unplanned consultation.

The essential components of effective guided asthma self-management education are:¹⁴⁰

- Self-monitoring of symptoms and/or peak flow
- A written asthma action plan to show how to recognize and respond to worsening asthma; and
- Regular review of asthma control, treatment and skills by a health care provider.

Self-management education that includes these components dramatically reduces asthma morbidity in both adults^{140,374} (Evidence A) and children^{141,374} (Evidence A). Benefits include a one-third to two-thirds reduction in asthma-related hospitalizations, emergency department visits and unscheduled doctor or clinic visits, missed work/school days, and nocturnal wakening.¹⁴⁰ It has been estimated that the implementation of a self-management program in 20 patients prevents one hospitalization, and successful completion of such a program by 8 patients prevents one emergency department visit.^{140,375} Less intensive interventions that involve self-management education but not a written action plan are less effective,³⁷⁶ and information alone is ineffective.³⁶⁸ A systematic meta-review of 270 RCTs on supported self-management for asthma confirmed that it reduces unscheduled healthcare use, improves asthma control, is applicable to a wide range of target groups and clinical settings, and does not increase health care costs (Evidence A).³⁷⁴

Self-monitoring of symptoms and/or peak flow

Patients should be trained to keep track of their symptoms (with or without a diary), and notice and take action if necessary when symptoms start to worsen. Peak expiratory flow (PEF) monitoring may sometimes be useful:

- Short-term monitoring
 - Following an exacerbation, to monitor recovery.
 - Following a change in treatment, to help in assessing whether the patient has responded.
 - If symptoms appear excessive (for objective evidence of degree of lung function impairment).
 - To assist in identification of occupational or domestic triggers for worsening asthma control
- Long-term monitoring
 - For earlier detection of exacerbations, mainly in patients with poor perception of airflow limitation.¹²⁴
 - For patients with a history of sudden severe exacerbations.
 - For patients' who have difficult-to-control or severe asthma

For patients carrying out peak-flow monitoring, use of a laterally compressed PEF chart (showing 2 months on a landscape format page) allows more accurate identification of worsening asthma than other charts.¹³⁵ One such chart is available for download from www.woolcock.org.au/moreinfo/. There is increasing interest in internet or phone-based monitoring of asthma. Based on existing studies, the main benefit is likely to be for more severe asthma³⁷⁷ (Evidence B).

Written asthma action plans

Personal written asthma action plans show patients how to make short-term changes to their treatment in response to changes in their symptoms and/or PEF. They also describe how and when to access medical care.^{378,379}

The benefits of self-management education for asthma morbidity are greater in adults when the action plans include both a step up in ICS and the addition of OCS, and for PEF-based plans, when they are based on personal best rather than percent predicted PEF³⁷⁹ (Evidence A).

The efficacy of self-management education is similar regardless of whether patients self-adjust their medications according to an individual written plan or whether the medication adjustments are made by a doctor³⁷⁶ (Evidence A). Thus patients who are unable to undertake guided self-management can still achieve benefit from a structured program of regular medical review.

Examples of written asthma action plan templates, including for patients with low literacy, can be found on several websites (e.g. Asthma UK, www.asthma.org.uk; Asthma Society of Canada, www.asthma.ca; Family Physician Airways Group of Canada, www.fpagc.com; National Asthma Council Australia, www.nationalasthma.org.au) and in research publications (e.g. ^{380,381}). Health care providers should become familiar with action plans that are relevant to their local health care system, treatment options, and cultural and literacy context. Details of the specific treatment adjustments that can be recommended for written asthma action plans are described in the next chapter (Box 4-2, p.107).

Regular review by a health care provider

The third component of effective asthma self-management education is regular review by a health care provider. Follow-up consultations should take place at regular intervals. Regular review should include the following.

- Ask the patient if they have any questions and concerns
 - Discuss issues, and provide additional educational messages as necessary; if available, refer the patient to someone trained in asthma education.
- Assess asthma control
 - Review the patient's level of symptom control and risk factors (Box 2-2, p.31).
 - Ask about flare-ups to identify contributory factors and whether the patient's response was appropriate (e.g. was an action plan used?)
 - Review the patient's symptom or PEF diary if they keep one.
 - Assess comorbidities
- Assess treatment issues
 - Watch the patient use their inhaler, and correct and re-check technique if necessary (Box 3-12 p.70).
 - Assess medication adherence and ask about adherence barriers (Box 3-13, p.71)
 - Ask about adherence with other interventions, (e.g. smoking cessation)
 - Review the asthma action plan and update it if level of asthma control or treatment have changed³⁸²

A single page prompt to clinicians has been shown to improve the provision of preventive care to children with asthma during office visits.³⁸³ Follow-up by tele-healthcare is unlikely to benefit in mild asthma but may be of benefit in those with severe disease at risk of hospital admission.³⁷⁷

PART D. MANAGING ASTHMA WITH COMORBIDITIES AND IN SPECIFIC POPULATIONS

KEY POINTS

- Identify and manage comorbidities such as rhinosinusitis, obesity and gastro-esophageal reflux disease. Comorbidities may contribute to respiratory symptoms and impaired quality of life, and some contribute to poor asthma control.
- For patients with dyspnea or wheezing on exertion:
 - Distinguish between exercise-induced bronchoconstriction (EIB) and symptoms that result from obesity or a lack of fitness, or are the result of alternative conditions such as inducible laryngeal obstruction
 - Provide advice about preventing and managing EIB
- All adolescents and adults with asthma should receive as-needed (in mild asthma) or daily ICS-containing controller medication to reduce their risk of severe exacerbations
- Refer patients with difficult-to-treat or severe asthma to a specialist or severe asthma service, after addressing common problems such as incorrect diagnosis, incorrect inhaler technique, ongoing environmental exposures, and poor adherence (see Section 3E, p.84).

MANAGING COMORBIDITIES

Several comorbidities are commonly present in patients with asthma, particularly those with difficult-to-treat or severe asthma.⁸⁷ Active management of comorbidities is recommended because they may contribute to symptom burden, impair quality of life, and lead to medication interactions. Some comorbidities also contribute to poor asthma control.³⁸⁴

Obesity

Clinical features

Asthma is more difficult to control in obese patients.³¹⁵⁻³¹⁸ This may be due to a different type of airway inflammation, contributory comorbidities such as obstructive sleep apnea and gastroesophageal reflux disease (GERD), mechanical factors, or other as yet undefined factors. In addition, lack of fitness and reduction in lung volume due to abdominal fat may contribute to dyspnea.

Diagnosis

Document body mass index (BMI) for all patients with asthma. Because of other potential contributors to dyspnea and wheeze in obese patients, it is important to confirm the diagnosis of asthma with objective measurement of variable airflow limitation (Box 1-2, p.19). Asthma is more common in obese than non-obese patients,⁴⁸ but both over- and under-diagnosis of asthma occur in obesity.^{29,49}

Management

As for other patients with asthma, ICS are the mainstay of treatment in obese patients (Evidence B), although their response may be reduced.³¹⁸ Weight reduction should be included in the treatment plan for obese patients with asthma (Evidence B). Increased exercise alone appears to be insufficient (Evidence B);³²³ however a weight loss program plus twice-weekly aerobic and strength exercises improved symptom control, lung function and inflammatory markers compared with weight loss alone (Evidence B).³²⁴ Weight loss improves asthma control, lung function, health status and reduces medication needs in obese patients,^{319,320} but the quality of some studies is poor. The most striking results have been observed after bariatric surgery,^{321,322} but even 5–10% weight loss can lead to improved asthma control and quality of life.³²³

Gastroesophageal reflux disease (GERD)

Clinical features

GERD can cause symptoms such as heartburn, and epigastric or chest pain, and is also a common cause of dry cough. Symptoms and/or diagnosis of GERD are more common in people with asthma than in the general population,³⁸⁴ but this may be in part due to cough being attributed to asthma; in addition, some asthma medications such as beta₂-agonists and theophylline cause relaxation of the lower esophageal sphincter. Asymptomatic gastroesophageal reflux is not a likely cause of poorly controlled asthma.³⁸⁴

Diagnosis

In patients with confirmed asthma, GERD should be considered as a possible cause of a dry cough; however, there is no value in screening patients with uncontrolled asthma for GERD (Evidence A). For patients with asthma and symptoms suggestive of reflux, an empirical trial of anti-reflux medication, such as a proton pump inhibitor or motility agent, may be considered, as in the general population. If the symptoms do not resolve, specific investigations such as 24-hour pH monitoring or endoscopy may be considered.

Management

A review of proton pump inhibitors in patients with confirmed asthma, most of whom had a diagnosis of GERD, showed a significant but small benefit for morning PEF, but no significant benefit for other asthma outcomes.³⁸⁵ In a study of adult patients with symptomatic asthma but without symptoms of GERD, treatment with high-dose proton pump inhibitors did not reduce asthma symptoms or exacerbations.³⁸⁶ In general, benefits of proton pump inhibitors in asthma appear to be limited to patients with both symptomatic reflux and night-time respiratory symptoms.³⁸⁷ Other treatment options include motility agents, lifestyle changes and fundoplication. In summary, symptomatic reflux should be treated, but patients with poorly controlled asthma should not be treated with anti-reflux therapy unless they also have symptomatic reflux (Evidence A). Few data are available for children with asthma symptoms and symptoms of GERD.^{388,389}

Anxiety and depression

Clinical features

Psychiatric disorders, particularly depressive and anxiety disorders, are more prevalent among people with asthma.³⁹⁰ Psychiatric comorbidity is also associated with worse asthma symptom control and medication adherence, and worse asthma-related quality of life.³⁹¹ Anxious and depressive symptoms have been associated with increased asthma-related exacerbations and emergency visits.³⁹² Panic attacks may be mistaken for asthma.

Diagnosis

Although several tools are available for screening for anxious and depressive symptomatology in primary care, the majority have not been validated in asthma populations. Difficulties in distinguishing anxiety or depression from asthma symptoms may therefore lead to misdiagnosis. It is important to be alert to possible depression and/or anxiety in people with asthma, particularly when there is a previous history of these conditions. Where appropriate, patients should be referred to psychiatrists or evaluated with a disease-specific psychiatric diagnostic tool to identify potential cases of depression and/or anxiety.

Management

There have been few good quality pharmacological and non-pharmacological treatment trials for anxiety or depression in patients with asthma, and results are inconsistent. A Cochrane review of 15 randomized controlled trials of psychological interventions for adults with asthma included cognitive behavior therapy, psychoeducation, relaxation, and biofeedback.³⁹³ Results for anxiety were conflicting, and none of the studies found significant treatment differences for depression. Drug treatments and cognitive behavior therapy³⁹⁴ have been described as having some potential in patients with asthma; however, current evidence is limited, with a small number of studies and methodological shortcomings.

Food allergy and anaphylaxis

Clinical features

Rarely, food allergy is a trigger for asthma symptoms (<2% of people with asthma). In patients with confirmed food-induced allergic reactions (anaphylaxis), co-existing asthma is a strong risk factor for more severe and even fatal reactions. Food-induced anaphylaxis often presents as life-threatening asthma.⁸⁹ An analysis of 63 anaphylaxis-related deaths in the United States noted that almost all had a past history of asthma; peanuts and tree nuts were the foods most commonly responsible.³⁹⁵ A UK study of 48 anaphylaxis-related deaths found that most were regularly treated for asthma, and that in most of these, asthma was poorly controlled.³⁹⁶

Diagnosis

In patients with confirmed food allergy, it is important to assess for asthma. Children with food allergy have a four-fold increased likelihood of having asthma compared with children without food allergy.³⁹⁷ Refer patients with suspected food allergy or intolerance for specialist allergy assessment. This may include appropriate allergy testing such as skin prick testing and/or blood testing for specific IgE. On occasion, carefully supervised food challenges may be needed.

Management

Patients who have a confirmed food allergy that puts them at risk for anaphylaxis must be trained and have an epinephrine auto-injector available at all times. They, and their family, must be educated in appropriate food avoidance strategies, and in the medical notes, they should be flagged as being at high risk. It is especially important to ensure that their asthma is well controlled, they have a written action plan, understand the difference between asthma and anaphylaxis, and are reviewed on a regular basis.

Rhinitis, sinusitis and nasal polyps

Clinical features

Evidence clearly supports a link between diseases of the upper and lower airways.³⁹⁸ Most patients with asthma, either allergic or non-allergic, have concurrent rhinitis, and 10–40% of patients with allergic rhinitis have asthma.³⁹⁹ Depending on sensitization and exposure, allergic rhinitis may be seasonal (e.g. ragweed or grass pollen), perennial (e.g. mite allergens), or intermittent (e.g. furred pets).³⁹⁸

Rhinitis is defined as irritation and inflammation of the mucous membranes of the nose. Allergic rhinitis may be accompanied by ocular symptoms (conjunctivitis). Rhinosinusitis is defined as inflammation of the nose and paranasal sinuses characterized by more than two symptoms including nasal blockage/obstruction and/or nasal discharge (anterior/posterior nasal drip).⁴⁰⁰ Other symptoms may include facial pain/pressure and/or a reduction or loss of smell. Sinusitis rarely occurs in the absence of rhinitis.

Rhinosinusitis is defined as acute when symptoms last <12 weeks with complete resolution, and chronic when symptoms occur on most days for at least 12 weeks without complete resolution. Chronic rhinosinusitis is an inflammatory condition of the paranasal sinuses that encompasses two clinically distinct entities: chronic rhinosinusitis without nasal polyposis and chronic rhinosinusitis with nasal polyposis.⁴⁰¹ The heterogeneity of chronic rhinosinusitis may explain the wide variation in prevalence rates in the general population ranging from 1–10% without polyps and 4% with polyps. Chronic rhinosinusitis is associated with more severe asthma, especially in patients with nasal polyps.⁴⁰²

Diagnosis

Rhinitis can be classified as either allergic or non-allergic depending on whether allergic sensitization is demonstrated. Variation in symptoms by season or with environmental exposure (e.g. furred pets) suggests allergic rhinitis. Examination of the upper airway should be arranged for patients with severe asthma.

Management

Evidence-based guidelines (Allergic Rhinitis in Asthma, ARIA)⁴⁰³ recommend intranasal corticosteroids for treatment of allergic rhinitis. In a case-control study, treatment of rhinitis with intranasal corticosteroids was associated with less need

for asthma-related hospitalization and emergency department visits,⁴⁰⁴ but a meta-analysis found improvement in asthma outcomes only in patients not also receiving ICS.⁴⁰⁵ However, few placebo-controlled studies have systematically evaluated the effect of proper treatment and management of chronic rhinosinusitis on asthma control. A recent placebo-controlled trial of nasal mometasone in adults and children with chronic rhinosinusitis and poorly-controlled asthma showed no benefit for asthma outcomes, suggesting that, while chronic rhinosinusitis can contribute to respiratory symptoms, e.g. chronic cough, its treatment in patients with asthma should be targeted at the symptoms of rhinosinusitis rather than to improve asthma control.⁴⁰⁶

MANAGING ASTHMA IN SPECIFIC POPULATIONS OR SETTINGS

This section includes brief advice about managing asthma in specific populations or settings in which the usual treatment approach may need to be modified. Also refer to the *Diagnosis of respiratory symptoms in special populations* section of Chapter 1 (p.25).

Settings with limited resources

Communities with limited resources are found not only in low and middle income countries (LMIC), but also in affluent nations. In these settings, in general, the GINA strategy may be followed for asthma management at the individual level (Box 3-3), as it offers options for low cost diagnostic procedures, and therapeutic interventions which have been shown to be effective and reduce costs among the underserved.^{407,408} In dealing with asthma control at the population level (Box 3-3), it is critical to prioritize the most cost-effective approach to asthma treatment in primary health care, which includes the use of ICS and SABA;⁴⁰⁹ these are listed as essential medications by the World Health Organization. Budesonide-formoterol is also listed as an essential medication by the WHO, but at present access is limited. For diagnosis of asthma and monitoring of treatment response, the World Health Organization also lists PEF meters as essential tools in the Package of Essential Non-communicable Diseases Interventions,⁵² with pulse oximeters also recommended when resources permit, for assessment of severity of acute asthma. It is possible to build capacity of primary health care teams, including nurses and other health professionals, for the development of an integrated approach to the most common diseases and symptoms, including asthma.⁴¹⁰

Adolescents

Clinical features

Care of teenagers with asthma should take into account the rapid physical, emotional, cognitive and social changes that occur during adolescence. Asthma control may improve or worsen, although remission of asthma is seen more commonly in males than females.⁴¹¹ Exploratory and risk-taking behaviors such as smoking occur at a higher rate in adolescents with chronic diseases than in healthy adolescents.

Management

General principles for managing chronic disease in adolescents have been published by WHO.⁴¹² Adolescents and their parent/carers should be encouraged in the transition towards asthma self-management by the adolescent. This may involve the transition from a pediatric to an adult health care facility. During consultations, the adolescent should be seen separately from the parent/carer so that sensitive issues such as smoking, adherence and mental health can be discussed privately, and confidentiality agreed. Information and self-management strategies should be tailored to the patient's stage of psychosocial development and desire for autonomy; adolescents are often focused on short-term rather than long-term outcomes. An empathic approach should be used to identify beliefs and behaviors that may be barriers to optimal treatment; for example, adolescents may be concerned about the impact of treatment on their physical or sexual capabilities. Medication regimens should be tailored to the adolescent's needs and lifestyle, and reviews arranged regularly so that the medication regimen can be adjusted for changing needs. Information about local youth-friendly resources and support services should be provided, where available.

Exercise-induced bronchoconstriction (EIB)

Clinical features

Physical activity is an important stimulus for asthma symptoms for many patients, with symptoms and bronchoconstriction typically worsening after cessation of exercise. However, shortness of breath or wheezing during exercise may also relate to obesity or a lack of fitness, or to comorbid or alternative conditions such as inducible laryngeal obstruction.^{16,34}

Management

Regular controller treatment with ICS significantly reduces EIB¹⁶ (Evidence A). Training and sufficient warm-up reduce the incidence and severity of EIB¹⁶ (Evidence A). Taking SABAs, LABAs or chromones prior to exercise prevents EIB (Evidence A), but tolerance to the protective effects of SABAs and LABAs against EIB develops with regular (more than once-daily) use (Evidence A).¹⁶ However, in a 6-week study in patients with mild asthma, low dose budesonide-formoterol, taken as needed for relief of symptoms and before exercise, was non-inferior for reducing EIB to regular daily ICS with as-needed SABA.¹⁷⁹ More studies are needed, but this suggests that patients with mild asthma who are prescribed as-needed ICS-formoterol to prevent exacerbations and control symptoms can use the same medication prior to exercise, if needed, and do not need to be prescribed a SABA for pre-exercise use (Evidence B).

Breakthrough EIB often indicates poorly controlled asthma, and stepping up controller treatment (after checking inhaler technique and adherence) generally results in the reduction of exercise-related symptoms.

Athletes

Clinical features

Athletes, particularly those competing at a high level, have an increased prevalence of various respiratory conditions compared to non-athletes. They experience a higher prevalence of asthma, EIB, allergic or non-allergic rhinitis, chronic cough, inducible laryngeal obstruction, and recurrent respiratory infections. Airway hyperresponsiveness is common in elite athletes, often without reported symptoms. Asthma in elite athletes is commonly characterized by less correlation between symptoms and pulmonary function; higher lung volumes and expiratory flows; less eosinophilic airway inflammation; more difficulty in controlling symptoms; and some improvement in airway dysfunction after cessation of training.

Management

Preventative measures to avoid high exposure to air pollutants, allergens (if sensitized) and chlorine levels in pools, particularly during training periods, should be discussed with the athlete. They should avoid training in extreme cold or pollution (Evidence C), and the effects of any therapeutic trials of asthma medications should be documented. Adequate anti-inflammatory therapy, especially ICS, is advised; minimization of use of beta₂-agonists will help to avoid the development of tolerance.¹⁶ Information on treatment of exercise-induced asthma in athletes can be found in a Joint Task Force Report prepared by the European Respiratory Society, the European Academy of Allergy and Clinical Immunology, and GA(2)LEN⁴¹³ and the World Anti-Doping Agency website (www.wada-ama.org).

Pregnancy

Clinical features

Asthma control often changes during pregnancy; in approximately one-third of women asthma symptoms worsen, in one-third they improve, and in the remaining one-third they remain unchanged.⁴¹⁴ Exacerbations are common in pregnancy, particularly in the second trimester.⁹⁰ Exacerbations and poor asthma control during pregnancy may be due to mechanical or hormonal changes, or to cessation or reduction of asthma medications due to concerns by the mother and/or the health care provider. Pregnant women appear to be particularly susceptible to the effects of viral respiratory infections,⁴¹⁵ including influenza. Exacerbations and poor symptom control are associated with worse outcomes for both

the baby (pre-term delivery, low birth weight, increased perinatal mortality) and the mother (pre-eclampsia).⁹⁰ If asthma is well controlled throughout pregnancy there is little or no increased risk of adverse maternal or fetal complications.⁴⁰

Management

Although there is a general concern about any medication use in pregnancy, the advantages of actively treating asthma in pregnancy markedly outweigh any potential risks of usual controller and reliever medications⁴⁰ (Evidence A). For this reason, using medications to achieve good symptom control and prevent exacerbations is justified even when their safety in pregnancy has not been unequivocally proven. Use of ICS, beta₂-agonists, montelukast or theophylline is not associated with an increased incidence of fetal abnormalities.⁴¹⁶ Importantly, ICS reduce the risk of exacerbations of asthma during pregnancy^{40,417,418} (Evidence A), and cessation of ICS during pregnancy is a significant risk factor for exacerbations⁹⁰ (Evidence A). One study reported that a treatment algorithm in non-smoking pregnant women based on monthly FENO and ACQ was associated with significantly fewer exacerbations and better fetal outcomes than an algorithm based only on ACQ.⁴¹⁹ However, the ACQ-only algorithm did not reflect current clinical recommendations, as LABA was introduced only after ICS had been increased to moderate dose, and ICS could be stopped; 58% of women in the ACQ-only group were being treated without ICS by the end of pregnancy. On balance, given the evidence in pregnancy and infancy for adverse outcomes from exacerbations during pregnancy⁴⁰ (Evidence A) and for safety of usual doses of ICS and LABA⁴¹⁶ (Evidence A), a low priority should be placed on stepping down treatment (however guided) until after delivery, and ICS should not be stopped during pregnancy (Evidence D).

Despite lack of evidence for adverse effects of asthma treatment in pregnancy, many women and doctors remain concerned.⁴²⁰ Pregnant patients with asthma should be advised that poorly controlled asthma, and exacerbations, provide a much greater risk to their baby than do current asthma treatments. Educational resources about asthma management during pregnancy (e.g.⁴²¹) may provide additional reassurance. During pregnancy, monthly monitoring of asthma is recommended.⁴²¹ It is feasible for this to be achieved by pharmacist-clinician collaboration, with monthly telephone monitoring of asthma symptom control.⁴²²

Respiratory infections should be monitored and managed appropriately during pregnancy.⁴¹⁵ During acute asthma exacerbations, pregnant women may be less likely to be treated appropriately than non-pregnant patients.⁹⁰ To avoid fetal hypoxia, it is important to aggressively treat acute exacerbations during pregnancy with SABA, oxygen and early administration of systemic corticosteroids.

During labor and delivery, usual controller medications should be taken, with reliever if needed. Acute exacerbations during labor and delivery are uncommon, but bronchoconstriction may be induced by hyperventilation during labor, and should be managed with SABA. Neonatal hypoglycemia may be seen, especially in preterm babies, when high doses of beta-agonists have been given within the last 48 hours prior to delivery. If high doses of SABA have been given during labor and delivery, blood glucose levels should be monitored in the baby (especially if preterm) for the first 24 hours.⁴²³

Women – perimenstrual asthma (catamenial asthma)

Clinical features

In approximately 20% of women, asthma is worse in the premenstrual phase. These women tend to be older, have more severe asthma, a higher body mass index, a longer duration of asthma, and a greater likelihood of aspirin exacerbated respiratory disease. They more often have dysmenorrhea, premenstrual syndrome, shorter menstrual cycles, and longer menstrual bleeding. The role of hormone levels and systemic inflammation remains unclear.⁴²⁴

Management

In addition to the usual strategies for management of asthma, oral contraceptives and/or leukotriene receptor antagonists may be helpful⁴²⁴ (Evidence D). Further research is needed.

Occupational asthma

Clinical features

In the occupational setting, rhinitis often precedes the development of asthma (see p.9 regarding diagnosis of occupational asthma). Once a patient has become sensitized to an occupational allergen, the level of exposure necessary to induce symptoms may be extremely low; resulting exacerbations become increasingly severe, and with continued exposure, persistent symptoms and irreversible airflow limitation may result.³⁶

Management

Detailed information is available in evidence-based guidelines about management of occupational asthma.³⁶ All patients with adult-onset asthma should be asked about their work history and other exposures (Evidence A). The early identification and elimination of occupational sensitizers and the removal of sensitized patients from any further exposure are important aspects of the management of occupational asthma (Evidence A). Attempts to reduce occupational exposure have been successful, especially in industrial settings.³⁶ Cost-effective minimization of latex sensitization can be achieved by using non-powdered low-allergen gloves instead of powdered latex gloves.³⁶ Patients with suspected or confirmed occupational asthma should be referred for expert assessment and advice, if this is available, because of the economic and legal implications of the diagnosis (Evidence A)

The elderly

Clinical features

Lung function generally decreases with longer duration of asthma and increasing age, due to stiffness of the chest wall, reduced respiratory muscle function, loss of elastic recoil and airway wall remodeling. Older patients may not report asthma symptoms, and may attribute breathlessness to normal aging or comorbidities such as cardiovascular disease and obesity.⁴²⁵⁻⁴²⁷ Comorbid arthritis may contribute to reduced exercise capacity and lack of fitness, and make inhaler device use difficult. Asthma costs may be higher amongst older patients, because of higher hospitalization rates and medication costs.⁴²⁶

Management

Decisions about management of asthma in older people with asthma need to take into account both the usual goals of symptom control and risk minimization and the impact of comorbidities, concurrent treatments and lack of self-management skills.^{425,426} Data on efficacy of asthma medications in the elderly are limited because these patients are often excluded from major clinical trials. Side-effects of beta₂-agonists such as cardiotoxicity, and corticosteroid side-effects such as skin bruising, osteoporosis, and cataracts, are more common in the elderly than in younger adults.⁴²⁵ Clearance of theophylline is also reduced.⁴²⁵ Elderly patients should be asked about all of the other medications they are taking, including eye-drops, and potential drug interactions should be considered. Factors such as arthritis, muscle weakness, impaired vision and inspiratory flow should be considered when choosing inhaler devices for older patients,^{426,428} and inhaler technique should be checked at each visit. Older patients may have difficulties with complex medication regimens, and prescribing of multiple inhaler devices should be avoided if possible. Large print versions may be needed for written information such as asthma action plans. Patients with cognitive impairment may require a carer to help them use their asthma medications. For diagnosis and initial management of patients with asthma-COPD overlap, see Chapter 5, p.119.

Surgery and asthma

Clinical features

There is no evidence of increased peri-operative risk for the general asthma population.⁴²⁹ However, there is an increased risk for patients with COPD,⁴²⁹ and this may also apply to asthma patients with reduced FEV₁. The incidence of severe peri-operative bronchospasm in people with asthma is low, but it may be life threatening.⁴³⁰

Management

For elective surgery, meticulous attention should be paid pre-operatively to achieving good asthma control, as detailed elsewhere in this chapter, especially for patients with more severe asthma, uncontrolled symptoms, exacerbation history, or persistent airflow limitation⁴³⁰ (Evidence B). For patients requiring emergency surgery, the risks of proceeding without first achieving good asthma control should be weighed against the need for immediate surgery. Patients taking long-term high-dose ICS or who have received OCS for more than 2 weeks during the previous 6 months should receive hydrocortisone peri-operatively as they are at risk of adrenal crisis in the context of surgery⁴³¹ (Evidence B). More immediate intra-operative issues relating to asthma management are reviewed in detail elsewhere.⁴³⁰ For all patients, maintaining regular controller therapy throughout the peri-operative period is important.

Aspirin-exacerbated respiratory disease

Clinical features

The clinical picture and course of aspirin-exacerbated respiratory disease (AERD, previously called aspirin-induced asthma) are well established.²⁹¹ It starts with nasal congestion and anosmia, and progresses to chronic rhinosinusitis with nasal polyps that re-grow rapidly after surgery. Asthma and hypersensitivity to aspirin develop subsequently. Following ingestion of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), an acute asthma attack develops within minutes to 1–2 hours. It is usually accompanied by rhinorrhea, nasal obstruction, conjunctival irritation, and scarlet flush of the head and neck, and may sometimes progress to severe bronchospasm, shock, loss of consciousness, and respiratory arrest.^{432,433} AERD is more likely to be associated with low lung function and severe asthma,^{434,435} and with increased need for emergency care.⁴³⁵ The prevalence of AERD is 7% in general adult asthma populations, and 15% in severe asthma.^{435,436}

Diagnosis

A history of exacerbation following ingestion of aspirin or other NSAIDs is highly suggestive of AERD. Aspirin challenge (oral, bronchial or nasal) is the gold standard for diagnosis^{437,438} as there are no reliable *in vitro* tests, but oral aspirin challenge tests must only be conducted in a specialized center with cardiopulmonary resuscitation capabilities because of the high risk of severe reactions.^{437,438} Bronchial (inhalational) and nasal challenges with lysine aspirin are safer than oral challenges and may be safely performed in allergy centers.^{438,439}

Management

Patients with AERD should avoid aspirin or NSAID-containing products and other medications that inhibit cyclooxygenase-1 (COX-1), but this does not prevent progression of the disease. Where an NSAID is indicated for other medical conditions, a COX-2 inhibitor (e.g. celecoxib, or etoricoxib), or paracetamol (acetaminophen), may be considered^{440,441} with appropriate health care provider supervision and observation for at least 2 hours after administration⁴⁴² (Evidence B). ICS are the mainstay of asthma therapy in AERD, but OCS are sometimes required; LTRA may also be useful^{433,442} (Evidence B). An additional option is desensitization, which may be conducted under specialist care in a clinic or hospital.⁴⁴³ Desensitization to aspirin followed by daily aspirin treatment can significantly improve overall symptoms and quality of life, decrease formation of nasal polyps and sinus infections, reduce the need for OCS and sinus surgery, and improve nasal and asthma scores.^{438,444}

Allergic bronchopulmonary aspergillosis (ABPA)

Clinical features

Allergic bronchopulmonary aspergillosis (ABPA) is a complex pulmonary disease characterized by repeated episodes of wheezing, fleeting pulmonary opacities and development of bronchiectasis, sometimes with malaise, weight loss and hemoptysis. Some patients expectorate brownish sputum plugs. ABPA is most commonly found in asthma or cystic fibrosis, due to a hypersensitivity response to *Aspergillus fumigatus*, a common indoor and outdoor mold.

Diagnosis

Diagnosis of ABPA is based on composite criteria including immediate hypersensitivity reaction to *A. fumigatus*, total serum IgE, specific IgG to *A. fumigatus*, radiological features and blood eosinophils.⁴⁴⁵ Sensitization to fungal allergens, without the full picture of ABPA, is often found in asthma, particularly in severe asthma, where it is sometimes called 'severe asthma with fungal sensitization'.

Management

Current first-line therapy is with oral corticosteroids (e.g. 4 month tapering course), with itraconazole reserved for those with exacerbations or requiring long-term OCS.^{445,446} One open-label study comparing itraconazole and OCS found that patients treated with itraconazole had a slightly lower response rate at 6 weeks but similar long-term response rates, with substantially fewer side-effects than with OCS.⁴⁴⁷ A randomized double-blind placebo-controlled study in patients with severe asthma and ABPA found significantly fewer exacerbations with omalizumab (anti-IgE) than placebo.⁴⁴⁸ In ABPA patients with bronchiectasis, regular physiotherapy and daily drainage are recommended.

Difficult-to-treat and severe asthma are covered in the next section, Chapter 3 Part E.

PART E. DIFFICULT-TO-TREAT AND SEVERE ASTHMA IN ADULTS AND ADOLESCENTS

KEY POINTS

- Difficult-to-treat asthma is asthma that is uncontrolled despite GINA Step 4 or 5 treatment or that requires such treatment to maintain good symptom control and reduce exacerbations. It does not mean a 'difficult patient'.
- Severe asthma is asthma that is uncontrolled despite adherence with maximal optimized Step 4 or Step 5 therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased. Approximately 3-10% of people with asthma have severe asthma.
- Severe asthma places a large physical, mental, emotional, social and economic burden on patients
- Assess all patients with difficult to treat asthma to confirm the diagnosis of asthma, and to identify and manage factors that may be contributing to symptoms, poor quality of life, or exacerbations. Refer for expert advice at any stage, or if asthma does not improve in response to optimizing treatment.
- For patients with persistent symptoms and/or exacerbations despite high dose ICS, the clinical or inflammatory phenotype should be assessed, as this may guide the selection of add-on treatment
- Add-on treatments for severe asthma include tiotropium, LTRA and low dose macrolides, and biologic agents for severe allergic or severe Type 2 asthma. Maintenance OCS should be avoided if other options are available, because of its serious side-effects
- Assess the response to any add-on treatment, stop ineffective treatments, and consider other options
- Utilize multidisciplinary team care for severe asthma, if available
- For patients with severe asthma, continue to optimize patient care in collaboration with the primary care clinician, and taking into account the patient's social and emotional needs
- Invite patients with severe asthma to enrol in a registry or clinical trial, if available and relevant, to help fill evidence gaps

Although the majority of patients can achieve the goal of well controlled asthma, some patients' asthma will not be well controlled even with optimal therapy. The material that follows is from the GINA Pocket Guide for health professionals on Diagnosis and Management of Difficult-to-Treat and Severe Asthma in Adolescent and Adult Patients v2.0, published in April 2019. A copy of the Pocket Guide can be downloaded from the GINA website www.ginasthma.org.

Other resources about severe asthma include an online toolkit published by the Australian Centre of Excellence in Severe Asthma (www.toolkit.severeasthma.org.au).

DEFINITIONS: UNCONTROLLED, DIFFICULT-TO-TREAT AND SEVERE ASTHMA

Understanding the definitions of difficult-to-treat and severe asthma starts with the concept of uncontrolled asthma. *Uncontrolled asthma* includes one or both of the following:

- Poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma)
- Frequent exacerbations ($\geq 2/\text{year}$) requiring oral corticosteroids (OCS), or serious exacerbations ($\geq 1/\text{year}$) requiring hospitalization

*Difficult-to-treat asthma*¹³⁶ is asthma that is uncontrolled despite GINA Step 4 or 5 treatment (e.g. medium or high dose inhaled corticosteroids (ICS) with a second controller; maintenance OCS), or that requires such treatment to maintain good symptom control and reduce the risk of exacerbations. It does not mean a 'difficult patient'. In many cases, asthma may appear to be difficult-to-treat because of modifiable factors such as incorrect inhaler technique, poor adherence, smoking or comorbidities, or because the diagnosis is incorrect.

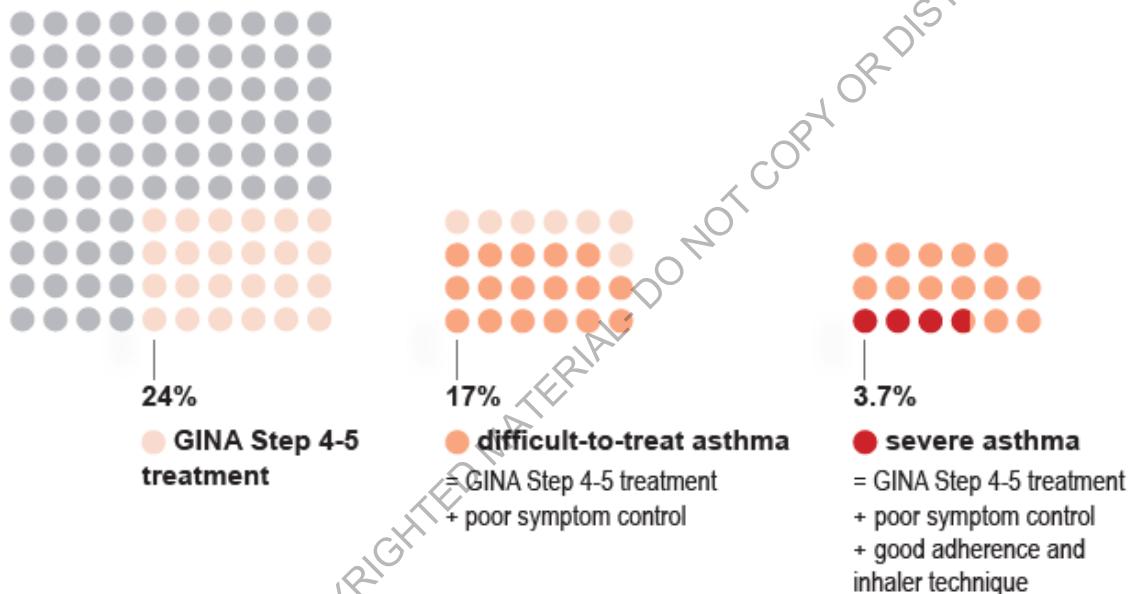
Severe asthma¹³⁶ is a subset of difficult-to-treat asthma (Box 3-15). It means asthma that is uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased.¹³⁶ At present, therefore, ‘severe asthma’ is a retrospective label. It is sometimes called ‘severe refractory asthma’¹³⁶ since it is defined by being relatively refractory to high dose inhaled therapy. However, with the advent of biologic therapies, the word ‘refractory’ is no longer appropriate.

Asthma is not classified as severe if it markedly improves when contributory factors such as inhaler technique and adherence are addressed.¹³⁶

PREVALENCE: HOW MANY PEOPLE HAVE SEVERE ASTHMA?

A study in the Netherlands estimated that around 3.7% of asthma patients have severe asthma, based on the number of patients prescribed Step 4 or 5 treatment, who had poor symptom control (by Asthma Control Questionnaire) and had good adherence and inhaler technique (Box 3-15).⁴⁴⁹

Box 3-15. What proportion of adults have difficult-to-treat or severe asthma?



IMPORTANCE: THE IMPACT OF SEVERE ASTHMA

The patient perspective

Patients with severe asthma experience a heavy burden of symptoms, exacerbations and medication side-effects. Frequent shortness of breath, wheeze, chest tightness and cough interfere with day-to-day living, sleeping, and physical activity, and patients often have frightening or unpredictable exacerbations (also called attacks or severe flare-ups).

Medication side-effects are particularly common and problematic with OCS,²⁴³ which in the past were a mainstay of treatment for severe asthma. Adverse effects of long-term OCS include obesity, diabetes, osteoporosis, cataracts, diabetes, hypertension and adrenal suppression; psychological side-effects such as depression and anxiety are particularly concerning for patients.⁴⁵⁰ Even short-term use of OCS is associated with sleep disturbance, and increased risk of infection, fracture and thromboembolism.⁴⁵¹ Strategies to minimize need for OCS are therefore a high priority.

Severe asthma often interferes with family, social and working life, limits career choices and vacation options, and affects emotional and mental health. Patients with severe asthma often feel alone and misunderstood, as their experience is so different from that of most people with asthma.⁴⁵⁰

Adolescents with severe asthma

The teenage years are a time of great psychological and physiological development which can impact on asthma management. It is vital to ensure that the young person has a good understanding of their condition and treatment and appropriate knowledge to enable supported self-management. The process of transition from pediatric to adult care should help support the young person in gaining greater autonomy and responsibility for their own health and wellbeing.

Healthcare utilization and costs

Severe asthma has very high healthcare costs due to medications, physician visits, hospitalizations, and the costs of OCS side-effects. In a UK study, healthcare costs per patient were higher than for type 2 diabetes, stroke, or chronic obstructive pulmonary disease (COPD).⁴⁵² In a Canadian study, severe uncontrolled asthma was estimated to account for more than 60% of asthma costs.⁴⁵³

Patients with severe asthma and their families also bear a significant financial burden, not only for medical care and medications, but also through lost earnings and career choices.

ASSESSMENT AND MANAGEMENT OF DIFFICULT-TO-TREAT AND SEVERE ASTHMA

The clinical decision tree starting on page 87, provides brief information about what should be considered in each phase of diagnosis and management of difficult-to-treat and severe asthma. The decision tree is divided into three broad areas:

- Sections 1-4 (green) are for use in primary care and/or specialist care
- Sections 5-7 (blue) are mainly relevant to respiratory specialists
- Section 8 (brown) is about maintaining ongoing collaborative care between the patient, GP, specialist and other health professionals

Development of the Pocket Guide and decision tree included extensive collaboration with experts in human-centered design to enhance the utility of these resources for end-users. This included translating existing high level flowcharts and text-based information to a more detailed visual format, and applying information architecture and diagramming principles.

Further information follows the decision tree.

GP OR SPECIALIST CARE

Investigate and manage adult and adolescent patients with difficult-to-treat asthma

Consider referring to specialist or severe asthma clinic at any stage

DIAGNOSIS:
"Difficult-to-treat asthma"

1 Confirm the diagnosis (asthma/differential diagnoses)

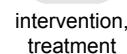
For adolescents and adults with symptoms and/or exacerbations despite GINA Step 4 treatment, or taking maintenance OCS

2 Look for factors contributing to symptoms, exacerbations and poor quality of life:

- Incorrect inhaler technique
- Suboptimal adherence
- Comorbidities including obesity, GERD, chronic rhinosinusitis, OSA
- Modifiable risk factors and triggers at home or work, including smoking, environmental exposures, allergen exposure (if sensitized on skin prick testing or specific IgE); medications such as beta-blockers and NSAIDs
- Overuse of SABA relievers
- Medication side effects
- Anxiety, depression and social difficulties

Key

decision, filters



intervention, treatment



diagnosis, confirmation

→p.91

→p.92

Consider referring to specialist or severe asthma clinic at any stage

3 Optimize management, including:

- Asthma education
- Optimize treatment (e.g. check and correct inhaler technique and adherence; switch to ICS-formoterol maintenance and reliever therapy, if available)
- Treat comorbidities and modifiable risk factors
- Consider non-biologic add-on therapy (e.g. LABA, tiotropium, LM/LTRA, if not used)
- Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza vaccination)
- Consider trial of high dose ICS, if not used

4 Review response after ~3-6 months

Is asthma still uncontrolled?

yes

DIAGNOSIS:
"Severe asthma"

If not done by now, refer to a specialist, if possible.

no

Consider stepping down treatment, OCS first (if used.)

Does asthma become uncontrolled when treatment is stepped down?

yes

Continue optimizing management

Restore previous dose

no

For more details

→p.93

Assess and treat severe asthma phenotypes

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

5 Assess the severe asthma phenotype and factors contributing to symptoms, quality of life and exacerbations

- Assess the severe asthma phenotype during high dose ICS treatment (or lowest possible dose of OCS)**

Type 2 inflammation

Could patient have Type 2 airway inflammation?

Note: these are *not* the criteria for add-on biologic therapy (see 6b)

- Blood eosinophils $\geq 150/\mu\text{l}$ and/or
- FeNO $\geq 20 \text{ ppb}$ and/or
- Sputum eosinophils $\geq 2\%$, and/or
- Asthma is clinically allergen-driven and/or
- Need for maintenance OCS (Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)

yes

no

6a Consider non-biologic treatments

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis (clinical Type 2 phenotypes with specific add-on treatment)

Is add-on Type 2 biologic therapy available/affordable?

yes

If add-on Type 2 biologic therapy is NOT available/affordable

- Consider higher dose ICS, if not used
- Consider non-biologic add-on therapy (e.g. LABA, tiotropium, LM/LTRA, macrolide*)
- Consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

- Investigate for comorbidities/differential diagnoses and treat/refer as appropriate**
 - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO
 - Skin prick testing or specific IgE for relevant allergens, if not already done
 - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
- Consider need for social/psychological support**
- Involve multidisciplinary team care (if available)**
- Invite patient to enroll in registry (if available) or clinical trial (if appropriate)**

If no evidence of Type 2 inflammation:

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
 - Sputum induction
 - High resolution chest CT
 - Bronchoscopy for alternative/additional diagnoses
- Consider add-on treatments
 - Trial of tiotropium or macrolide* (if not already tried)
 - Consider add-on low dose OCS, but implement strategies to minimize side-effects
 - Stop ineffective add-on therapies
- Consider bronchial thermoplasty (+ registry)

Not currently eligible for biologics

*Off-label

Assess and treat severe asthma phenotypes cont'd

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

6b Consider add-on biologic Type 2 targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
 - have eosinophilic or allergic biomarkers, or
 - need maintenance OCS
- Consider local payer eligibility criteria and predictors of response when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Anti-IgE

Is the patient eligible for anti-IgE for severe allergic asthma?

- Sensitization on skin prick testing or specific IgE L
- Total serum IgE and weight within dosage range L
- Exacerbations in last year L

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils $\geq 260/\mu\text{l}$ ++
- FeNO $\geq 20 \text{ ppb}$ +
- Allergen-driven symptoms +
- Childhood-onset asthma +

Anti-IL5 / Anti-IL5R

Is the patient eligible for anti-IL5 / anti-IL5R for severe eosinophilic asthma?

- Exacerbations in last year L
- Blood eosinophils $\geq 300/\mu\text{l}$ L

What factors may predict good asthma response to anti-IL5/5R?

- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult-onset of asthma ++
- Nasal polyposis ++

Anti-IL4R

Is the patient eligible for anti-IL4R

... for severe eosinophilic/Type 2 asthma?

- Exacerbations in last year L
- Blood eosinophils $\geq 150/\mu\text{l}$ L or FeNO $\geq 25 \text{ ppb}$ L
- ... or because of need for maintenance OCS L?

What factors may predict good asthma response to anti-IL4R?

- Higher blood eosinophils +++
- Higher FeNO +++

Anti-IL4R may also be used to treat

- Moderate/severe atopic dermatitis
- Nasal polyposis

Eligible for none?
Return to section 6a

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils $\geq 260/\mu\text{l}$ ++
- FeNO $\geq 20 \text{ ppb}$ +
- Allergen-driven symptoms +
- Childhood-onset asthma +

Choose one if eligible; trial for at least 4 months and assess response

Extend trial to 6-12 months

unclear

Good asthma response? L
yes Good response to T2-targeted therapy
no**STOP add-on**

Consider switching to a different Type 2-targeted therapy, if eligible

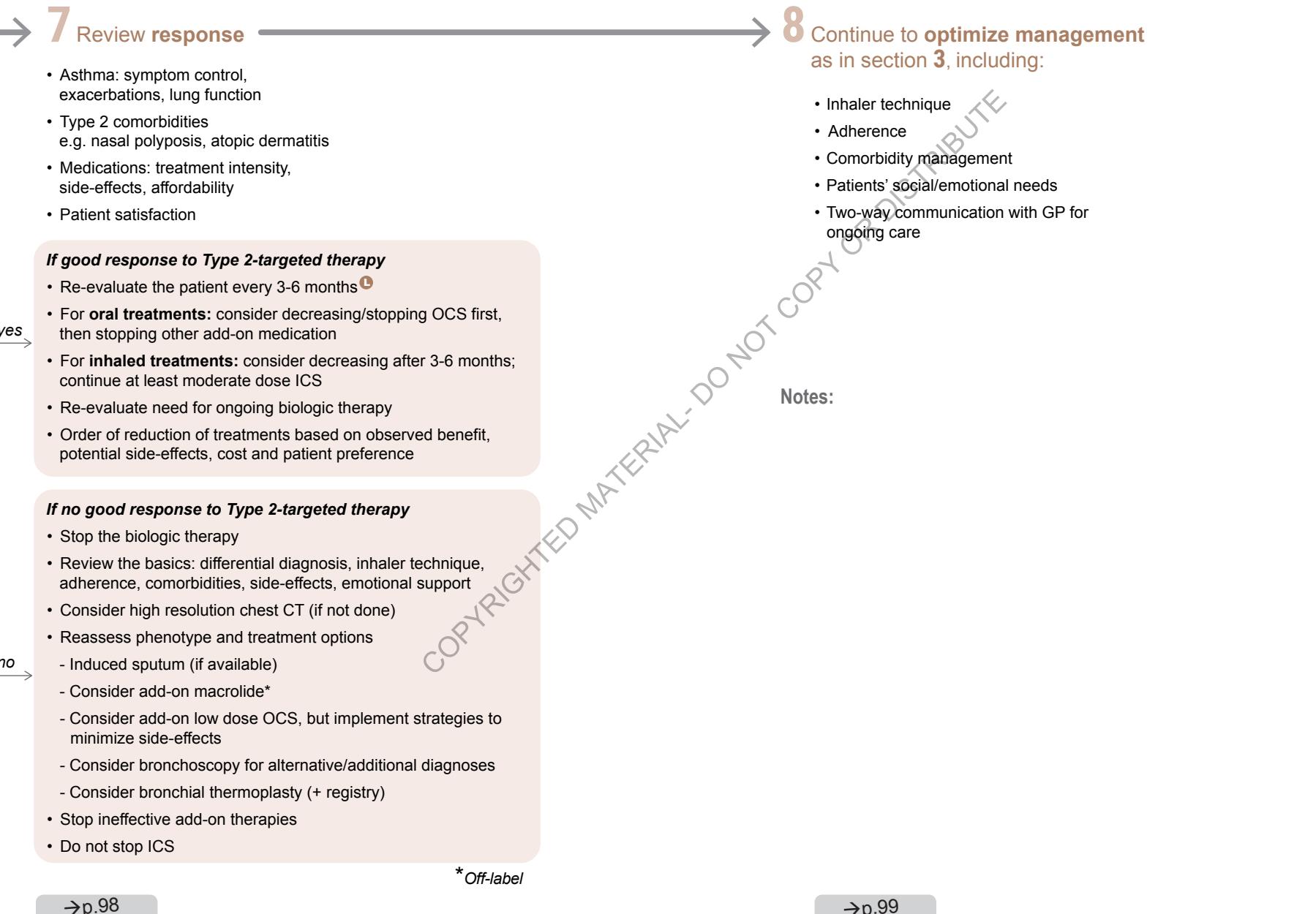
no

Little/no response to T2-targeted therapy

^L Check local eligibility criteria for specific biologic therapies as these may vary from those listed

Monitor / Manage severe asthma treatment

Continue to optimize management



INVESTIGATE AND MANAGE ADULT AND ADOLESCENT PATIENTS WITH DIFFICULT-TO-TREAT ASTHMA

1. CONFIRM THE DIAGNOSIS (ASTHMA OR DIFFERENTIAL DIAGNOSES)

Stages 1-5 can be carried out in primary or specialist care. Difficult-to-treat asthma is defined if the patient has persistent symptoms and/or exacerbations despite prescribing of GINA Step 4-5 treatment (e.g. medium or high dose ICS with another controller such as LABA, or maintenance oral corticosteroids (OCS)). It does not mean a 'difficult patient'.

Consider referral to a specialist or severe asthma clinic at any stage, particularly if:

- There is difficulty confirming the diagnosis of asthma
- Patient has frequent urgent healthcare utilization
- Patient needs frequent or maintenance OCS
- Occupational asthma is suspected
- Food allergy or anaphylaxis, as this increases the risk of death
- Symptoms are suggestive of infective or cardiac cause
- Symptoms are suggestive of complications such as bronchiectasis
- Presence of multiple comorbidities

Are the symptoms due to asthma?

Perform a careful history and physical examination to identify whether symptoms are typical of asthma, or are more likely due to an alternative diagnosis or comorbidity. Investigate according to clinical suspicion.

- Dyspnea: COPD, obesity, cardiac disease, deconditioning
- Cough: inducible laryngeal obstruction (also called vocal cord dysfunction, VCD), upper airway cough syndrome (also called post-nasal drip), gastro-esophageal reflux disease (GERD), bronchiectasis, ACE inhibitors
- Wheeze: obesity, COPD, tracheobronchomalacia, VCD

How can the diagnosis of asthma be confirmed?

Confirmation of the diagnosis is important, because in 12–50% of people assumed to have severe asthma, asthma is not found to be the correct diagnosis.⁴⁵⁴ Perform spirometry, before and after bronchodilator, to assess baseline lung function and seek objective evidence of variable expiratory airflow limitation. If initial reversibility testing is negative (<200mL or <12% increase in FEV1), consider repeating when symptomatic. Check full flow-volume curve to assess for upper airway obstruction. If spirometry is normal or is not available, provide the patient with a peak flow diary for assessing variability; consider bronchial provocation testing if patient is able to withhold bronchodilators (short-acting beta₂-agonist (SABA) for >6 hours, LABA for up to 2 days depending on duration of action). Strategies for confirming the diagnosis of asthma in patients already taking controller treatment are shown in Box 1-4 (p.23).

Airflow limitation may be persistent in patients with long-standing asthma, due to remodeling of the airway walls, or limited lung development in childhood. It is important to document lung function when the diagnosis of asthma is first made. Specialist advice should be obtained if the history is suggestive of asthma but the diagnosis cannot be confirmed by spirometry.

2. LOOK FOR FACTORS CONTRIBUTING TO SYMPTOMS AND EXACERBATIONS

Systematically consider factors that may be contributing to uncontrolled symptoms or exacerbations, or poor quality of life, and that can be treated. The most important modifiable factors include:

- **Incorrect inhaler technique** (seen in up to 80% patients): ask the patient to show you how they use their inhaler; compare with a checklist or video
- **Suboptimal adherence** (up to 75% asthma patients): ask empathically about frequency of use (e.g. 'Many patients don't use their inhaler as prescribed. In the last 4 weeks, how many days a week have you been taking

it – not at all, 1 day a week, 2, 3 or more? or, ‘Do you find it easier to remember your inhaler in the morning or the evening?’ (see Box 3-13, p.71). Ask about barriers to medication use, including cost, and concerns about necessity or side-effects. Check dates on inhalers and view dispensing data, if available.

- **Comorbidities:** review history and examination for comorbidities that can contribute to respiratory symptoms, exacerbations, or poor quality of life. These include anxiety and depression, obesity, deconditioning, chronic rhinosinusitis, inducible laryngeal obstruction (often referred to as VCD), GERD, COPD, obstructive sleep apnea, bronchiectasis, cardiac disease, and kyphosis due to osteoporosis. Investigate according to clinical suspicion.
- **Modifiable risk factors and triggers:** identify factors that increase the risk of exacerbations, e.g. smoking, environmental tobacco exposure, other environmental exposures at home or work including allergens (if sensitized), indoor and outdoor air pollution, molds and noxious chemicals, and medications such as beta-blockers or non-steroid anti-inflammatory drugs (NSAIDs). For allergens, check for sensitization using skin prick testing or specific IgE.
- **Regular or over-use of SABAs** causes beta-receptor down-regulation and lack of response,⁴⁵⁵ leading in turn to greater use. Overuse may also be habitual. Dispensing of ≥3 SABA canisters per year (average 1.5 puffs per day, or more) is associated with increased risk of ED visit or hospitalization independent of severity,⁴⁵⁶ and dispensing of ≥12 canisters per year (one a month) increases the risk of death.⁸³ Risks are higher with nebulized SABA.
- **Anxiety, depression and social and economic problems:** these are very common in asthma, particularly in difficult asthma⁴⁵⁰ and contribute to symptoms, impaired quality of life, and poor adherence.
- **Medication side-effects:** systemic effects, particularly with frequent or continuous OCS, or long-term high dose ICS may contribute to poor quality of life and increase the likelihood of poor adherence. Local side-effects of dysphonia or thrush may occur with high dose or potent ICS especially if inhaler technique is poor. Consider drug interactions including risk of adrenal suppression with use of P450 inhibitors such as itraconazole.

3. REVIEW AND OPTIMIZE MANAGEMENT

Review and optimize treatment for asthma, and for comorbidities and risk factors identified in Section 2. For more details, see Chapter 3D, p.75.

- Provide asthma self-management education, and confirm that patient has (and knows how to use) a personalized written or electronic asthma action plan. Refer to an asthma educator if available.
- Optimize inhaled controller medications: confirm that the inhaler is suitable for the patient; check and correct inhaler technique with a physical demonstration and teach-back method, check inhaler technique again at each visit.⁴⁵⁷ Address intentional and unintentional barriers to adherence.³⁶² For patients with a history of exacerbations, switch to ICS-formoterol maintenance and reliever regimen if available, to reduce the risk of exacerbations.¹⁷⁷
- Treat comorbidities and modifiable risk factors identified in Section 2 of the decision tree, where there is evidence for benefit; however, there is no evidence to support routine treatment of asymptomatic GERD (see p.76). Avoid medications that make asthma worse (beta-blockers including eye-drops; aspirin and other NSAIDs in patients with aspirin-exacerbated respiratory disease, p.82). Refer for management of mental health problems if relevant.
- Consider non-pharmacologic add-on therapy, e.g. smoking cessation, physical exercise, healthy diet, weight loss, mucus clearance strategies, influenza vaccination, breathing exercises, allergen avoidance, if feasible, for patients who are sensitized and exposed. For details see Box 3-9, p.60.
- Consider trial of non-biologic medication added to medium/high dose ICS, e.g. LABA, tiotropium, leukotriene modifier if not already tried
- Consider trial of high dose ICS, if not currently used.

4. REVIEW RESPONSE AFTER 3-6 MONTHS

Schedule a review visit to assess the response to the above interventions. Timing of the review visit depends on clinical urgency and what changes to treatment have been made.

When assessing the response to treatment, specifically review:

- Symptom control: symptom frequency, reliever use, night waking due to asthma, activity limitation
- Exacerbations since previous visit, and how they were managed
- Medication side-effects
- Inhaler technique and adherence
- Lung function
- Patient satisfaction and concerns

Is asthma still uncontrolled, despite optimized therapy?

YES: if asthma is still uncontrolled, the diagnosis of severe asthma has been confirmed. If not done by now, refer the patient to a specialist or severe asthma clinic if possible.

NO: if asthma is now well-controlled, consider stepping down treatment. Start by decreasing/ceasing OCS first (if used), then remove other add-on therapy, then decrease ICS dose (do not stop ICS). See Box 3-7 (p.56) for how to gradually down-titrate treatment intensity.

Does asthma become uncontrolled when treatment is stepped down?

YES: if asthma symptoms become uncontrolled or an exacerbation occurs when high dose treatment is stepped down, the diagnosis of severe asthma has been confirmed. Restore the patient's previous dose to regain good asthma control, and refer to a specialist or severe asthma clinic if possible, if not done already.

NO: if symptoms and exacerbations remain well-controlled despite treatment being stepped down, the patient does not have severe asthma. Continue optimizing management.

ASSESS AND TREAT SEVERE ASTHMA PHENOTYPES

5. ASSESS THE SEVERE ASTHMA PHENOTYPE AND OTHER CONTRIBUTORS

Further assessment and management should be by a specialist, preferably in a multidisciplinary severe asthma clinic if available. The team may include a certified asthma educator and health professionals from fields such as speech pathology, ENT, social work and mental health.

Assessment includes:

- Assessment of the patient's inflammatory phenotype: Type 2 or non-Type 2?
- More detailed assessment of comorbidities and differential diagnoses
- Need for social/psychological support
- Invite patient to enroll in a registry (if available) or clinical trial (if appropriate)

What is Type 2 inflammation?

Type 2 inflammation is found in ~50% of people with severe asthma. It is characterized by cytokines such as interleukin (IL)-4, IL-5 and IL-13, which are often produced by the adaptive immune system on recognition of allergens. It may also be activated by viruses, bacteria and irritants that stimulate the innate immune system via production of IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) by epithelial cells. Type 2 inflammation is often characterized by eosinophils or increased FeNO, and may be accompanied by atopy, whereas non- Type 2 inflammation is often characterized by neutrophils.⁴⁵⁸ In many patients with asthma, Type 2 inflammation rapidly improves when ICS are taken regularly and correctly; this is classified as mild or moderate asthma. In severe asthma, Type 2 inflammation may be relatively

refractory to high dose ICS. It may respond to OCS but their serious adverse effects²⁴³ mean that alternative treatments should be sought.

Could the patient have refractory or underlying Type 2 inflammation?

The possibility of refractory Type 2 inflammation should be considered if any of the following are found while the patient is taking high-dose ICS or daily OCS:

- Blood eosinophils $\geq 150/\mu\text{l}$, and/or
- FeNO $\geq 20\text{ ppb}$, and/or
- Sputum eosinophils $\geq 2\%$, and/or
- Asthma is clinically allergen-driven
- Patients requiring maintenance OCS may also have underlying Type 2 inflammation. However, biomarkers of Type 2 inflammation (blood eosinophils, sputum eosinophils and FeNO) are often suppressed by OCS. If possible, therefore, these tests should be performed before starting OCS (a short course, or maintenance treatment), or on the lowest possible OCS dose.

The above criteria are suggested for initial assessment; those for blood eosinophils and FeNO are based on lowest levels associated with response to some biologics. They are not the criteria for eligibility for Type 2-targeted biologic therapy, which may differ - see section 6b and local criteria. Consider repeating blood eosinophils and FeNO up to 3 times (e.g. when asthma worsens, before giving OCS), before assuming asthma is non-Type 2.

Why is the inflammatory phenotype assessed on high dose ICS?

- Most RCT evidence about Type 2 targeted biologics is in such patients
- Currently, the high cost of biologic therapies generally precludes their widespread clinical use in patients whose symptoms or exacerbations and Type 2 biomarkers are found to respond to ICS when it is taken correctly
- Modifiable ICS treatment problems such as poor adherence and incorrect inhaler technique are common causes of uncontrolled Type 2 inflammation

What other tests may be considered at the specialist level?

Additional investigations may be appropriate for identifying less common comorbidities and differential diagnoses contributing to symptoms and/or exacerbations. Tests should be based on clinical suspicion, and may include:

- Blood tests: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins including Aspergillus
- Allergy testing for clinically relevant allergens: skin prick test or specific IgE, if not already done
- Other pulmonary investigations: DLCO; CXR or high resolution chest CT
- Other directed testing, e.g. ANCA, CT sinuses, BNP, echocardiogram
- Consider testing for parasitic infections, if Type 2 targeted biologic therapy is considered; this is because parasitic infection may be the cause of the blood eosinophilia, and because Type 2 targeted treatment in a patient with untreated parasitic infection could potentially lead to disseminated disease

Consider need for social/psychological support

Refer patients to support services, where available, to help them deal with the emotional, social and financial burden of asthma and its treatment, including during and after severe exacerbations.⁴⁵⁰ Consider the need for psychological or psychiatric referral, including for patients with anxiety and/or depression.

Involve multidisciplinary team care (if available)

Multidisciplinary assessment and treatment of patients with severe asthma increases the identification of comorbidities, and improves outcomes.⁴⁵⁹

Invite patient to enroll in a registry (if available) or clinical trial (if appropriate)

Systematic collection of data will help in understanding the mechanisms and burden of severe asthma. There is a need for pragmatic clinical trials in severe asthma, including studies comparing two or more active treatments.

6A. IF THERE IS NO EVIDENCE OF TYPE 2 INFLAMMATION

If the patient has no evidence of persistent Type 2 inflammation (section 5):

- Review the basics for factors that may be contributing to symptoms or exacerbations: differential diagnosis, inhaler technique, adherence, comorbidities, medication side-effects (Section 2)
- Recommend avoidance of relevant exposures (tobacco smoke, pollution, allergens if sensitized and there is evidence of benefit from withdrawal, irritants, infections). Ask about exposures at home and at work
- Consider additional diagnostic investigations (if available and not already done): sputum induction to confirm inflammatory phenotype, high resolution chest CT, bronchoscopy to exclude unusual comorbidities or alternative diagnoses such as tracheobronchomalacia or sub-glottic stenosis; functional laryngoscopy for inducible laryngeal obstruction.
- Consider a trial of non-biologic add-on treatment if not already tried, e.g. tiotropium, leukotriene modifier, low-dose macrolide^{230,231} (off-label; consider potential for antibiotic resistance). Consider add-on low dose OCS, but implement strategies such as alternate-day treatment to minimize side-effects. Stop ineffective add-on therapies.
- Consider bronchial thermoplasty, with registry enrollment. However, the evidence for efficacy and long-term safety is limited.^{113,276}

No biologic options are currently available for non-Type 2 severe asthma.

6a Non-biologic options if there IS evidence of Type 2 inflammation

For patients with elevated Type 2 biomarkers despite high dose ICS (see section 5), consider non-biologic options first, given the current high cost of biologic therapy:

- **Assess adherence objectively** by monitoring of prescribing or dispensing records, blood prednisone levels,⁴⁶⁰ or electronic inhaler monitoring.³⁴⁹ In one study, suppression of high FeNO after 5 days of directly-observed therapy was an indicator of past poor adherence.⁴⁶¹
- **Consider clinical Type 2 phenotypes** for which specific add-on treatment is available (see Chapter 3D, p.75). For example, for aspirin-exacerbated respiratory disease (AERD), consider add-on leukotriene modifier and possibly aspirin desensitization (p.82). For allergic bronchopulmonary aspergillosis (ABPA), consider add-on OCS ± anti-fungal agent (p.82). For chronic rhinosinusitis and/or nasal polypsis, consider intensive intranasal corticosteroids; surgical advice may be needed (p.77). For patients with atopic dermatitis, topical steroidal or non-steroidal therapy may be helpful.
- **Consider increasing the ICS dose** for 3-6 months, and review again

6B CONSIDER ADD-ON BIOLOGIC TYPE 2 TARGETED TREATMENTS

If available and affordable, consider an add-on Type 2 targeted biologic for patients with exacerbations or poor symptom control despite taking at least high dose ICS-LABA, and who have allergic or eosinophilic biomarkers or need maintenance OCS. Where relevant, test for parasitic infection, and treat if present, before commencing Type 2 targeted treatment (see section 5).

Always check local criteria for eligibility and funding.

Consider whether to start first with anti-IgE, anti-IL5/5R or anti-IL4R. When choosing between available therapies, consider the following:

- Does the patient satisfy local payer eligibility criteria?
- Predictors of asthma response (see below)
- Cost
- Dosing frequency
- Delivery route (IV or SC; potential for self-administration)
- Patient preference

Local payer eligibility criteria for biologic therapy may vary substantially. **For any biologic therapy**, ensure that the manufacturer's and/or regulator's instructions for storage, administration and the duration of monitoring post-administration are followed. Provide the patient with advice about what to do if they experience any adverse effects, including hypersensitivity reactions.

There is an urgent need for head-to-head comparisons of different biologics in patients eligible for more than one biologic.

Add-on anti-IgE for severe allergic asthma

Currently approved: omalizumab for ages ≥ 6 years, given by SC injection every 2-4 weeks, with dose based on weight and serum IgE. Self- administration may be an option.

Mechanism: binds to Fc part of free IgE, preventing binding of IgE to Fc ϵ R1 receptors, reducing free IgE and down-regulating receptor expression.

Eligibility criteria vary between payers, but usually include:

- Sensitization to inhaled allergen(s) on skin prick testing or specific IgE, and
- Total serum IgE and body weight within local dosing range, and
- More than a specified number of exacerbations within the last year

Benefits: RCTs in severe asthma: 34% decrease in severe exacerbations,⁴⁶² but no significant difference in symptoms or quality of life.²³² In open-label studies in patients with severe allergic asthma and ≥ 1 severe exacerbation in last 12 months, there was a 50-65% reduction in exacerbation rate,^{463,464} a significant improvement in quality of life,²⁵ and 40-50% reduction in OCS dose.^{463,464}

Potential predictors of good asthma response to omalizumab:

- Baseline IgE level does not predict likelihood of response⁴⁶³
- In RCTs: a greater decrease in exacerbations was observed (cf. placebo) if blood eosinophils $\geq 260/\mu\text{l}$ ^{465,466} or FeNO $\geq 20\text{ppb}$,⁴⁶⁵ but in a large observational study, exacerbations were reduced with both low or high blood eosinophils^{464,467}
- Childhood-onset asthma
- Clinical history suggesting allergen-driven symptoms

Adverse effects: injection site reactions; anaphylaxis in ~0.2% patients

Suggested initial trial: at least 4 months

Add-on anti-IL5 or anti-IL5R for severe eosinophilic asthma

Currently approved: For ages ≥ 12 years: mepolizumab (anti-IL5), 100mg by SC injection 4-weekly, and benralizumab (anti-IL5 receptor α), 30mg by SC injection every 4 weeks for 3 doses then every 8 weeks. For ages ≥ 18 years: reslizumab (anti-IL5), 3mg/kg by IV infusion every 4 weeks.

Mechanism: mepolizumab and reslizumab bind circulating IL-5; benralizumab binds to IL-5 receptor alpha subunit leading to apoptosis (cell death) of eosinophils.

Eligibility criteria: these vary by product and between payers, but usually include:

- More than a specified number of severe exacerbations in the last year, and
- Blood eosinophils above specified level (e.g. $\geq 300/\mu\text{l}$). In some cases there is a different eosinophil cutpoint for patients taking OCS.

Outcomes: RCTs in severe asthma patients with exacerbations in the last year, with varying eosinophil criteria: anti-IL5 and anti-IL5R led to $\sim 55\%$ reduction in severe exacerbations, and improved quality of life, lung function and symptom control.²³⁸ All reduced blood eosinophils; almost completely with benralizumab.²³⁸ In patients taking OCS, median OCS dose was able to be reduced by $\sim 50\%$ with mepolizumab or benralizumab compared with placebo. Mepolizumab may improve nasal polyposis.⁴⁶⁸

Potential predictors of good asthma response:

- Higher blood eosinophils (strongly predictive)⁴⁶⁹
- Higher number of severe exacerbations in previous year (strongly predictive)⁴⁶⁹
- Adult-onset asthma⁴⁷⁰
- Nasal polyposis⁴⁷¹
- Maintenance OCS at baseline⁴⁷¹

Adverse effects: injection site reactions; anaphylaxis is rare; adverse events generally similar between active and placebo groups

Suggested initial trial: at least 4 months

Add-on anti-IL4R for severe eosinophilic/Type 2 asthma or patients requiring maintenance OCS

Currently approved: For ages ≥ 12 years: dupilumab (anti-IL4 receptor α), 200mg or 300mg by SC injection every 2 weeks for severe eosinophilic/Type 2 asthma; 300mg by SC injection every 2 weeks for OCS-dependent severe asthma or if there is concomitant moderate/severe atopic dermatitis. Self-administration may be an option.

Mechanism: binds to interleukin-4 (IL-4) receptor alpha, blocking both IL-4 and IL-13 signaling

Eligibility criteria: these vary between payers, but usually include:

- More than a specified number of severe exacerbations in the last year, and
- Type 2 biomarkers above a specified level (e.g. blood eosinophils $\geq 300/\mu\text{l}$ or FeNO $\geq 25 \text{ ppb}$); OR
- Requirement for maintenance OCS

Dupilumab is also indicated for treatment of moderate-severe atopic dermatitis⁴⁷² and may improve nasal polyposis.⁴⁷³

Outcomes: RCTs in uncontrolled (ACQ-5 ≥ 1.5) severe asthma patients with at least one exacerbation in the last year: anti-IL4R led to $\sim 50\%$ reduction in severe exacerbations, and significantly improved quality of life, symptom control and lung function.²³⁹ In patients with OCS-dependent severe asthma, without minimum requirements of blood eosinophil count or FeNO, treatment with anti-IL4R reduced median OCS dose by 50% versus placebo.⁴⁷⁴

Potential predictors of good asthma response:

- Higher blood eosinophils (strongly predictive)²³⁹
- Higher FeNO²³⁹

Adverse effects: injection-site reactions; transient blood eosinophilia

Suggested initial trial: at least 4 months

Review response to an initial trial of add-on Type 2 targeted therapy

- At present, there are no well-defined criteria for a good response, but consider exacerbations, symptom control, lung function, side-effects, treatment intensity (including OCS dose), and patient satisfaction
- If the response is unclear, consider extending the trial to 6-12 months
- If there is no response, stop the biologic therapy, and consider switching to a trial of a different Type 2 targeted therapy, if available and the patient is eligible; review response as above

MANAGE AND MONITOR SEVERE ASTHMA TREATMENT

7. REVIEW RESPONSE AND IMPLICATIONS FOR TREATMENT

Review the patient's response to add-on biologic therapy after 3-4 months, and every 3-6 months for ongoing care, including:

- Asthma: symptom control, e.g. Asthma Control Test, Asthma Control Questionnaire; frequency and severity of exacerbations (e.g. were OCS needed), lung function
- Type 2 comorbidities, e.g. nasal polyposis, atopic dermatitis
- Medications: treatment intensity, including dose of OCS, side-effects, affordability
- Patient satisfaction

If the patient has had a good response to Type 2 targeted therapy:

Re-evaluate the need for each asthma medication every 3-6 months, but do not completely stop inhaled therapy. Base the order of reduction or cessation of add-on treatments on the observed benefit when they were started, patient risk factors, medication side-effects, cost, and patient satisfaction.

For oral treatments, consider gradually decreasing or stopping OCS first, because of their significant adverse effects. Tapering may be supported by internet-based monitoring of symptom control and FeNO.⁴⁷⁵ Monitor patients for risk of adrenal suppression, and provide patient and GP with advice about the need for extra corticosteroid doses during injury, illness or surgery for up to 6 months after cessation of long-term OCS. Continue to assess for presence of osteoporosis, and review need for preventative strategies including bisphosphonates.²⁴⁴

For inhaled treatments, consider reducing the ICS dose after 3-6 months, but do not completely stop inhaled therapy. Current consensus advice is to continue at least medium dose ICS. Patients should be reminded of the importance of continuing their inhaled controller.

For biologic treatments, current consensus advice is that, generally, for a patient with a good response, a trial of withdrawal of the biologic should not be considered until after at least 12 months of treatment, and only if asthma remains well-controlled on medium dose ICS therapy, and (for allergic asthma) there is no further exposure to a previous well-documented allergic trigger. There are limited studies of cessation of biologic therapy,^{476,477} in these studies, symptom control worsened and/or exacerbations recurred for many (but not all) patients after cessation of the biologic.

If the patient has NOT had a good response to any Type 2 targeted therapy:

Review the basics for factors contributing to symptoms, exacerbations and poor quality of life (see Section 2): diagnosis, inhaler technique, adherence, modifiable risk factors and triggers including smoking and other environmental exposures at home or work, comorbidities including obesity, medication side-effects or drug interactions, socio-economic and mental health issues.

Consider additional investigations (if not already done): high resolution chest CT; induced sputum to confirm inflammatory phenotype, consider referral if available, including for diagnosis of alternative conditions.

Reassess treatment options (if not already done), such as add-on low-dose macrolide²³⁰ (off-label; consider potential for antibiotic resistance); consider add-on low-dose maintenance OCS, but implement strategies such as alternate-day therapy and add-on bisphosphonates²⁴⁴ to minimize side-effects, and alert patient to the need for additional corticosteroid therapy during illness or surgery. Consider bronchial thermoplasty (+ registry).

Stop ineffective add-on therapies, but do not completely stop ICS

8. CONTINUE TO COLLABORATIVELY OPTIMIZE PATIENT CARE

Ongoing management of a patient with severe asthma involves a collaboration between the patient, the GP, specialist(s), and other health professionals, to optimize clinical outcomes and patient satisfaction.

Continue to review the patient every 3-6 months including:

- Clinical asthma measures (symptom control; exacerbations; lung function)
- Comorbidities⁴⁵⁹
- The patient's risk factors for exacerbations
- Treatments (check inhaler technique and adherence; review need for add-on treatments; assess side-effects including of OCS; optimize comorbidity management and non-pharmacologic strategies)
- The patient's social and emotional needs⁴⁵⁰

The optimal frequency and location of review (GP or specialist) will depend on the patient's asthma control, risk factors and comorbidities, and their confidence in self-management, and may depend on local payer requirements and availability of specialist physicians.

Communicate regularly about:

- Outcome of review visits (as above)
- Patient concerns
- Action plan for worsening asthma or other risks
- Changes to medications (asthma and non-asthma); potential side-effects
- Indications and contact details for expedited review

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE

Chapter 4.

Management of worsening asthma and exacerbations

COPYRIGHTED MATERIAL
DO NOT DISTRIBUTE

KEY POINTS

- Exacerbations represent an acute or sub-acute worsening in symptoms and lung function from the patient's usual status, or in some cases, a patient may present for the first time during an exacerbation.
- The terms 'episodes', 'attacks' and 'acute severe asthma' are also often used, but they have variable meanings. The term 'flare-up' is preferable for use in discussions with most patients.
- Patients who are at increased risk of asthma-related death should be identified, and flagged for more frequent review.
- Written asthma action plans
 - All patients should be provided with a written asthma action plan appropriate for their level of asthma control and health literacy, so they know how to recognize and respond to worsening asthma.
 - On the action plan, state when and how to change reliever and controller medications, use oral corticosteroids, and access medical care if symptoms fail to respond to treatment.
 - Advise patients who have a history of rapid deterioration to go to an acute care facility or see their doctor immediately their asthma starts to worsen.
 - Base the action plan on changes in symptoms or (only in adults) peak expiratory flow.
- Management of exacerbations in a primary care or acute care facility:
 - Assess exacerbation severity from the degree of dyspnea, respiratory rate, pulse rate, oxygen saturation and lung function, while starting short-acting beta₂-agonist (SABA) and oxygen therapy.
 - Arrange immediate transfer to an acute care facility if there are signs of severe exacerbation, or to intensive care if the patient is drowsy, confused, or has a silent chest. During transfer, give inhaled SABA and ipratropium bromide, controlled oxygen and systemic corticosteroids.
 - Start treatment with repeated administration of SABA (in most patients, by pressurized metered dose inhaler and spacer), early introduction of oral corticosteroids, and controlled flow oxygen if available. Review response of symptoms, oxygen saturation and lung function after 1 hour. Give ipratropium bromide only for severe exacerbations. Consider intravenous magnesium sulfate for patients with severe exacerbations not responding to initial treatment.
 - Do not routinely request a chest X-ray, and do not routinely prescribe antibiotics for asthma exacerbations.
 - Decide about hospitalization based on the patient's clinical status, lung function, response to treatment, recent and past history of exacerbations, and ability to manage at home.
 - Arrange ongoing treatment before the patient goes home. This should include starting controller treatment or stepping up the dose of existing controller treatment for 2–4 weeks, and reducing reliever medication to as-needed use.
- Arrange early follow-up after any exacerbation, regardless of where it was managed.
 - Review the patient's symptom control and risk factors for further exacerbations.
 - For most patients, prescribe regular controller therapy to reduce the risk of further exacerbations. Continue increased controller doses for 2–4 weeks.
- Check inhaler technique and adherence.

For management of asthma exacerbations in children 5 years and younger, see Chapter 6, p.146.

OVERVIEW

Definition of asthma exacerbations

Exacerbations of asthma are episodes characterized by a progressive increase in symptoms of shortness of breath, cough, wheezing or chest tightness and progressive decrease in lung function, i.e. they represent a change from the patient's usual status that is sufficient to require a change in treatment.¹⁴ Exacerbations may occur in patients with a pre-existing diagnosis of asthma or, occasionally, as the first presentation of asthma.

What triggers asthma exacerbations?

Exacerbations usually occur in response to exposure to an external agent (e.g. viral upper respiratory tract infection, pollen or pollution) and/or poor adherence with controller medication; however, a subset of patients present more acutely and without exposure to known risk factors.^{478,479} Severe exacerbations can occur in patients with mild or well-controlled asthma symptoms.^{9,169} Box 2-2B (p.31) lists factors that increase a patient's risk of exacerbations, independent of their level of symptom control.

Common exacerbation triggers include:

- Viral respiratory infections⁴⁸⁰
- Allergen exposure e.g. grass pollen,⁴⁸¹ soy bean dust,⁴⁸² fungal spores
- Food allergy⁸⁹
- Outdoor air pollution⁹⁴
- Seasonal changes and/or returning to school in fall (autumn)⁴⁸³
- Poor adherence with ICS⁴⁸⁴
- Epidemics of severe asthma exacerbations may occur suddenly, putting high pressure on local health system responses. Such epidemics have been reported in association with springtime thunderstorms and either rye grass pollen or fungal spores,⁴⁸⁵ and with environmental exposure to soy bean dust.⁴⁸²

Identifying patients at risk of asthma-related death

In addition to factors known to increase the risk of asthma exacerbations (Box 2-2, p.31), some features are specifically associated with an increase in the risk of asthma-related death (Box 4-1). The presence of one or more of these risk factors should be quickly identifiable in the clinical notes, and these patients should be encouraged to seek urgent medical care early in the course of an exacerbation.

Box 4-1. Factors that increase the risk of asthma-related death

- A history of near-fatal asthma requiring intubation and mechanical ventilation⁴⁸⁶
- Hospitalization⁴⁸⁶ or emergency care visit for asthma in the past year
- Currently using or having recently stopped using oral corticosteroids (a marker of event severity)⁴⁸⁶
- Not currently using inhaled corticosteroids^{84,486}
- Over-use of SABAs, especially use of more than one canister of salbutamol (or equivalent) monthly^{101,487}
- A history of psychiatric disease or psychosocial problems,⁹⁵
- Poor adherence with asthma medications and/or poor adherence with (or lack of) a written asthma action plan⁹⁵
- Food allergy in a patient with asthma^{396,488}

Terminology about exacerbations

The academic term ‘exacerbation’ is commonly used in scientific and clinical literature, although hospital-based studies more often refer to ‘acute severe asthma’. However, the term ‘exacerbation’ is not suitable for use in clinical practice, as it is difficult for many patients to pronounce and remember.^{489,490} The term ‘flare-up’ is simpler, and conveys the sense that asthma is present even when symptoms are absent. The term ‘attack’ is used by many patients and health care providers but with widely varying meanings, and it may not be perceived as including gradual worsening.^{489,490} In pediatric literature, the term ‘episode’ is commonly used, but understanding of this term by parent/carers is not known.

DIAGNOSIS OF EXACERBATIONS

Exacerbations represent a change in symptoms and lung function from the patient’s usual status.¹⁴ The decrease in expiratory airflow can be quantified by lung function measurements such as peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV₁),⁴⁹¹ compared with the patient’s previous lung function or predicted values. In the acute setting, these measurements are more reliable indicators of the severity of the exacerbation than symptoms. The frequency of symptoms may, however, be a more sensitive measure of the onset of an exacerbation than PEF.⁴⁹²

A minority of patients perceive airflow limitation poorly and can experience a significant decline in lung function without a change in symptoms.^{124,125,133} This especially affects patients with a history of near-fatal asthma and also appears to be more common in males.

Severe exacerbations are potentially life threatening and their treatment requires careful assessment and close monitoring. Patients with severe exacerbations should be advised to see their health care provider promptly or, depending on the organization of local health services, to proceed to the nearest facility that provides emergency access for patients with acute asthma.

SELF-MANAGEMENT OF EXACERBATIONS WITH A WRITTEN ASTHMA ACTION PLAN

All patients with asthma should be provided with guided self-management education as described in Chapter 3 (p.69), including monitoring of symptoms and/or lung function, a written asthma action plan, and regular review by a health professional.³⁷⁴ (For children 5 years and younger, see Chapter 6, p.129) A sample written asthma action plan template is included in the GINA toolbox, available from the GINA website at www.ginasthma.org/gina-implementation-guide.

Treatment options for written asthma action plans

A written asthma action plan helps patients to recognize and respond appropriately to worsening asthma. It should include specific instructions for the patient about changes to reliever and controller medications, how to use oral corticosteroids (OCS) if needed (Box 4-2) and when and how to access medical care.

The criteria for initiating an increase in controller medication will vary from patient to patient. For patients taking conventional maintenance ICS-containing treatment, this should generally be increased when there is a clinically important change from the patient’s usual level of asthma control, for example, if asthma symptoms are interfering with normal activities, or PEF has fallen by >20% for more than 2 days.³⁷⁹

Inhaled reliever medication

For patients with mild asthma prescribed as-needed combination low dose ICS-formoterol (see Box 3-5A, p.46), increasing the as-needed doses of ICS-formoterol when asthma worsens reduces the risk of severe exacerbations requiring OCS by two-thirds compared with SABA-only treatment,¹⁷⁴ and is non-inferior for progression to severe exacerbation compared with daily ICS plus as-needed SABA.^{174,178} Patients prescribed as-needed ICS-formoterol should be advised to seek medical attention if they need more than 12 inhalations (i.e. more than 72mcg formoterol) in a day.

For patients prescribed an inhaled short-acting beta₂-agonist (SABA) bronchodilator as their reliever, repeated SABA dosing provides temporary relief until the cause of the worsening symptoms passes or increased controller treatment

has had time to take effect. However, use of SABA reliever is less effective in preventing progression to severe exacerbation requiring OCS than use of low-dose ICS-formoterol reliever, either with¹⁷⁷ or without^{174,178} daily maintenance controller (see Chapter 3).

The need for repeated doses of SABA over more than 1–2 days signals the need to review, and possibly increase, controller treatment if this has not already been done. This is particularly important if there has been a lack of response to increased use of beta₂-agonist therapy.

Combination low dose ICS (budesonide or beclometasone) with formoterol maintenance and reliever regimen

The combination of rapid-onset LABA (formoterol) and low dose ICS (budesonide or beclometasone) in a single inhaler as both the controller and the reliever medication is effective in improving asthma symptom control,¹⁵⁷ and it reduces exacerbations requiring OCS, and hospitalizations^{177,202-205} compared with the same or higher dose of controller with as-needed SABA reliever (Evidence A). The recommended maximum total dose of formoterol in 24 hours with this regimen is 72 mcg. The benefit of this regimen in preventing exacerbations appears to be due to intervention at a *very early stage* of worsening asthma.^{493,494} This regimen was also effective in reducing exacerbations in children aged 4–11 years,²¹⁷ (Evidence B), but it is not approved for this age group in many countries. This approach should not be attempted with other combination ICS-LABA controller therapies with a slower-onset LABA, or that lack evidence of efficacy and safety with a maintenance and reliever regimen.

Other ICS and ICS-LABA maintenance controller regimens

In a systematic review of self-management studies, action plans in which the ICS dose was at least doubled were associated with improved asthma outcomes and reduced health care utilization³⁷⁹ (Evidence A). In placebo-controlled trials, temporarily doubling the dose of ICS was not effective⁴⁹⁵ (Evidence A); however, the delay before increasing the ICS dose (mean 5–7 days^{496,497}) may have contributed. There is evidence in adults⁴⁹⁸ and young children⁴⁹⁹ that higher ICS doses might help prevent worsening asthma progressing to a severe exacerbation. Patients who quadrupled their ICS dose (to average of 2000mcg/day BDP equivalent) after their PEF fell were significantly less likely to require OCS.⁵⁰⁰ For adults taking combination ICS-LABA as a fixed dose maintenance controller medication, the ICS dose may be increased by adding a separate ICS inhaler^{498,501} (Evidence D). More research is needed to standardize this strategy. In an open-label primary care randomized controlled trial of adult and adolescent patients using ICS with or without LABA, early quadrupling of ICS dose (to average 3200mcg/day BDP equivalent) was associated with a modest reduction in prescribing of OCS.⁵⁰¹ However, a double-blind placebo-controlled study in children 5–11 years with high adherence to low dose ICS found no difference in the rate of severe exacerbations requiring OCS if maintenance ICS was quintupled (to 1600mcg BDP equivalent) versus continuing maintenance low-dose therapy.⁵⁰² Given the shape of the ICS dose-response curve, the effect of increasing maintenance ICS when asthma worsens may be greater when background adherence is lower. In adult patients with an acute deterioration, high-dose ICS for 7–14 days (500–1600mcg BDP-HFA equivalent) had an equivalent benefit to a short course of OCS⁴⁹⁸ (Evidence A).

Leukotriene receptor antagonists

For patients using a leukotriene receptor antagonist (LTRA) as their controller, there are no specific studies about how to manage worsening asthma. Clinician judgment should be used (Evidence D).

Oral corticosteroids

For most patients, the written asthma action plan should provide instructions for when and how to commence OCS. Typically, a short course of OCS is used (e.g. 40–50 mg/day usually for 5–7 days,⁴⁹⁸ Evidence B) for patients who:

- Fail to respond to an increase in reliever and controller medication for 2–3 days
- Deteriorate rapidly or who have a PEF or FEV₁ <60% of their personal best or predicted value
- Have a history of sudden severe exacerbations.

For children 6–11 years, the recommended dose of OCS is 1–2 mg/kg/day to a maximum of 40 mg/day (Evidence B), usually for 3–5 days. Patients should be advised about common side-effects, including sleep disturbance, increased appetite, reflux, and mood changes.⁵⁰³ Patients should contact their doctor if they start taking OCS (Evidence D).

Reviewing response

Patients should see their doctor immediately or present to an acute care unit if their asthma continues to deteriorate despite following their written asthma action plan, or if their asthma suddenly worsens.

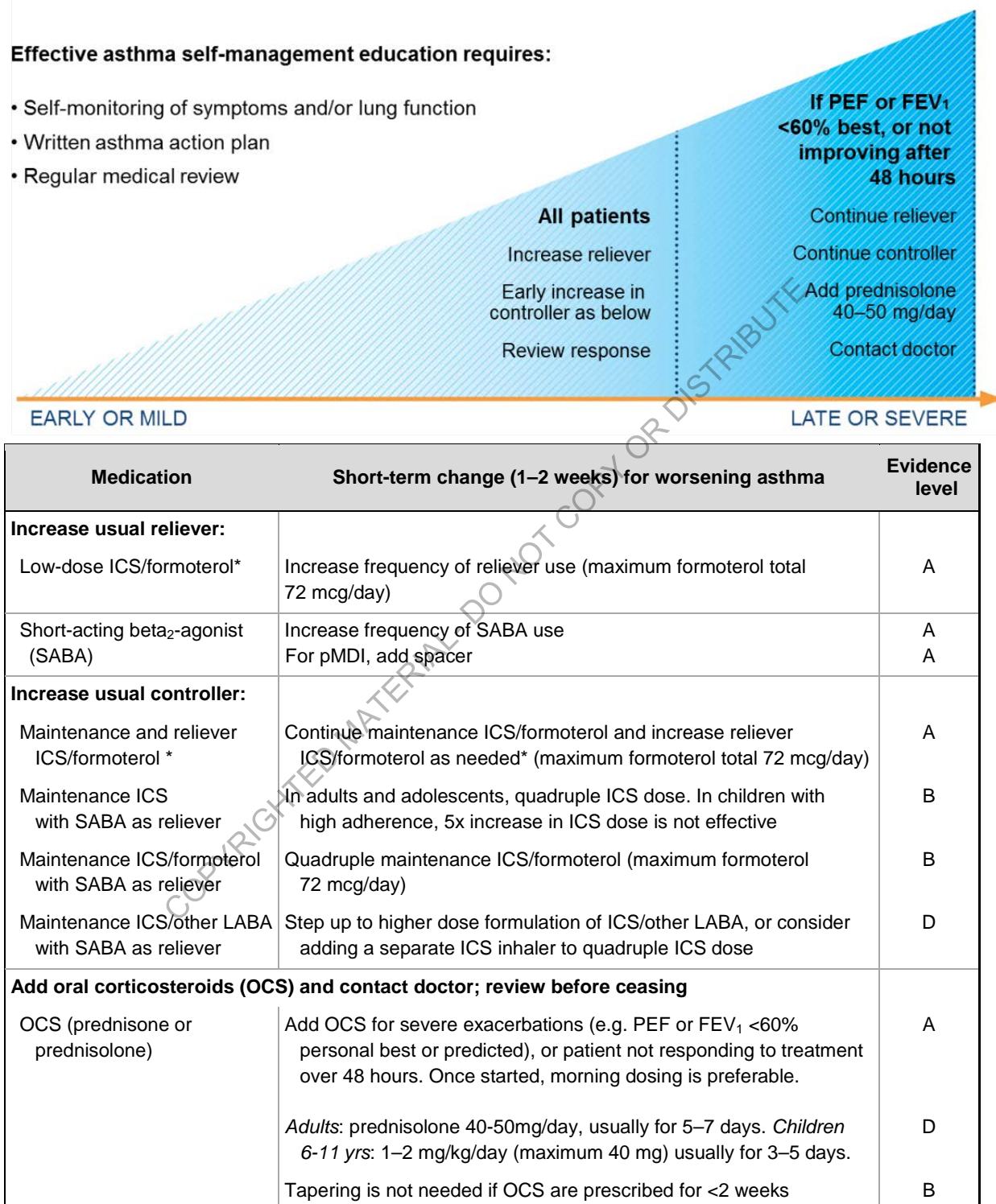
Follow up after a self-managed exacerbation

After a self-managed exacerbation, patients should see their primary care health care provider for a semi-urgent review (e.g. within 1–2 weeks), for assessment of symptom control and additional risk factors for exacerbations (Box 2-2, p.31), and to identify the potential cause of the exacerbation. The written asthma action plan should be reviewed to see if it met the patient's needs. Maintenance controller treatment can generally be resumed at previous levels 2–4 weeks after the exacerbation (Evidence D), unless the history suggests that the exacerbation occurred on a background of long-term poorly controlled asthma. In this situation, provided inhaler technique and adherence have been checked, a step up in treatment is indicated (Box 3-5, p.46).

Adult and adolescent patients with more than 1-2 exacerbations per year despite Step 4-5 therapy should be referred to a specialist center for assessment (see decision tree in Chapter 3E, p.84).

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE

Box 4-2. Self-management of worsening asthma in adults and adolescents with a written asthma action plan



BDP: beclometasone dipropionate; FEV₁: forced expiratory volume in 1 second; ICS: inhaled corticosteroid;

PEF: peak expiratory flow; SABA: short-acting beta₂-agonist. Options are listed in order of evidence.

*ICS-formoterol as-needed for relief of symptoms in mild asthma (off-label), or as part of maintenance and reliever regimen: low dose budesonide or beclometasone with formoterol. Maintenance and reliever regimen is not approved for children <12 years in many countries.

MANAGEMENT OF ASTHMA EXACERBATIONS IN PRIMARY CARE

Assessing exacerbation severity

A brief focused history and relevant physical examination should be conducted concurrently with the prompt initiation of therapy, and findings documented in the notes. If the patient shows signs of a severe or life-threatening exacerbation, treatment with SABA, controlled oxygen and systemic corticosteroids should be initiated while arranging for the patient's urgent transfer to an acute care facility where monitoring and expertise are more readily available. Milder exacerbations can usually be treated in a primary care setting, depending on resources and expertise.

History

The history should include:

- Timing of onset and cause (if known) of the present exacerbation
- Severity of asthma symptoms, including any limiting exercise or disturbing sleep
- Any symptoms of anaphylaxis
- Any risk factors for asthma-related death (Box 4-1, p.103)
- All current reliever and controller medications, including doses and devices prescribed, adherence pattern, any recent dose changes, and response to current therapy.

Physical examination

The physical examination should assess:

- Signs of exacerbation severity (Box 4-3, p.109) and vital signs (e.g. level of consciousness, temperature, pulse rate, respiratory rate, blood pressure, ability to complete sentences, use of accessory muscles, wheeze).
- Complicating factors (e.g. anaphylaxis, pneumonia, pneumothorax)
- Signs of alternative conditions that could explain acute breathlessness (e.g. cardiac failure, inducible laryngeal obstruction, inhaled foreign body or pulmonary embolism).

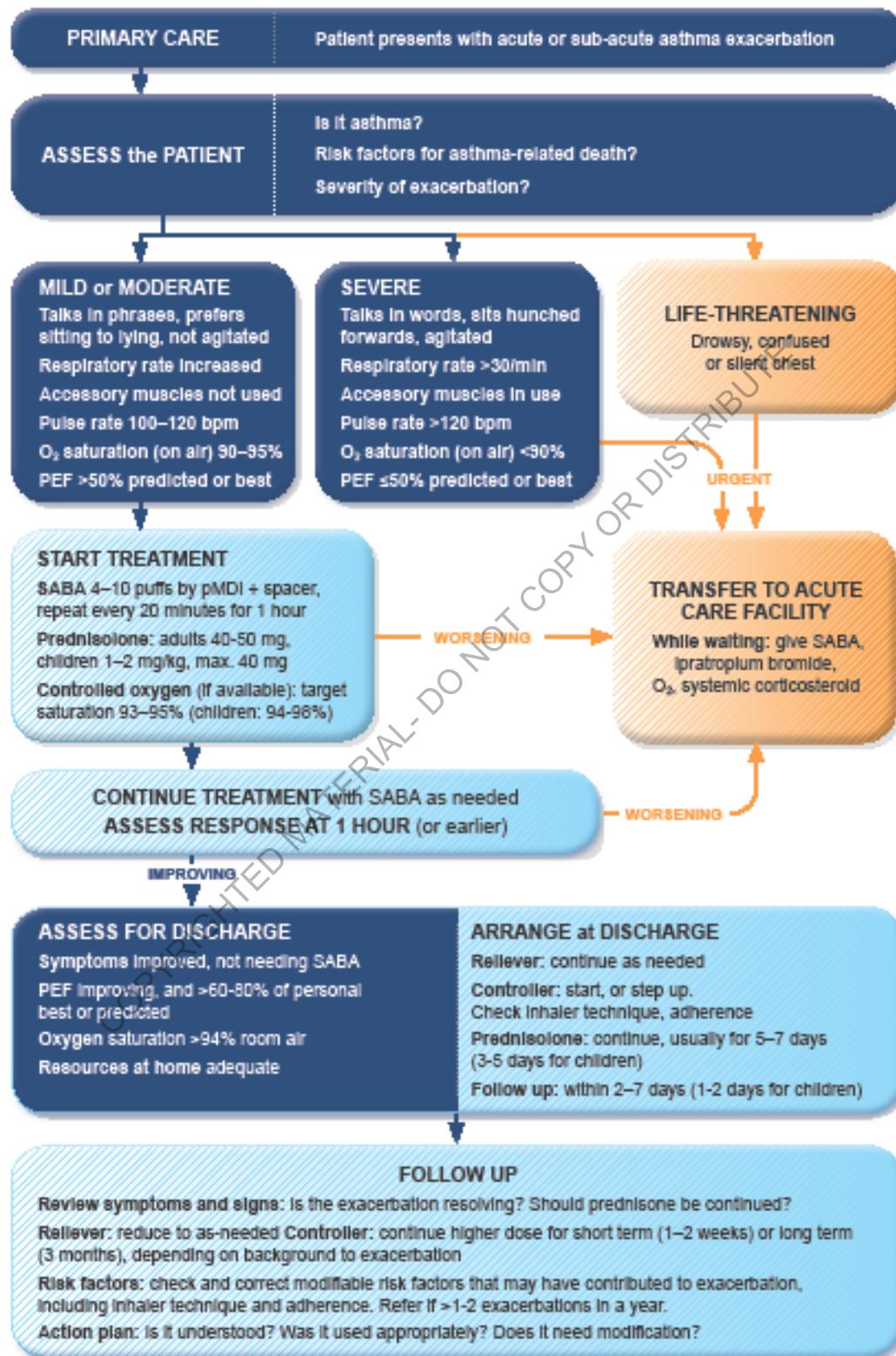
Objective measurements

- Pulse oximetry. Saturation levels <90% in children or adults signal the need for aggressive therapy.
- PEF in patients older than 5 years (Box 4-3, p.109)

Treating exacerbations in primary care

The main initial therapies include repetitive administration of short-acting inhaled bronchodilators, early introduction of systemic corticosteroids, and controlled flow oxygen supplementation.⁴⁹¹ The aim is to rapidly relieve airflow obstruction and hypoxemia, address the underlying inflammatory pathophysiology, and prevent relapse.

Box 4-3. Management of asthma exacerbations in primary care (adults, adolescents, children 6–11 years)



O₂: oxygen; PEF: peak expiratory flow; SABA: short-acting beta₂-agonist (doses are for salbutamol).

Inhaled short-acting beta₂-agonists

For mild to moderate exacerbations, repeated administration of inhaled SABA (up to 4–10 puffs every 20 minutes for the first hour) is an effective and efficient way to achieve rapid reversal of airflow limitation⁵⁰⁴ (Evidence A). After the first hour, the dose of SABA required varies from 4–10 puffs every 3–4 hours up to 6–10 puffs every 1–2 hours, or more often. No additional SABA is needed if there is a good response to initial treatment (e.g. PEF >60–80% of predicted or personal best for 3–4 hours).

Delivery of SABA via a pMDI and spacer or a DPI leads to a similar improvement in lung function as delivery via nebulizer^{504,505} (Evidence A); however, patients with acute severe asthma were not included in these studies. The most cost-effective route of delivery is pMDI and spacer,⁵⁰⁶ provided the patient can use this device. Because of the static charge on plastic spacers, they should be pre-washed with detergent and air-dried to be ready for immediate use.

Controlled oxygen therapy (if available)

Oxygen therapy should be titrated against pulse oximetry (if available) to maintain oxygen saturation at 93–95% (94–98% for children 6–11 years). Controlled or titrated oxygen therapy gives better clinical outcomes than high-flow 100% oxygen therapy^{507–509} (Evidence B). Oxygen should not be withheld if oximetry is not available, but the patient should be monitored for deterioration, somnolence or fatigue.

Systemic corticosteroids

OCS should be given promptly, especially if the patient is deteriorating, or had already increased their reliever and controller medications before presenting (Evidence B). The recommended dose for adults is 1 mg prednisolone/kg/day or equivalent up to a maximum of 50 mg/day, and 1–2 mg/kg/day for children 6–11 years up to a maximum of 40 mg/day). OCS should usually be continued for 5–7 days^{510,511} (Evidence B). Patients should be advised about common side-effects, including sleep disturbance, increased appetite, reflux and mood changes.⁵⁰³

Controller medication

Patients already prescribed controller medication should be provided with advice about increasing the dose for the next 2–4 weeks, as summarized in Box 4-2 (p.107). Patients not currently taking controller medication should be commenced on regular ICS-containing therapy, as SABA-only treatment of asthma is no longer recommended. An exacerbation requiring medical care indicates that the patient is at increased risk of future exacerbations (Box 2-2, p.31).

Antibiotics (not recommended)

Evidence does not support a role of antibiotics in asthma exacerbations unless there is strong evidence of lung infection (e.g. fever and purulent sputum or radiographic evidence of pneumonia).⁵¹² Aggressive treatment with corticosteroids should be implemented before antibiotics are considered.

Reviewing response

During treatment, patients should be closely monitored, and treatment titrated according to their response. Patients who present with signs of a severe or life-threatening exacerbation (Box 4-3, p.109), who fail to respond to treatment, or who continue to deteriorate should be transferred immediately to an acute care facility. Patients with little or slow response to SABA treatment should be closely monitored.

For many patients, lung function can be monitored after SABA therapy is initiated. Additional treatment should continue until PEF or FEV₁ reaches a plateau or (ideally) returns to the patient's previous best. A decision can then be made whether to send the patient home or transfer them to an acute care facility.

Follow up

Discharge medications should include as-needed reliever medication, a short course of OCS and regular controller treatment. SABA-only treatment is not recommended. Inhaler technique and adherence should be reviewed before discharge. Patients should be advised to use their reliever inhaler only as-needed, rather than routinely. A follow-up appointment should be arranged for about 2–7 days later, depending on the clinical and social context.

At the review visit the health care provider should assess whether the flare-up has resolved, and whether OCS can be ceased. They should assess the patient's level of symptom control and risk factors; explore the potential cause of the exacerbation; and review the written asthma action plan (or provide one if the patient does not already have one). Maintenance controller treatment can generally be stepped back to pre-exacerbation levels 2–4 weeks after the exacerbation, unless the exacerbation was preceded by symptoms suggestive of chronically poorly controlled asthma. In this situation, provided inhaler technique and adherence have been checked, a step up in treatment (Box 3-5, p.46) is indicated.

MANAGEMENT OF ASTHMA EXACERBATIONS IN THE EMERGENCY DEPARTMENT

Severe exacerbations of asthma are life-threatening medical emergencies, which are most safely managed in an acute care setting e.g. emergency department (Box 4-4). Management of asthma in the intensive care unit is beyond the scope of this report and readers are referred to a recent comprehensive review.⁵¹³

Assessment

History

A brief history and physical examination should be conducted concurrently with the prompt initiation of therapy.

- Time of onset and cause (if known) of the present exacerbation
- Severity of asthma symptoms, including any limiting exercise or disturbing sleep
- Any symptoms of anaphylaxis
- Risk factors for asthma-related death (Box 4-1, p.103)
- All current reliever and controller medications, including doses and devices prescribed, adherence pattern, any recent dose changes, and response to current therapy.

Physical examination

The physical examination should assess:

- Signs of exacerbation severity (Box 4-4), including vital signs (e.g. level of consciousness, temperature, pulse rate, respiratory rate, blood pressure, ability to complete sentences, use of accessory muscles)
- Complicating factors (e.g. anaphylaxis, pneumonia, atelectasis, pneumothorax or pneumomediastinum)
- Signs of alternative conditions that could explain acute breathlessness (e.g. cardiac failure, inducible laryngeal obstruction, inhaled foreign body or pulmonary embolism).

Objective assessments

Objective assessments are also needed as the physical examination alone may not indicate the severity of the exacerbation.^{514,515} However, patients, and not their laboratory values, should be the focus of treatment.

- *Measurement of lung function:* this is strongly recommended. If possible, and without unduly delaying treatment, PEF or FEV₁ should be recorded before treatment is initiated, although spirometry may not be possible in children with acute asthma. Lung function should be monitored at one hour and at intervals until a clear response to treatment has occurred or a plateau is reached.
- *Oxygen saturation:* this should be closely monitored, preferably by pulse oximetry. This is especially useful in children if they are unable to perform PEF. In children, oxygen saturation is normally >95%, and saturation <92% is a predictor of the need for hospitalization⁵¹⁶ (Evidence C). Saturation levels <90% in children or adults signal the

- need for aggressive therapy. Subject to clinical urgency, saturation should be assessed before oxygen is commenced, or 5 minutes after oxygen is removed or when saturation stabilizes.
- *Arterial blood gas measurements are not routinely required:*⁵¹⁷ They should be considered for patients with PEF or FEV₁ <50% predicted,⁵¹⁸ or for those who do not respond to initial treatment or are deteriorating. Supplemental controlled oxygen should be continued while blood gases are obtained. During an asthma exacerbation PaCO₂ is often below normal (<40 mmHg). Fatigue and somnolence suggest that pCO₂ may be increasing and airway intervention may be needed. PaO₂<60 mmHg (8 kPa) and normal or increased PaCO₂ (especially >45 mmHg, 6 kPa) indicate respiratory failure.
 - *Chest X-ray (CXR) is not routinely recommended:* In adults, CXR should be considered if a complicating or alternative cardiopulmonary process is suspected (especially in older patients), or for patients who are not responding to treatment where a pneumothorax may be difficult to diagnose clinically.⁵¹⁹ Similarly, in children, routine CXR is not recommended unless there are physical signs suggestive of pneumothorax, parenchymal disease or an inhaled foreign body. Features associated with positive CXR findings in children include fever, no family history of asthma, and localized lung examination findings.⁵²⁰

Treatment in acute care settings such as the emergency department

The following treatments are usually administered concurrently to achieve rapid improvement.⁵²¹

Oxygen

To achieve arterial oxygen saturation of 93–95% (94–98% for children 6–11 years), oxygen should be administered by nasal cannulae or mask. In severe exacerbations, controlled low flow oxygen therapy using pulse oximetry to maintain saturation at 93–95% is associated with better physiological outcomes than with high flow 100% oxygen therapy^{507–509} (Evidence B). However, oxygen therapy should not be withheld if pulse oximetry is not available (Evidence D). Once the patient has stabilized, consider weaning them off oxygen using oximetry to guide the need for ongoing oxygen therapy.

Inhaled short-acting beta₂-agonists

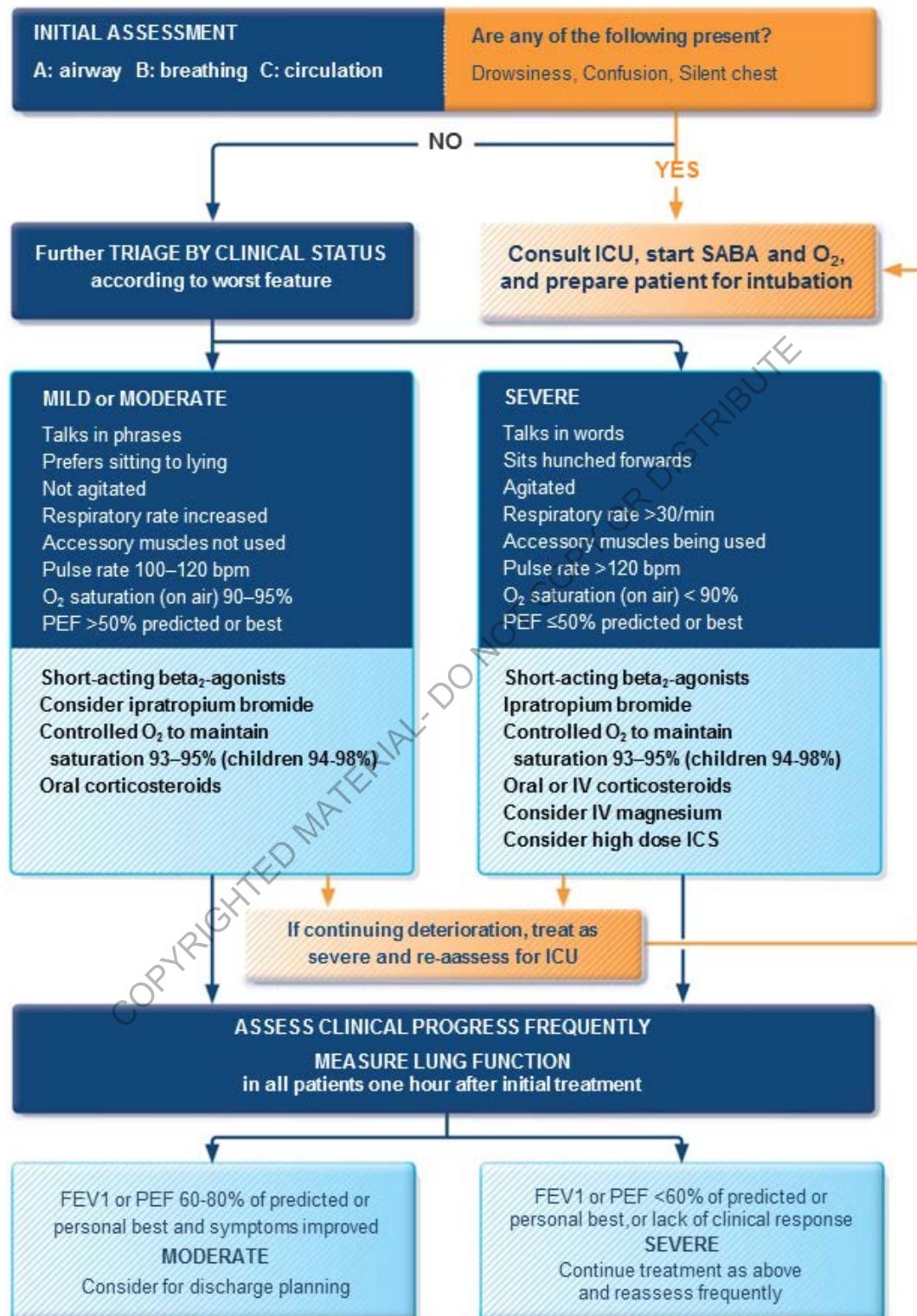
Inhaled SABA therapy should be administered frequently for patients presenting with acute asthma. The most cost-effective and efficient delivery is by pMDI with a spacer^{504,506} (Evidence A). Evidence is less robust in severe and near-fatal asthma. Systematic reviews of intermittent versus continuous nebulized SABA in acute asthma provide conflicting results. One found no significant differences in lung function or hospital admissions⁵²² but a later review with additional studies found reduced hospitalizations and better lung function with continuous compared with intermittent nebulization, particularly in patients with worse lung function.⁵²³ An earlier study in hospitalized patients found that intermittent on-demand therapy led to a significantly shorter hospital stay, fewer nebulizations and fewer palpitations when compared with 4-hourly intermittent therapy.⁵²⁴ A reasonable approach to inhaled SABA in exacerbations, therefore, would be to initially use continuous therapy, followed by intermittent on-demand therapy for hospitalized patients.

There is no evidence to support the routine use of intravenous beta₂-agonists in patients with severe asthma exacerbations⁵²⁵ (Evidence A).

Epinephrine (for anaphylaxis)

Intramuscular epinephrine (adrenaline) is indicated in addition to standard therapy for acute asthma associated with anaphylaxis and angioedema. It is not routinely indicated for other asthma exacerbations.

Box 4-4. Management of asthma exacerbations in acute care facility, e.g. emergency department



ICS: inhaled corticosteroids; ICU: intensive care unit; IV: intravenous; O₂: oxygen; PEF: peak expiratory flow; FEV₁: forced expiratory volume in 1 sec

Systemic corticosteroids

Systemic corticosteroids speed resolution of exacerbations and prevent relapse, and should be utilized in all but the mildest exacerbations in adults, adolescents and children 6–11 years.⁵²⁶⁻⁵²⁸ (Evidence A). Where possible, systemic corticosteroids should be administered to the patient within 1 hour of presentation.^{527,528} Use of systemic corticosteroids is particularly important in the emergency department if:

- Initial SABA treatment fails to achieve lasting improvement in symptoms
- The exacerbation developed while the patient was taking OCS
- The patient has a history of previous exacerbations requiring OCS

Route of delivery: oral administration is as effective as intravenous. The oral route is preferred because it is quicker, less invasive and less expensive.^{529,530} For children, a liquid formulation is preferred to tablets. OCS require at least 4 hours to produce a clinical improvement. Intravenous corticosteroids can be administered when patients are too dyspneic to swallow; if the patient is vomiting; or when patients require non-invasive ventilation or intubation. In patients discharged from the emergency department, an intramuscular corticosteroid may be an alternative to a course of OCS for preventing relapse,⁵³¹ especially if there are concerns about adherence with oral therapy.⁵³² However, there is insufficient evidence to recommend intramuscular over oral corticosteroids.⁵³³

Dosage: daily doses of OCS equivalent to 50 mg prednisolone as a single morning dose, or 200 mg hydrocortisone in divided doses, are adequate for most patients (Evidence B). For children, an OCS dose of 1–2 mg/kg up to a maximum of 40 mg/day is adequate.⁵³⁴

Duration: 5- and 7-day courses in adults have been found to be as effective as 10- and 14-day courses respectively,^{510,511} and a 3–5-day course in children is usually considered sufficient (Evidence B). Oral dexamethasone for 1-2 days⁵³⁵ can also be used but there are concerns about metabolic side-effects if it is continued beyond 2 days.^{536,537} Evidence from studies in which all patients were taking maintenance ICS after discharge suggests that there is no benefit in tapering the dose of OCS, either in the short term⁵³⁸ or over several weeks⁵³⁹ (Evidence B).

Inhaled corticosteroids

Within the emergency department: high-dose ICS given within the first hour after presentation reduces the need for hospitalization in patients not receiving systemic corticosteroids⁵²⁸ (Evidence A). When given in addition to systemic corticosteroids, evidence is conflicting⁵²⁸ (Evidence B). Overall, ICS are well tolerated; however, cost is a significant factor, and the agent, dose and duration of treatment with ICS in the management of asthma in the emergency department remain unclear.

On discharge home: patients should be prescribed regular ongoing ICS-containing treatment since the occurrence of a severe exacerbation is a risk factor for future exacerbations (Evidence B) (Box 2-2, p.31), and ICS-containing medications significantly reduce the risk of asthma-related death or hospitalization¹⁷⁰ (Evidence A). SABA-only treatment of asthma is no longer recommended. For short-term outcomes such as relapse requiring admission, symptoms, and quality of life, a systematic review found no significant differences when ICS were added to systemic corticosteroids after discharge.⁵⁴⁰ There was some evidence, however, that post-discharge ICS were as effective as systemic corticosteroids for milder exacerbations, but the confidence limits were wide.⁵⁴⁰ (Evidence B). Cost may be a significant factor for patients in the use of high-dose ICS, and further studies are required to establish their role.⁵⁴⁰

Other treatments

Ipratropium bromide

For adults and children with moderate-severe exacerbations, treatment in the emergency department with both SABA and ipratropium, a short-acting anticholinergic, was associated with fewer hospitalizations and greater improvement in PEF and FEV₁ compared with SABA alone.⁵⁴¹⁻⁵⁴³ For children hospitalized for acute asthma, no benefits were seen from adding ipratropium to SABA, including no reduction in length of stay.⁵⁴⁴

Aminophylline and theophylline

Intravenous aminophylline and theophylline should not be used in the management of asthma exacerbations, in view of their poor efficacy and safety profile, and the greater effectiveness and relative safety of SABA.⁵⁴⁵ The use of intravenous aminophylline is associated with severe and potentially fatal side-effects, particularly in patients already treated with sustained-release theophylline. In adults with severe asthma exacerbations, add-on treatment with aminophylline does not improve outcomes compared with SABA alone.⁵⁴⁵

Magnesium

Intravenous magnesium sulfate is not recommended for routine use in asthma exacerbations; however, when administered as a single 2 g infusion over 20 minutes, it reduces hospital admissions in some patients, including adults with FEV₁ <25–30% predicted at presentation; adults and children who fail to respond to initial treatment and have persistent hypoxemia; and children whose FEV₁ fails to reach 60% predicted after 1 hour of care⁵⁴⁶⁻⁵⁴⁸ (Evidence A). Randomized, controlled trials that excluded patients with more severe asthma showed no benefit with the addition of intravenous or nebulized magnesium compared with placebo in the routine care of asthma exacerbations in adults and adolescents⁵⁴⁹⁻⁵⁵¹ or children.^{550,552} (Evidence B).

Helium oxygen therapy

A systematic review of studies comparing helium-oxygen with air–oxygen suggests there is no role for this intervention in routine care (Evidence B), but it may be considered for patients who do not respond to standard therapy; however, availability, cost and technical issues should be considered.⁵⁵³

Leukotriene receptor antagonists

There is limited evidence to support a role for oral or intravenous LTRAs in acute asthma. Small studies have demonstrated improvement in lung function^{554,555} but the clinical role of these agents requires more study.

ICS-LABA combinations

The role of these medications in the emergency department or hospital is unclear. One study showed that high-dose budesonide-formoterol in patients in the emergency department, all of whom received prednisolone, had similar efficacy and safety profile to SABA,⁵⁵⁶ but more studies are needed. Another study examined addition of salmeterol to OCS for hospitalized patients, but was not adequately powered to support a recommendation.⁵⁵⁷

Antibiotics (not recommended)

Evidence does not support a role of antibiotics in asthma exacerbations unless there is strong evidence of lung infection (e.g. fever or purulent sputum or radiographic evidence of pneumonia).⁵¹² Aggressive treatment with corticosteroids should be implemented before antibiotics are considered.

Sedatives

Sedation should be strictly avoided during exacerbations of asthma because of the respiratory depressant effect of anxiolytic and hypnotic drugs. An association between the use of these drugs and avoidable asthma deaths has been reported.^{558,559}

Non-invasive ventilation (NIV)

The evidence regarding the role of NIV in asthma is weak. A systematic review identified five studies involving 206 participants with acute severe asthma treated with NIV or placebo.⁵⁶⁰ Two studies found no difference in need for endotracheal intubation but one study identified fewer admissions in the NIV group. No deaths were reported in either study. Given the small size of the studies, no recommendation is offered. If NIV is tried, the patient should be monitored closely (Evidence D). It should not be attempted in agitated patients, and patients should not be sedated in order to receive NIV (Evidence D).

Reviewing response

Clinical status and oxygen saturation should be re-assessed frequently, with further treatment titrated according to the patient's response (Box 4-4, p.113). Lung function should be measured after one hour, i.e. after the first three bronchodilator treatments, and patients who deteriorate despite intensive bronchodilator and corticosteroid treatment should be re-evaluated for transfer to the intensive care unit.

Criteria for hospitalization versus discharge from the emergency department

From retrospective analyses, clinical status (including the ability to lie flat) and lung function 1 hour after commencement of treatment are more reliable predictors of the need for hospitalization than the patient's status on arrival.^{561,562}

Consensus recommendations in another study were:⁵⁶³

- If pre-treatment FEV₁ or PEF is <25% predicted or personal best, or post-treatment FEV₁ or PEF is <40% predicted or personal best, hospitalization is recommended.
- If post-treatment lung function is 40–60% predicted, discharge may be possible after considering the patient's risk factors (Box 4-1, p.103) and availability of follow-up care.
- If post-treatment lung function is >60% predicted or personal best, discharge is recommended after considering risk factors and availability of follow-up care.

Other factors associated with increased likelihood of need for admission include:⁵⁶⁴⁻⁵⁶⁶

- Female sex, older age and non-white race
- Use of more than eight beta₂-agonist puffs in the previous 24 hours
- Severity of the exacerbation (e.g. need for resuscitation or rapid medical intervention on arrival, respiratory rate >22 breaths/minute, oxygen saturation <95%, final PEF <50% predicted)
- Past history of severe exacerbations (e.g. intubations, asthma admissions)
- Previous unscheduled office and emergency department visits requiring use of OCS

Overall, these risk factors should be considered by clinicians when making decisions on admission/discharge for patients with asthma managed in the acute care setting. The patient's social circumstances should also be considered.

Discharge planning

Prior to discharge from the emergency department or hospital to home, arrangements should be made for a follow-up appointment within one week, and strategies to improve asthma management including medications, inhaler skills and written asthma action plan, should be addressed (Box 4-5).²⁴⁸

Follow up after emergency department presentation or hospitalization for asthma

Following discharge, the patient should be reviewed by their health care provider regularly over subsequent weeks until good symptom control is achieved and personal best lung function is reached or surpassed. Incentives such as free transport and telephone reminders improve primary care follow up but have shown no effect on long-term outcomes.²⁴⁸

Patients discharged following an emergency department presentation or hospitalization for asthma should be especially targeted for an asthma education program, if one is available. Patients who were hospitalized may be particularly receptive to information and advice about their illness. Health care providers should take the opportunity to review:

- The patient's understanding of the cause of their asthma exacerbation
- Modifiable risk factors for exacerbations (including, where relevant, smoking) (Box 3-8, p.57)
- The patient's understanding of the purposes and correct uses of medications
- The actions the patient needs to take to respond to worsening symptoms or peak flows.

After emergency department presentation, comprehensive intervention programs that include optimal controller management, inhaler technique, and elements of self-management education (self-monitoring, written action plan and regular review¹⁴⁰) are cost effective and have shown significant improvement in asthma outcomes²⁴⁸ (Evidence B).

Referral for expert advice should be considered for patients who have been hospitalized for asthma, or who repeatedly present to an acute care setting despite having a primary care provider. No recent studies are available, but earlier studies suggest that follow-up by a specialist is associated with fewer subsequent emergency department visits or hospitalizations and better asthma control.²⁴⁸

Box 4-5. Discharge management after hospital or emergency department care for asthma

Medications

Inhaled corticosteroids (ICS)

Initiate ICS prior to discharge, if not previously prescribed (Box 3-4, p.45). Patients currently prescribed ICS-containing medication should generally have their treatment stepped up for 2–4 weeks (Box 4-2, p.107) and should be reminded about the importance of adherence with daily use.

Oral corticosteroids (OCS)

Prescribe at least a 5–7 day course of OCS for adults (prednisolone or equivalent 40–50 mg/day) and 3–5 days for children (1–2 mg/kg/day to a maximum of 40 mg/day). Review progress before ceasing OCS. If the OCS is dexamethasone, treatment is only for total 1–2 days. For patients considered at risk of poor adherence, intramuscular corticosteroids may be considered⁵³³ (Evidence B).

Reliever medication

Transfer patients back to as-needed rather than regular reliever medication use, based on symptomatic and objective improvement. If ipratropium bromide was used in the emergency department or hospital, it may be quickly discontinued, as it is unlikely to provide ongoing benefit.

Risk factors that contributed to the exacerbation

Identify factors that may have contributed to the exacerbation and implement strategies to reduce modifiable risk factors (Box 3-8, p.57). An exacerbation severe enough to require hospitalization may follow irritant or allergen exposure, inadequate long-term treatment, problems with adherence, and/or lack of a written asthma action plan, as well as unavoidable factors such as viral respiratory infections.

Self-management skills and written asthma action plan

- Review inhaler technique (Box 3-12, p.70).
- Review technique with PEF meter if used.
- Provide a written asthma action plan (Box 4-2, p.107) or review the patient's existing plan, either at discharge or as soon as possible afterwards. Patients discharged from the emergency department with an action plan and PEF meter have better outcomes than patients discharged without these resources.⁵⁶⁷
- Evaluate the patient's response to the exacerbation. If it was inadequate, review the action plan and provide written guidance to assist if asthma worsens again.^{567,568}
- Review the patient's use of controller treatment before and during the exacerbation. Was it increased promptly and by how much? Were OCS added and if not, why not? Consider providing a short-course of OCS to be on hand for subsequent exacerbations.

Follow up appointment

A follow-up appointment within 2 days of discharge should be made with the patient's usual health care provider, to ensure that treatment is continued, that asthma symptoms are well controlled, and that the patient's lung function reaches their personal best (if known).

ICS: inhaled corticosteroids; OCS: oral corticosteroids; PEF: peak expiratory flow

COPYRIGHTED MATERIAL-DO NOT COPY OR DISTRIBUTE

Chapter 5.

**Diagnosis and initial treatment
of
asthma, COPD
and asthma-COPD
overlap (ACO)**

A joint project of GINA and GOLD

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE

KEY POINTS

- Distinguishing asthma from COPD can be problematic, particularly in smokers and older adults. Some patients may have clinical features of both asthma and COPD
- The descriptive term asthma-COPD overlap (ACO) may be useful to maintain awareness by clinicians, researchers and regulators of the needs of these patients, since most guidelines and clinical trials are about asthma alone or COPD alone.
- However, the term asthma-COPD overlap does *not* describe a single disease entity. Instead, as for asthma and COPD, it includes patients with several different forms of airways disease (phenotypes) caused by a range of different underlying mechanisms.
- Thus, in order to avoid the impression that this is a single disease, the term Asthma COPD Overlap Syndrome (ACOS), used in previous versions of this document, is no longer advised.
- Outside specialist centers, a stepwise approach to diagnosis is advised, with recognition of the presence of chronic airways disease, syndromic categorization as characteristic asthma, characteristic COPD, or ACO, confirmation of chronic airflow limitation by spirometry and, if necessary, referral for specialized investigations.
- Although initial recognition and treatment of ACO may be made in primary care, referral for confirmatory investigations is encouraged, as outcomes for ACO are often worse than for asthma or COPD alone.
- The evidence base for treating ACO is very limited, due to a lack of pharmacotherapy studies in this population.
- Recommendations for initial treatment, for clinical efficacy and safety, are:
 - For patients with features of asthma: prescribe adequate controller therapy including inhaled corticosteroids (ICS), but not long-acting bronchodilators alone as monotherapy;
 - For patients with COPD: prescribe appropriate symptomatic treatment with bronchodilators or combination ICS-bronchodilator therapy, but not ICS alone as monotherapy;
 - For ACO, treat with ICS in a low or moderate dose (depending on level of symptoms); add-on treatment with LABA and/or LAMA is usually also necessary. If there are features of asthma, avoid LABA monotherapy;
 - All patients with chronic airflow limitation should receive appropriate treatment for other clinical problems, including advice about smoking cessation, physical activity, and treatment of comorbidities.
- This consensus-based description of asthma-COPD overlap is intended to provide interim advice to clinicians, while stimulating further study of the characteristics, underlying mechanisms and treatments for this common clinical problem.

OBJECTIVE

The main aims of this consensus-based document are to assist clinicians, especially those in primary care or non-pulmonary specialties, to:

- *Identify* patients who have a disease of chronic airflow limitation
- *Distinguish* typical asthma from typical COPD and from asthma-COPD overlap (ACO)
- *Decide* on initial treatment and/or need for referral

It also aims to stimulate research into ACO, by promoting:

- Study of characteristics and outcomes in broad populations of patients with chronic airflow limitation, rather than only in populations with diagnoses of asthma or COPD, and
- Research into underlying mechanisms contributing to ACO, that might allow development of specific interventions for prevention and management of various types of chronic airways disease.

BACKGROUND TO DIAGNOSING ASTHMA, COPD AND ASTHMA-COPD OVERLAP

In children and young adults, the differential diagnosis in patients with respiratory symptoms is different from that in older adults. Once infectious disease and non-pulmonary conditions (e.g. congenital heart disease, inducible laryngeal obstruction) have been excluded, the most likely chronic airway disease in children is asthma. This is often accompanied by allergic rhinitis. In some children with asthma,¹¹⁷ and in many adults with a history of asthma,^{569,570} persistent airflow limitation may be found. In adults (usually after the age of 40 years) COPD becomes more common, and distinguishing asthma with chronic airflow limitation from COPD becomes problematic, particularly amongst smokers.⁵⁷¹⁻⁵⁷⁴

A significant proportion of patients who present with chronic respiratory symptoms, particularly older patients, have diagnoses and/or features of both asthma and COPD, and are found to have persistent airflow limitation (i.e. that is not completely reversible after bronchodilatation).⁵⁷⁵⁻⁵⁷⁹ Several diagnostic terms, most including the word 'overlap', have been applied to such patients, and the topic has been extensively reviewed.^{47,574,576,580,581} However, there is no generally agreed term or defining features for this category of chronic airflow limitation, although a definition based upon consensus has been published for overlap in patients with existing COPD.⁵⁸²

In spite of these uncertainties, there is broad agreement that patients with features of both asthma and COPD experience frequent exacerbations,^{47,576} have poor quality of life,^{47,583} a more rapid decline in lung function and high mortality,⁵⁷⁶ and consume a disproportionate amount of healthcare resources^{47,584} than asthma or COPD alone. In these reports, the proportion of patients with features of both asthma and COPD is unclear and will have been influenced by the initial inclusion criteria used for the studies from which the data were drawn.

In epidemiological studies, reported prevalence rates for ACO have ranged between 9% and 55%, with variation by gender and age;^{578,583,585,586} the wide range reflects the different criteria that have been used by different investigators for diagnosing asthma and COPD. Concurrent doctor-diagnosed asthma and COPD has been reported in between 15 and 20% of patients.^{577,580,587,588}

This document provides an approach to identifying patients with asthma or COPD, and for distinguishing these from those with overlapping features of asthma and COPD, for which the descriptive term asthma-COPD overlap (ACO) is suggested. The term Asthma COPD Overlap Syndrome (ACOS)^{576,580} is no longer advised, as this was often interpreted as implying a single disease.

DEFINITIONS

Just as asthma and COPD are heterogeneous diseases, each with a range of underlying mechanisms, ACO also does not represent a single disease or a single phenotype. However, few studies have included broad populations, so the mechanisms underlying ACO are largely unknown, and a formal definition of ACO cannot be provided. Instead, this document presents features that identify and characterize typical asthma, typical COPD and asthma-COPD overlap, ascribing equal weight to features of asthma and of COPD. It is acknowledged that within this description of ACO will lie a number of phenotypes that may in due course be identified by more detailed characterization on the basis of clinical, pathophysiological and genetic identifiers.⁵⁸⁹⁻⁵⁹¹ For example, long-term studies suggest that about half of patients with persistent airflow limitation in adult life reached this position by rapid decline from normal lung function in early adulthood, whereas the other half had a normal rate of decline from low initial lung function in early adulthood.⁵⁷⁰ Some patients with COPD have increased sputum and/or blood eosinophils, which were previously regarded as characteristic of asthma, and this may be associated with risk of exacerbations and response to corticosteroids.⁵⁹²⁻⁵⁹⁴

The primary objective of the present approach, based on *current* evidence, is to provide practical interim advice for clinicians, particularly those in primary care and non-pulmonary specialties, about diagnosis, safe initial treatment, and referral where necessary.

A summary of the key characteristics of typical asthma, typical COPD and asthma-COPD overlap is presented in Box 5-2a, showing the similarities and differences in history and investigations.

Box 5-1. Current definitions of asthma and COPD, and clinical description of asthma-COPD overlap

Asthma
Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. [GINA 2018] ⁵⁹⁵
COPD
Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. [GOLD 2018] ⁵⁹⁶
Asthma-COPD overlap (ACO) – not a definition, but a description for clinical use
Asthma-COPD overlap (ACO) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. Asthma-COPD overlap is therefore identified in clinical practice by the features that it shares with both asthma and COPD. This is not a definition, but a description for clinical use, as asthma-COPD overlap includes several different clinical phenotypes and there are likely to be several different underlying mechanisms.

STEPWISE APPROACH TO DIAGNOSIS OF PATIENTS WITH RESPIRATORY SYMPTOMS**STEP 1: Does the patient have chronic airways disease?**

A first step in diagnosing these conditions is to identify patients at risk of, or with significant likelihood of having chronic airways disease, and to exclude other potential causes of respiratory symptoms. This is based on a detailed medical history, physical examination, and other investigations.^{50,573,597,598}

Clinical History

Features that prompt consideration of chronic airways disease include:

- History of chronic or recurrent cough, sputum production, dyspnea, or wheezing; or repeated acute lower respiratory tract infections
- Report of a previous doctor diagnosis of asthma or COPD
- History of prior treatment with inhaled medications
- History of smoking tobacco and/or other substances
- Exposure to environmental hazards, e.g. occupational or domestic exposures to airborne pollutants

Physical examination

- May be normal
- Evidence of hyperinflation and other features of chronic lung disease or respiratory insufficiency
- Abnormal auscultation (wheeze and/or crackles)

Radiology

- May be normal, particularly in early stages
- Abnormalities on chest X-ray or CT scan (performed for other reasons such as screening for lung cancer), including hyperinflation, airway wall thickening, air trapping, hyperlucency, bullae or other features of emphysema.
- May identify an alternative diagnosis, including bronchiectasis, evidence of lung infections such as tuberculosis, interstitial lung diseases or cardiac failure.

Screening questionnaires

Many screening questionnaires have been proposed to help the clinician identifying subjects at risk of chronic airways disease, based on the above risk factors and clinical features.⁵⁹⁹⁻⁶⁰¹ These questionnaires are usually context-specific, so they are not necessarily relevant to all countries (where risk factors and comorbid diseases differ), to all practice settings and uses (population screening *versus* primary or secondary care), or to all groups of patients (case-finding *versus* self-presenting with respiratory symptoms *versus* referred consultation). Examples of these questionnaires are provided on both the GINA and GOLD websites.

STEP 2. The syndromic diagnosis of asthma, COPD and asthma-COPD overlap in an adult patient

Given the extent of overlap between features of asthma and COPD (Box 5-2a), the approach proposed focuses on the features that are *most helpful* in identifying and distinguishing typical asthma and typical COPD (Box 5-2b).

a. Assemble the features that favor a diagnosis of asthma or of COPD

From a careful history that considers age, symptoms (in particular onset and progression, variability, seasonality or periodicity and persistence), past history, social and occupational risk factors including smoking history, previous diagnoses and treatment and response to treatment, together with lung function, the features favoring the diagnostic profile of asthma or of COPD can be assembled. The check boxes in Box 5-2b can be used to identify the features that are most consistent with asthma and/or COPD. Note that not all of the features of asthma and COPD are listed, but only those that *most easily distinguish between asthma and COPD in clinical practice*.

b. Compare the number of features in favor of a diagnosis of asthma or a diagnosis of COPD

From Box 5-2b, count the number of checked boxes in each column. Having several (three or more) of the features listed for either asthma or for COPD, in the absence of those for the alternative diagnosis, provides a strong likelihood of a diagnosis of typical asthma or of typical COPD.⁶⁰¹

However, the absence of any of these typical features has less predictive value, and does not rule out the diagnosis of either disease. For example, a history of allergies increases the probability that respiratory symptoms are due to asthma, but is not essential for the diagnosis of asthma since non-allergic asthma is a well-recognized asthma phenotype; and atopy is common in the general population including in patients who develop COPD in later years. When a patient has similar numbers of features of both asthma and COPD, the diagnosis of ACO should be considered.

c. Consider the level of certainty around the diagnosis of asthma or COPD, or whether there are features of both suggesting asthma-COPD overlap

In clinical practice, when a condition has no pathognomonic features, clinicians recognize that diagnoses are made on the weight of evidence, provided there are no features that clearly make the diagnosis untenable. Clinicians are able to provide an estimate of their level of certainty and factor it into their decision to treat. Doing so consciously may assist in the selection of treatment and, where there is significant doubt, it may direct therapy towards the safest option - namely, treatment for the condition that should not be missed and left untreated. The higher the level of certainty about the diagnosis of asthma or COPD, the more attention needs to be paid to the safety and efficacy of the initial treatment choices (see Step 4, p.120).

Box 5-2a. Usual features of asthma, COPD and asthma-COPD overlap

Box 5-2b. Features that if present favor asthma or COPD

Feature	Asthma	COPD	Asthma-COPD overlap	More likely to be asthma if several of ...*	More likely to be COPD if several of...*
Age of onset	Usually childhood onset but can commence at any age.	Usually > 40 years of age	Usually age ≥40 years, but may have had symptoms in childhood or early adulthood	<input type="checkbox"/> Onset before age 20 years	<input type="checkbox"/> Onset after age 40 years
Pattern of respiratory symptoms	Symptoms may vary over time (day to day, or over longer periods), often limiting activity. Often triggered by exercise, emotions including laughter, dust or exposure to allergens	Chronic usually continuous symptoms, particularly during exercise, with 'better' and 'worse' days	Respiratory symptoms including exertional dyspnea are persistent but variability may be prominent	<input type="checkbox"/> Variation in symptoms over minutes, hours or days <input type="checkbox"/> Symptoms worse during the night or early morning <input type="checkbox"/> Symptoms triggered by exercise, emotions including laughter, dust or exposure to allergens	<input type="checkbox"/> Persistence of symptoms despite treatment <input type="checkbox"/> Good and bad days but always daily symptoms and exertional dyspnea <input type="checkbox"/> Chronic cough and sputum preceded onset of dyspnea, unrelated to triggers
Lung function	Current and/or historical variable airflow limitation, e.g. BD reversibility, AHR	FEV ₁ may be improved by therapy, but post-BD FEV ₁ /FVC < 0.7 persists	Airflow limitation not fully reversible, but often with current or historical variability	<input type="checkbox"/> Record of variable airflow limitation (spirometry, peak flow)	<input type="checkbox"/> Record of persistent airflow limitation (post-bronchodilator FEV ₁ /FVC < 0.7)
Lung function between symptoms	May be normal between symptoms	Persistent airflow limitation	Persistent airflow limitation	<input type="checkbox"/> Lung function normal between symptoms	<input type="checkbox"/> Lung function abnormal between symptoms
Past history or family history	Many patients have allergies and a personal history of asthma in childhood, and/or family history of asthma	History of exposure to noxious particles and gases (mainly tobacco smoking and biomass fuels)	Frequently a history of doctor-diagnosed asthma (current or previous), allergies and a family history of asthma, and/or a history of noxious exposures	<input type="checkbox"/> Previous doctor diagnosis of asthma <input type="checkbox"/> Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	<input type="checkbox"/> Previous doctor diagnosis of COPD, chronic bronchitis or emphysema <input type="checkbox"/> Heavy exposure to a risk factor: tobacco smoke, biomass fuels
Time course	Often improves spontaneously or with treatment, but may result in fixed airflow limitation	Generally, slowly progressive over years despite treatment	Symptoms are partly but significantly reduced by treatment. Progression is usual and treatment needs are high	<input type="checkbox"/> No worsening of symptoms over time. Symptoms vary either seasonally, or from year to year <input type="checkbox"/> May improve spontaneously or have an immediate response to BD or to ICS over weeks	<input type="checkbox"/> Symptoms slowly worsening over time (progressive course over years) <input type="checkbox"/> Rapid-acting bronchodilator treatment provides only limited relief.
Chest X-ray	Usually normal	Severe hyperinflation & other changes of COPD	Similar to COPD	<input type="checkbox"/> Normal	<input type="checkbox"/> Severe hyperinflation
Exacerbations	Exacerbations occur, but the risk of exacerbations can be considerably reduced by treatment	Exacerbations can be reduced by treatment. If present, comorbidities contribute to impairment	Exacerbations may be more common than in COPD but are reduced by treatment. Comorbidities can contribute to impairment	<p>*Syndromic diagnosis of airways disease: how to use Box 5-2b</p> <p>Shaded columns list features that, <u>when present</u>, best identify patients with typical asthma and COPD. For a patient, count the number of check boxes in each column. If three or more boxes are checked for either asthma or COPD, the patient is likely to have that disease. If there are similar numbers of checked boxes in each column, the diagnosis of ACO should be considered. See Step 2 for more details.</p>	
Airway inflammation	Eosinophils and/or neutrophils	Neutrophils ± eosinophils in sputum, lymphocytes in airways, may have systemic inflammation	Eosinophils and/or neutrophils in sputum.		

STEP 3. Spirometry

Spirometry is essential for the assessment of patients with suspected chronic disease of the airways. It must be performed at either the initial or a subsequent visit, if possible before and after a trial of treatment. Early confirmation or exclusion of the diagnosis of chronic airflow limitation may avoid needless trials of therapy, or delays in initiating other investigations. Spirometry confirms chronic airflow limitation but is of more limited value in distinguishing between asthma with fixed airflow obstruction, COPD and ACO (Box 5-3).

Measurement of peak expiratory flow (PEF), although not an alternative to spirometry, if performed repeatedly on the same meter over a period of 1–2 weeks may help to confirm the diagnosis of asthma by demonstrating excessive variability (Box 1-2, p.19), but a normal PEF does not rule out either asthma or COPD. A high level of variability in lung function may also be found in ACO.

After the results of spirometry and other investigations are available, the provisional diagnosis from the syndrome-based assessment must be reviewed and, if necessary, revised. As shown in Box 5-3, spirometry at a single visit is not always confirmatory of a diagnosis, and results must be considered in the context of the clinical presentation, and whether treatment has been commenced. ICS and long-acting bronchodilators influence results, particularly if a long withholding period is not used prior to performing spirometry. Further tests might therefore be necessary either to confirm the diagnosis or to assess the response to initial and subsequent treatment (see Step 5).

Box 5-3. Spirometric measures in asthma, COPD and asthma-COPD overlap

Spirometric variable	Asthma	COPD	Asthma-COPD overlap
Normal FEV ₁ /FVC pre- or post BD	Compatible with diagnosis	Not compatible with diagnosis	Not compatible with diagnosis
Post-BD FEV ₁ /FVC <0.7	Indicates airflow limitation but may improve spontaneously or on treatment	Required for diagnosis by GOLD criteria	Usually present
Post-BD FEV ₁ ≥80% predicted	Compatible with diagnosis (good asthma control or interval between symptoms)	Compatible with GOLD classification of mild airflow limitation if post-BD FEV ₁ /FVC <0.7	Compatible with diagnosis of mild ACO
Post-BD FEV ₁ <80% predicted	Compatible with diagnosis. Risk factor for asthma exacerbations	An indicator of severity of airflow limitation and risk of future events (e.g. mortality and COPD exacerbations)	An indicator of severity of airflow limitation and risk of future events (e.g. mortality and exacerbations)
Post-BD increase in FEV ₁ ≥12% and 200 ml from baseline (reversible airflow limitation).	Usual at some time in course of asthma, but may not be present when well-controlled or on controllers	Common and more likely when FEV ₁ is low	Common and more likely when FEV ₁ is low
Post-BD increase in FEV ₁ >12% and 400ml from baseline (marked reversibility)	High probability of asthma	Unusual in COPD. Consider ACO	Compatible with diagnosis of ACO

ACO: asthma-COPD overlap; BD: bronchodilator; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung Disease.

STEP 4: Commence initial therapy

If the syndromic assessment favors asthma as a single diagnosis

Commence treatment as described in the GINA strategy report.⁵⁹⁵ Pharmacotherapy is based on ICS, with add-on treatment if needed, e.g. add-on long-acting beta₂-agonist (LABA) and/or long-acting muscarinic antagonist (LAMA).

If the syndromic assessment favors COPD as a single disease

Commence treatment as in the current GOLD strategy report.⁵⁹⁶ Pharmacotherapy starts with symptomatic treatment with bronchodilators (LABA and/or LAMA) or combination therapy, but not ICS alone (as monotherapy).

If the differential diagnosis is equally balanced between asthma and COPD (i.e. asthma-COPD overlap)

If the syndromic assessment from history, clinical features and lung function suggests ACO, the recommended default position is to start treatment for asthma (Box 5-4, p.120) until further investigations have been performed. This approach recognizes the pivotal role of ICS in preventing morbidity and even death in patients with uncontrolled asthma symptoms, for whom even seemingly ‘mild’ symptoms (compared to those of moderate or severe COPD) might indicate significant risk of a life-threatening attack.⁵⁸⁰ Most pharmacotherapy studies have enrolled patients with asthma alone or COPD alone, but a large case-control study in community patients with newly-diagnosed COPD found that those who also had a diagnosis of asthma had a lower risk of COPD hospitalizations and death if treated with combination ICS-LABA than with LABA alone.⁶⁰²

- Pharmacotherapy for ACO includes an ICS (in a low or moderate dose (see Box 3-6, p.48), depending on level of symptoms and risk of adverse effects, including pneumonia).
- Usually also add a LABA and/or LAMA, or continue these together with ICS if already prescribed.

However, if there are features of asthma, do not treat with a LABA without ICS (often called LABA monotherapy).

For all patients with chronic airflow limitation

Provide advice, as described in the GINA and GOLD reports, about:

- Treatment of modifiable risk factors including advice about smoking cessation
- Treatment of comorbidities
- Non-pharmacological strategies including physical activity, and, for COPD or asthma-COPD overlap, pulmonary rehabilitation and vaccinations
- Appropriate self-management strategies
- Regular follow-up

In a majority of patients, the initial management of asthma and COPD can be satisfactorily carried out at primary care level. However, both the GINA and GOLD strategy reports make provision for referral for further diagnostic procedures at relevant points in patient management (see Step 5). This may be particularly important for patients with suspected ACO, given that it is associated with worse outcomes and greater health care utilization.

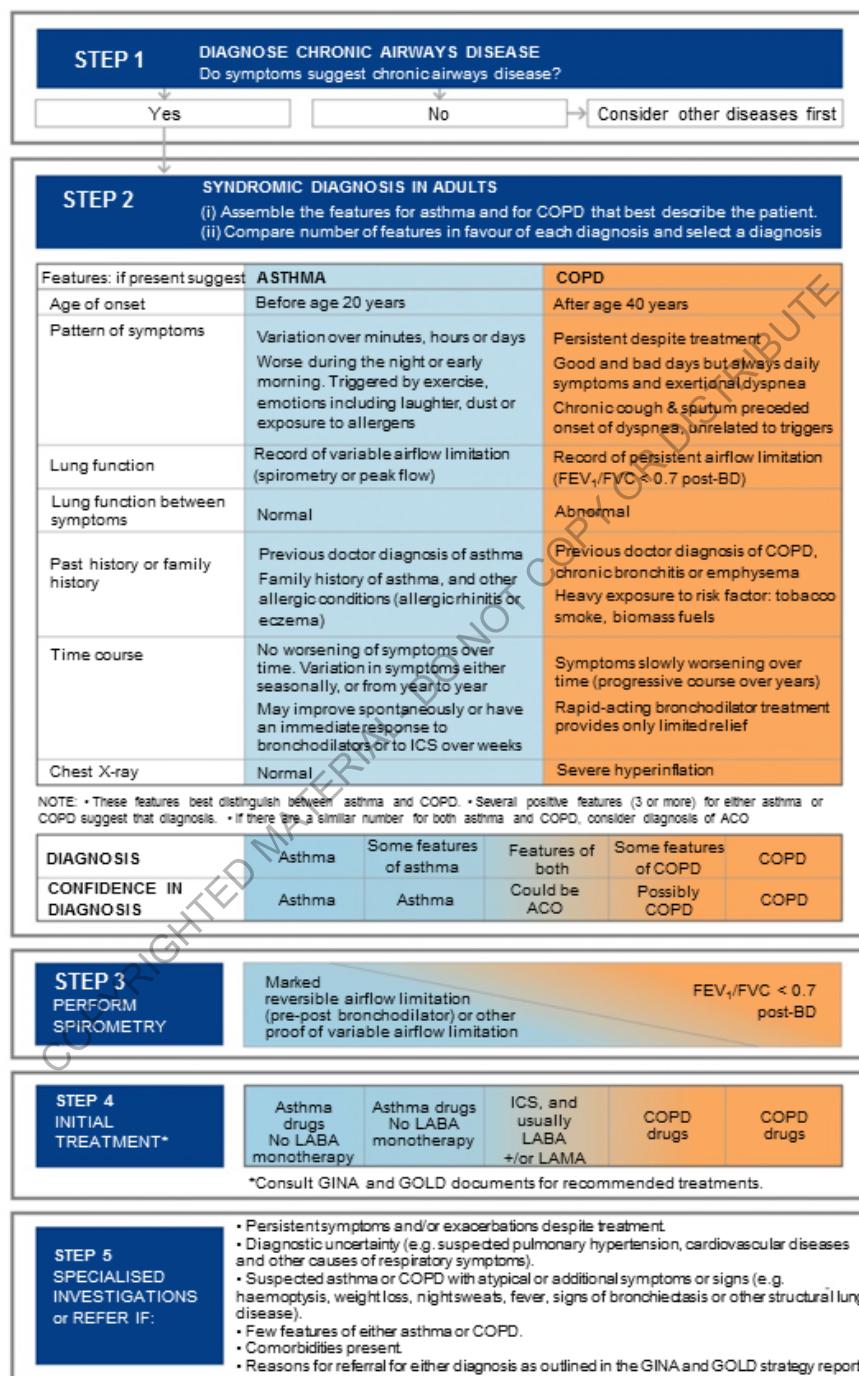
STEP 5: Referral for specialized investigations (if necessary)

Referral for expert advice and further diagnostic evaluation is necessary in the following contexts:

- Patients with persistent symptoms and/or exacerbations despite treatment.
- Diagnostic uncertainty, especially if an alternative diagnosis (e.g. bronchiectasis, post-tuberculous scarring, bronchiolitis, pulmonary fibrosis, pulmonary hypertension, cardiovascular diseases and other causes of respiratory symptoms) needs to be excluded.
- Patients with suspected asthma or COPD in whom atypical or additional symptoms or signs (e.g. haemoptysis, significant weight loss, night sweats, fever, signs of bronchiectasis or other structural lung disease) suggest an additional pulmonary diagnosis. This should prompt early referral, without necessarily waiting for a trial of treatment for asthma or COPD.
- When chronic airways disease is suspected but syndromic features of both asthma and COPD are few.

- Patients with comorbidities that may interfere with the assessment and management of their airways disease.
- Referral may also be appropriate for issues arising during on-going management of asthma, COPD or ACO, as outlined in the GINA and GOLD strategy reports.^{595,596}

Box 5-4. Summary of syndromic approach to diseases of chronic airflow limitation for clinical practice



Box 5-5 (p.128) summarizes specialized investigations that are sometimes used to distinguish asthma and COPD.

Box 5-5. Specialized investigations sometimes used in distinguishing asthma and COPD

	Asthma	COPD
Lung function tests		
DLCO	Normal (or slightly elevated).	Often reduced.
Arterial blood gases	Normal between exacerbations	May be chronically abnormal between exacerbations in more severe forms of COPD
Airway hyperresponsiveness (AHR)	Not useful on its own in distinguishing asthma from COPD, but higher levels of AHR favor asthma	
Imaging		
High resolution CT Scan	Usually normal but air trapping and increased bronchial wall thickness may be observed.	Low attenuation areas denoting either air trapping or emphysematous change can be quantitated; bronchial wall thickening and features of pulmonary hypertension may be seen.
Inflammatory biomarkers		
Test for atopy (specific IgE and/or skin prick tests)	Modestly increases probability of asthma; not essential for diagnosis	Conforms to background prevalence; does not rule out COPD
FENO	A high level (>50 ppb) in non-smokers is associated with eosinophilic airway inflammation	Usually normal. Low in current smokers.
Blood eosinophilia	Supports diagnosis of eosinophilic airway inflammation	May be present in COPD including during exacerbations
Sputum inflammatory cell analysis	Role in differential diagnosis is not established in large populations	

DLCO: diffusing capacity of the lungs for carbon monoxide; FENO: fractional concentration of exhaled nitric oxide; IgE: immunoglobulin E

FUTURE RESEARCH

Our understanding of asthma-COPD overlap is at a very preliminary stage, as most research has involved participants from existing studies which had specific inclusion and exclusion criteria (such as a physician diagnosis of asthma and/or COPD), a wide range of criteria have been used in existing studies for identifying ACO, and patients who do not have 'classical' features of asthma or of COPD, or who have features of both, have generally been excluded from randomized controlled trials of most therapeutic interventions for airways disease.^{603,604}

There is an urgent need for more research on this topic, in order to guide better recognition and appropriate treatment. This should include study of clinical and physiological characteristics, biomarkers, outcomes and underlying mechanisms, starting with broad populations of patients with respiratory symptoms or with chronic airflow limitation, rather than starting with populations with existing diagnoses of asthma or COPD. The present chapter provides interim advice, largely based on consensus, for the perspective of clinicians, particularly those in primary care and non-pulmonary specialties. Further research is needed to inform evidence-based definitions and a more detailed classification of patients who present overlapping features of asthma and COPD, and to encourage the development of specific interventions for clinical use.

Chapter 6.

**Diagnosis and
management of asthma
in children**

5 years and younger

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE

PART A. DIAGNOSIS

KEY POINTS

- Recurrent wheezing occurs in a large proportion of children 5 years and younger, typically with viral upper respiratory tract infections. Deciding when this is the initial presentation of asthma is difficult
- Previous classifications of wheezing phenotypes (episodic wheeze and multiple-trigger wheeze; or transient wheeze, persistent wheeze and late-onset wheeze) do not appear to identify stable phenotypes, and their clinical usefulness is uncertain. However, emerging research suggest that more stable phenotypes will be described and phenotype-directed therapy possible.
- A diagnosis of asthma in young children with a history of wheezing is more likely if they have:
 - Wheezing or coughing that occurs with exercise, laughing or crying, or in the absence of an apparent respiratory infection
 - A history of other allergic disease (eczema or allergic rhinitis), allergen sensitization or asthma in first-degree relatives
 - Clinical improvement during 2–3 months of controller treatment, and worsening after cessation.

ASTHMA AND WHEEZING IN YOUNG CHILDREN

Asthma is the most common chronic disease of childhood and the leading cause of childhood morbidity from chronic disease as measured by school absences, emergency department visits and hospitalizations.⁶⁰⁵ Asthma often begins in early childhood; in up to half of people with asthma, symptoms commence during childhood.⁶⁰⁶ Onset of asthma is earlier in males than females.⁶⁰⁷⁻⁶⁰⁹

No intervention has yet been shown to prevent the development of asthma or modify its long-term natural course. Atopy is present in the majority of children with asthma who are over 3 years old, and allergen-specific sensitization (and particularly multiple early-life sensitizations) is one of the most important risk factors for the development of asthma.⁶¹⁰

Viral-induced wheezing

Recurrent wheezing occurs in a large proportion of children aged 5 years or younger. It is typically associated with upper respiratory tract infections (URTI), which occur in this age group around 6–8 times per year.⁶¹¹ Some viral infections (respiratory syncytial virus and rhinovirus) are associated with recurrent wheeze throughout childhood. Wheezing in this age group is a highly heterogeneous condition, and not all wheezing indicates asthma. A large proportion of wheezing episodes in young children is virally induced whether the child has asthma or not. Therefore, deciding when wheezing with a respiratory infection is truly an isolated event or represents a recurrent clinical presentation of childhood asthma may be difficult.^{609,612}

Wheezing phenotypes

In the past, two main classifications of wheezing (called ‘wheezing phenotypes’) were proposed.

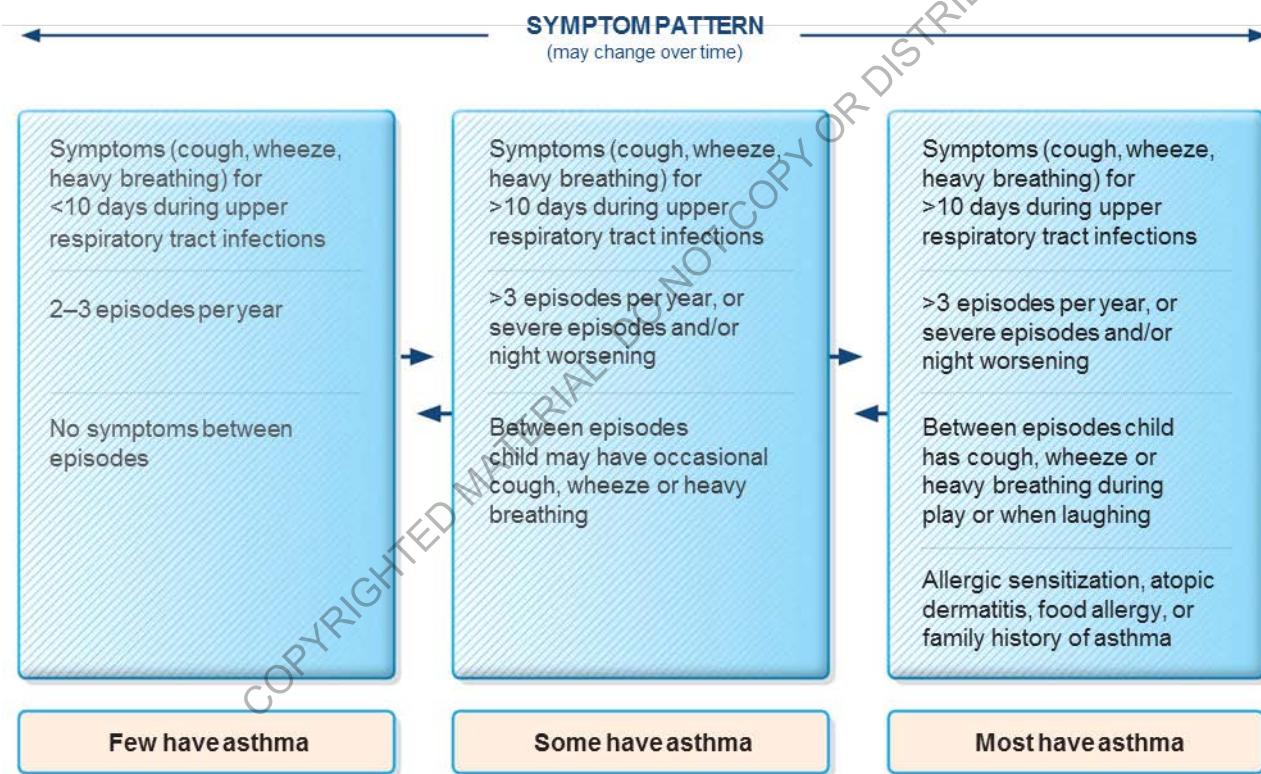
- *Symptom-based classification:*⁶¹³ this was based on whether the child had only *episodic wheeze* (wheezing during discrete time periods, often in association with URTI, with symptoms absent between episodes) or *multiple-trigger wheeze* (episodic wheezing with symptoms also occurring between these episodes, e.g. during sleep or with triggers such as activity, laughing, or crying).
- *Time trend-based classification:* this system was initially based on retrospective analysis of data from a cohort study.⁶⁰⁹ It included *transient wheeze* (symptoms began and ended before the age of 3 years); *persistent wheeze* (symptoms began before the age of 3 years and continued beyond the age of 6 years), and *late-onset wheeze* (symptoms began after the age of 3 years). These general patterns have been confirmed in subsequent studies using unsupervised statistical approaches.^{614,615}

However, prospective allocation of individual children to these phenotypes has been challenging in ‘real-life’ clinical situations, and the clinical usefulness of these, and other, classification and asthma prediction systems remain a subject of active investigation.^{616,617 615,618}

CLINICAL DIAGNOSIS OF ASTHMA

It may be challenging to make a confident diagnosis of asthma in children 5 years and younger, because episodic respiratory symptoms such as wheezing and cough are also common in children without asthma, particularly in those 0–2 years old,^{619,620} and it is not possible to routinely assess airflow limitation or bronchodilator responsiveness in this age group. A probability-based approach, based on the pattern of symptoms during and between viral respiratory infections,⁶²¹ may be helpful for discussion with parents/carers (Box 6-1 & 2). This allows individual decisions to be made about whether to give a trial of controller treatment. It is important to make decisions for each child individually, to avoid either over- or under-treatment.

Box 6-1. Probability of asthma diagnosis in children 5 years and younger



Symptoms suggestive of asthma in children 5 years and younger

As shown in Box 6-1 & 2 an asthma diagnosis in children 5 years and younger can often be based on:

- Symptom patterns (recurrent episodes of wheeze, cough, breathlessness (typically manifested by activity limitation), and nocturnal symptoms or awakenings)
- Presence of risk factors for development of asthma, such as family history of atopy, allergic sensitisation, allergy or asthma, or a personal history of food allergy or atopic dermatitis
- Therapeutic response to controller treatment.
- Exclusion of alternate diagnoses.

Box 6-1 is a schematic figure showing the estimated probability of an asthma diagnosis^{597,598} in children aged 5 years or younger who have viral-induced cough, wheeze or heavy breathing, based on the pattern of symptoms. Many young

children wheeze with viral infections and deciding when a child should be given controller treatment may be difficult. The frequency and severity of wheezing episodes and the temporal pattern of symptoms (only with viral colds or also in response to other triggers) should be taken into account. Any controller treatment should be viewed as a treatment trial, with follow up scheduled after 2–3 months to review the response. Review is also important since the pattern of symptoms tends to change over time in a large proportion of children.

A diagnosis of asthma in young children is therefore based largely on recurrent symptom patterns combined with a careful clinical assessment of family history and physical findings with careful consideration of the differential diagnostic possibilities. A positive family history of allergic disorders, or the presence of atopy or allergic sensitization provide additional predictive support, as early allergic sensitization increases the likelihood that a wheezing child will develop persistent asthma.⁶¹⁰

Box 6-2. Features suggesting a diagnosis of asthma in children 5 years and younger

Feature	Characteristics suggesting asthma
Cough	Recurrent or persistent non-productive cough that may be worse at night or accompanied by some wheezing and breathing difficulties Cough occurring with exercise, laughing, crying or exposure to tobacco smoke, particularly in the absence of an apparent respiratory infection
Wheezing	Recurrent wheezing, including during sleep or with triggers such as activity, laughing, crying or exposure to tobacco smoke or air pollution
Difficult or heavy breathing or shortness of breath	Occurring with exercise, laughing, or crying
Reduced activity	Not running, playing or laughing at the same intensity as other children; tires earlier during walks (wants to be carried)
Past or family history	Other allergic disease (atopic dermatitis or allergic rhinitis, food allergy). Asthma in first-degree relative(s)
Therapeutic trial with low dose inhaled corticosteroid (Box 6-5, p.143), and as-needed SABA	Clinical improvement during 2–3 months of controller treatment and worsening when treatment is stopped

Box 6-2A gives examples of questions that can be used to elucidate the features suggestive of an asthma diagnosis.

Box 6-2A. Questions that can be used to elicit features suggestive of asthma

- Does your child have wheezing? Wheezing is a high pitched noise which comes from the chest and not the throat. Use of a video questionnaire,⁶²² or asking a parent to record an episode on a smartphone if available can help to confirm the presence of wheeze and differentiate from upper airway abnormalities
- Does your child wake up at night because of coughing, wheezing, or 'difficult breathing', 'heavy breathing', or 'breathlessness'?
- Does your child have to stop running, or play less hard, because of coughing, wheezing or 'difficult breathing', 'heavy breathing', or 'shortness of breath'?
- Does your child cough, wheeze or get 'difficult breathing', 'heavy breathing', or 'shortness of breath' when laughing, crying, playing with animals, or when exposed to strong smells or smoke?
- Has your child ever had eczema, or been diagnosed with allergy to foods?
- Has anyone in your family had asthma, hay fever, food allergy, eczema, or any other disease with breathing problems?

Wheeze

Wheeze is the most common and specific symptom associated with asthma in children 5 years and younger. Wheezing occurs in several different patterns, but a wheeze that occurs recurrently, during sleep, or with triggers such as activity, laughing, or crying, is consistent with a diagnosis of asthma. Clinician confirmation is important, as parents may describe any noisy breathing as 'wheezing'.⁶²³ Some cultures do not have a word for wheeze.

Wheezing may be interpreted differently based on:

- Who observes it (e.g. parent/carer versus the health care provider)
- The environmental context (e.g. developed countries versus areas with a high prevalence of parasites that involve the lung)
- The cultural context (e.g. the relative importance of certain symptoms can differ between cultures, as can the diagnosis and treatment of respiratory tract diseases in general).

Cough

Cough due to asthma is generally non-productive, recurrent and/or persistent, and is usually accompanied by wheezing episodes and breathing difficulties. Allergic rhinitis may be associated with cough in the absence of asthma. A nocturnal cough (when the child is asleep) or a cough that occurs with exercise, laughing or crying, in the absence of an apparent respiratory infection, supports a diagnosis of asthma. The common cold and other respiratory illnesses are also associated with coughing. Prolonged cough in infancy, and cough without cold symptoms, are associated with later parent-reported physician-diagnosed asthma, independent of infant wheeze. Characteristics of cough in infancy may be early markers of asthma susceptibility, particularly among children with maternal asthma.⁶²⁴

Breathlessness

Parents may also use terms such as 'difficult breathing', 'heavy breathing', or 'shortness of breath'. Breathlessness that occurs during exercise and is recurrent increases the likelihood of the diagnosis of asthma. In infants and toddlers, crying and laughing are equivalent to exercise in older children.

Activity and social behavior

Physical activity is an important trigger of asthma symptoms in young children. Young children with poorly controlled asthma often abstain from strenuous play or exercise to avoid symptoms, but many parents are unaware of such changes in their children's lifestyle. Engaging in play is important for a child's normal social and physical development.

For this reason, careful review of the child's daily activities, including their willingness to walk and play, is important when assessing a potential asthma diagnosis in a young child. Parents may report irritability, tiredness and mood changes in their child as the main problems when asthma is not well controlled.

TESTS TO ASSIST IN DIAGNOSIS

While no tests specifically and definitively diagnose asthma with certainty, in children 5 years and younger, the following are useful adjuncts.

Therapeutic trial

A trial of treatment for at least 2–3 months with as-needed short-acting beta₂-agonist (SABA) and regular low dose inhaled corticosteroids (ICS) may provide some guidance about the diagnosis of asthma (Evidence D). Response should be evaluated by symptom control (daytime and night-time), and the frequency of wheezing episodes and exacerbations. Marked clinical improvement during treatment, and deterioration when treatment is stopped, support a diagnosis of asthma. Due to the variable nature of asthma in young children, a therapeutic trial may need to be repeated in order to be certain of the diagnosis.

Tests for allergic sensitization

Sensitization to allergens can be assessed using either skin prick testing or allergen-specific immunoglobulin E. Allergic sensitization is present in the majority of children with asthma once they are over 3 years of age; however, absence of sensitization to common aeroallergens does not rule out a diagnosis of asthma. Allergic sensitization is the best predictor for development of persistent asthma.⁶²⁵

Chest X-ray

Radiographs are rarely indicated; however, if there is doubt about the diagnosis of asthma in a wheezing or coughing child, a plain chest X-ray may help to exclude structural abnormalities (e.g. congenital lobar emphysema, vascular ring) chronic infections such as tuberculosis, an inhaled foreign body, or other diagnoses. Other imaging investigations may be appropriate, depending on the condition being considered.

Lung function testing

Due to the inability of most children 5 years and younger to perform reproducible expiratory maneuvers, lung function testing, bronchial provocation testing, and other physiological tests do not have a major role in the diagnosis of asthma at this age. However, by 5 years of age, many children are capable of performing reproducible spirometry if coached by an experienced technician and with visual incentives.

Exhaled nitric oxide

Measurement of fractional concentration of exhaled nitric oxide (FeNO) is not widely available for most children in this age group and currently remains primarily a research tool. FeNO can be measured in young children with tidal breathing, and normal reference values have been published for children aged 1–5 years.⁶²⁶ In pre-school children with recurrent coughing and wheezing, an elevated FeNO recorded 4 weeks from any URTI predicted physician-diagnosed asthma at school age,⁶²⁷ and increased the odds for wheezing, asthma and ICS use by school age, independent of clinical history and presence of specific IgE.⁶²⁸

Risk profiles

A number of risk profile tools to identify wheezing children aged 5 years and younger who are at high risk of developing persistent asthma symptoms have been evaluated for use in clinical practice.⁶¹⁵ The Asthma Predictive Index (API), based on the Tucson Children's Respiratory Study, is designed for use in children with four or more wheezing episodes in a year.⁶²⁹ One study showed that children with a positive API have a 4–10-fold greater chance of developing asthma

between the ages of 6–13 years than those with a negative API, and 95% of children with a negative API remained free of asthma.⁶²⁹ A modified API adding sensitization to an inhalant as a major criterion and to a food as a minor criterion and removing allergic rhinitis as a minor criterion⁶³⁰ has been validated in a separate cohort as predictive for development of persistent asthma.⁶³¹ The applicability and validation of the API in other contexts and the development of better prediction tools which can be used in a wider range of settings need more study. The API includes sensitization to aeroallergens measured by skin prick or blood tests and level of blood eosinophils; these tests may not be available in all care settings. Furthermore, use of the API in regions where eosinophilia is commonly seen due to helminth infections has not been assessed.

DIFFERENTIAL DIAGNOSIS

A definite diagnosis of asthma in this young age group is challenging but has important clinical consequences. It is particularly important in this age group to consider and exclude alternative causes that can lead to symptoms of wheeze, cough, and breathlessness before confirming an asthma diagnosis (Box 6-3).⁶¹⁹

Key indications for referral of a child 5 years or younger for further diagnostic investigations or therapeutic decisions

Any of the following features suggest an alternative diagnosis and indicate the need for further investigations:

- Failure to thrive
- Neonatal or very early onset of symptoms (especially if associated with failure to thrive)
- Vomiting associated with respiratory symptoms
- Continuous wheezing
- Failure to respond to asthma medications (inhaled ICS, oral steroids or SABA)
- No association of symptoms with typical triggers, such as viral URTI
- Focal lung or cardiovascular signs, or finger clubbing
- Hypoxemia outside context of viral illness.

Box 6-3. Common differential diagnoses of asthma in children 5 years and younger

Condition	Typical features
Recurrent viral respiratory tract infections	Mainly cough, runny congested nose for <10 days; no symptoms between infections
Gastroesophageal reflux	Cough when feeding; recurrent chest infections; vomits easily especially after large feeds; poor response to asthma medications
Foreign body aspiration	Episode of abrupt, severe cough and/or stridor during eating or play; recurrent chest infections and cough; focal lung signs
Persistent bacterial bronchitis	Persistent wet cough; poor response to asthma medications
Tracheomalacia	Noisy breathing when crying or eating, or during upper airway infections (noisy inspiration if extrathoracic or expiration if intrathoracic); harsh cough; inspiratory or expiratory retraction; symptoms often present since birth; poor response to asthma medications
Tuberculosis	Persistent noisy respirations and cough; fever unresponsive to normal antibiotics; enlarged lymph nodes; poor response to bronchodilators or inhaled corticosteroids; contact with someone who has tuberculosis
Congenital heart disease	Cardiac murmur; cyanosis when eating; failure to thrive; tachycardia; tachypnea or hepatomegaly; poor response to asthma medications
Cystic fibrosis	Cough starting shortly after birth; recurrent chest infections; failure to thrive (malabsorption); loose greasy bulky stools
Primary ciliary dyskinesia	Cough and recurrent, chest infections; neonatal respiratory distress, chronic ear infections and persistent nasal discharge from birth; poor response to asthma medications; situs inversus occurs in about 50% of children with this condition
Vascular ring	Respirations often persistently noisy; poor response to asthma medications
Bronchopulmonary dysplasia	Infant born prematurely; very low birth weight; needed prolonged mechanical ventilation or supplemental oxygen; difficulty with breathing present from birth
Immune deficiency	Recurrent fever and infections (including non-respiratory); failure to thrive

PART B. ASSESSMENT AND MANAGEMENT

KEY POINTS

- The goals of asthma management in young children are similar to those in older patients:
 - To achieve good control of symptoms and maintain normal activity levels
 - To minimize the risk of asthma flare-ups, impaired lung development and medication side-effects.
- Wheezing episodes in young children should be treated initially with inhaled short-acting beta₂-agonists, regardless of whether the diagnosis of asthma has been made.
- A trial of controller therapy should be given if the symptom pattern suggests asthma, alternative diagnoses have been excluded and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe.
- Response to treatment should be reviewed before deciding whether to continue it. If the response is absent or incomplete, reconsider alternative diagnoses.
- The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered dose inhaler and spacer, with face mask for <3 years and mouthpiece for most 3–5 year olds. Children should be switched from a face mask to mouthpiece as soon as they are able to demonstrate good technique.
- Review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children.

GOALS OF ASTHMA MANAGEMENT

As with other age groups, the goals of asthma management in young children are:

- To achieve good control of symptoms and maintain normal activity levels
- To minimize future risk; that is to reduce the risk of flare-ups, maintain lung function and lung development as close to normal as possible, and minimize medication side-effects.

Maintaining normal activity levels is particularly important in young children because engaging in play is important for their normal social and physical development. It is important to also elicit the goals of the parent/carer, as these may differ from conventional medical goals.

The goals of asthma management are achieved through a partnership between the parent/carer and the health professional team, with a cycle of:

- Assess (diagnosis, symptom control, risk factors, inhaler technique, adherence, parent preference)
- Adjust treatment (medications, non-pharmacological strategies, and treatment of modifiable risk factors)
- Review response including medication effectiveness and side-effects. This is carried out in combination with:

Education of parent/carer, and child (depending on the child's age)

- Skills training for effective use of inhaler devices and encouragement of good adherence
- Monitoring of symptoms by parent/carer
- A written personalized asthma action plan.

ASSESSMENT OF ASTHMA

What does 'asthma control' mean?

Asthma control means the extent to which the manifestations of asthma are controlled, with or without treatment.^{14,58} It has two components (Box 6-4, p.138): the child's asthma status over the previous four weeks (current symptom control), and how asthma may affect them in the future (future risk). In young children, as in older patients, both symptom control and future risk should be monitored (Evidence D). The rationale for this is described on p.33.

Assessing asthma symptom control

Defining satisfactory symptom control in children 5 years and younger depends on information derived from family members and carers, who may be unaware either of how often the child has experienced asthma symptoms, or that their respiratory symptoms represent uncontrolled asthma. Few objective measures to assess symptom control have been validated for children <4 years. The Childhood Asthma Control Test has can be used for children aged 4–11 years.⁷⁴ The Test for Respiratory and Asthma Control in Kids (TRACK) is a validated questionnaire for caregiver completion for preschool aged children with symptoms consistent with asthma; it includes both symptom control and courses of systemic corticosteroids in the previous year.⁷⁸

Box 6-4 shows a working schema for assessing asthma control in children ≤5 years, based on current expert opinion. It incorporates assessment of symptoms; the child's level of activity and their need for reliever/rescue treatment; and assessment of risk factors for adverse outcomes (Evidence D).

Box 6-4. GINA assessment of asthma control in children 5 years and younger

A. Symptom control	Level of asthma symptom control					
In the past 4 weeks, has the child had:	Well controlled	Partly controlled	Uncontrolled			
Daytime asthma symptoms for more than a few minutes, more than once a week?	Yes <input type="checkbox"/> No <input type="checkbox"/>					
Any activity limitation due to asthma? (Runs/plays less than other children, tires easily during walks/playing?)	Yes <input type="checkbox"/> No <input type="checkbox"/>	None of these	1–2 of these			
Reliever medication needed* more than once a week?	Yes <input type="checkbox"/> No <input type="checkbox"/>		3–4 of these			
Any night waking or night coughing due to asthma?	Yes <input type="checkbox"/> No <input type="checkbox"/>					
B. Future risk for poor asthma outcomes						
<i>Risk factors for asthma exacerbations within the next few months</i>						
<ul style="list-style-type: none"> • Uncontrolled asthma symptoms • One or more severe exacerbations (ED attendance, hospitalization, or course of OCS) in previous year • The start of the child's usual 'flare-up' season (especially if autumn/fall) • Exposures: tobacco smoke; indoor or outdoor air pollution; indoor allergens (e.g. house dust mite, cockroach, pets, mold), especially in combination with viral infection⁶³² • Major psychological or socio-economic problems for child or family • Poor adherence with controller medication, or incorrect inhaler technique • Outdoor pollution (NO₂ and particles)⁹⁴ 						
<i>Risk factors for fixed airflow limitation</i>						
<ul style="list-style-type: none"> • Severe asthma with several hospitalizations • History of bronchiolitis 						
<i>Risk factors for medication side-effects</i>						
<ul style="list-style-type: none"> • Systemic: Frequent courses of OCS, high-dose and/or potent ICS • Local: moderate/high-dose or potent ICS; incorrect inhaler technique; failure to protect skin or eyes when using ICS by nebulizer or spacer with face mask 						

ICS = inhaled corticosteroids; OCS = oral corticosteroids * Excludes reliever taken before exercise

Before stepping up treatment, ensure that the child's symptoms are due to asthma, and that the child has good inhaler technique and good adherence to existing treatment.

Assessing future risk of adverse outcomes

The relationship between symptom control and future risk of adverse outcomes, such as exacerbations (Box 6-4, p.138), has not been sufficiently studied in young children. Although exacerbations may occur in children after months of apparently good symptom control, the risk is greater if current symptom control is poor. Preschool children treated with daily low dose ICS experience fewer days with asthma symptoms along with reductions in the risk of exacerbations.⁶³⁰

The future risk of harm due to excessive doses of inhaled or systemic corticosteroids must also be avoided. This can be minimized by ensuring that the prescribed treatment is appropriate and reduced to the lowest dose that maintains satisfactory symptom control and minimizes exacerbations. The child's height should be measured and recorded at least yearly, as growth velocity may be lower in the first 1-2 years of ICS treatment,¹¹¹ and poorly-controlled asthma can affect growth.¹¹⁰ The minimum effective dose of ICS to maintain good asthma control should be used. If decreased growth velocity is seen, other factors should be considered, including poorly-controlled asthma, frequent use of oral corticosteroids, and poor nutrition, and referral should be considered.

If ICS is delivered through a face-mask or nebulizer, the skin on the nose and around the mouth should be cleaned shortly after inhalation in order to avoid local side-effects such as steroid rash (reddening and atrophy).

MEDICATIONS FOR SYMPTOM CONTROL AND RISK REDUCTION

Choosing medications for children 5 years and younger

Good control of asthma can be achieved in the overwhelming majority of young children with a pharmacological intervention strategy.⁶³³ This should be developed in a partnership between the family/carer and the health care provider. As with older children and adults, medications comprise only one component of asthma management in young children; other key components include education, skills training for inhaler devices and adherence, non-pharmacological strategies including environmental control where appropriate, regular monitoring, and clinical review (see later sections in this chapter).

When recommending treatment for a young child, both general and individual questions apply (Box 3-3, p.42).

- What is the 'preferred' medication option at each treatment step to control asthma symptoms and minimize future risk? These decisions are based on data for efficacy, effectiveness and safety from clinical trials, and on observational data. Recent studies suggest that consideration of factors such as allergic sensitization and/or peripheral blood count may help to better identify which children are more likely to have a short-term response to ICS.⁶³⁴ However, further studies are needed to assess the applicability of these findings in a wider range of settings, particularly in areas where blood eosinophilia may reflect helminth infection rather than asthma or atopy.
- How does this particular child differ from the 'average' child with asthma, in terms of:
 - Response to previous treatment
 - Parental preference (goals, beliefs and concerns about medications)
 - Practical issues (cost, inhaler technique and adherence)?

The following treatment recommendations for children of 5 years of age or younger are based on the available evidence and on expert opinion. Although the evidence is expanding it is still rather limited as most clinical trials in this age group have not characterized participants with respect to their symptom pattern, and different studies have used different outcomes and different definitions of exacerbations.

A stepwise treatment approach is recommended (Box 6-5, p.143), based on symptom patterns, risk of exacerbations and side-effects, and response to initial treatment. Generally, treatment includes the daily, long-term use of controller medications to keep asthma well-controlled, and reliever medications for as-needed symptom relief. The choice of inhaler device is also an important consideration (Box 6-7, p.145).

Which children should be prescribed regular controller treatment?

Intermittent or episodic wheezing of any severity may represent an isolated viral-induced wheezing episode, an episode of seasonal or allergen-induced asthma, or unrecognized uncontrolled asthma. The *initial* treatment of wheezing is identical for all of these – a SABA every 4–6 hours as needed until symptoms disappear, usually within 1 to 7 days. Further treatment of the acute wheezing episodes themselves is described below (see *Acute asthma exacerbations in children 5 years and younger*, p.146). However, uncertainty surrounds the addition of other drugs in these children, especially when the nature of the episode is unclear. In general, the following principles apply.

- *If the history and symptom pattern suggest a diagnosis of asthma* (Box 6-2, p.132; Box 6-2A, p.133) and respiratory symptoms are uncontrolled (Box 6-4, p.138) and/or wheezing episodes are frequent (e.g. three or more episodes in a season), regular controller treatment should be initiated (Step 2, Box 6-5, p.143) and the response evaluated (Evidence D). Regular controller treatment may also be indicated in a child with less frequent, but more severe episodes of viral- induced wheeze (Evidence D).
- *If the diagnosis of asthma is in doubt*, and inhaled SABA therapy or courses of antibiotics need to be repeated frequently, e.g. more than every 6–8 weeks, a trial of regular controller treatment should be considered to confirm whether the symptoms are due to asthma (Evidence D). Referral for specialist opinion should also be considered at this stage.

It is important to discuss the decision to prescribe controller treatment and the choice of treatment with the child's parents or carers. They should be aware of both the relative benefits and risks of the treatments, and the importance of maintaining normal activity levels for their child's normal physical and social development. Although effects of ICS on growth velocity are seen in pre-pubertal children in the first 1-2 years of treatment, this is not progressive or cumulative, and the one study that examined long-term outcomes showed a difference of only 0.7% in adult height.^{111,635} Poorly-controlled asthma itself adversely affects adult height.¹¹⁰ For more detail see Appendix Chapter 5B.

Treatment steps to control asthma symptoms and minimize future risk for children 5 years and younger

Asthma treatment in young children follows a stepwise approach (Box 6-5), with medication adjusted up or down to achieve good symptom control and minimize future risk of exacerbations and medication side-effects. The need for controller treatment should be re-assessed regularly. More details about asthma medications for children 0–5 years are provided in Appendix Chapter 5, Part C.

Before considering a step-up of controller treatment

If symptom control is poor and/or exacerbations persist despite 3 months of adequate controller therapy, check the following *before any step up in treatment is considered*.

- Confirm that the symptoms are due to asthma rather than a concomitant or alternative condition (Box 6-3, p.105). Refer for expert assessment if the diagnosis is in doubt.
- Check and correct inhaler technique.
- Confirm good adherence with the prescribed dose.
- Consider trial of one of the other treatment options for that step, as many children may respond to one of the options,
- Enquire about risk factors such as allergen or tobacco smoke exposure (Box 6-4, p.138).

STEP 1: As-needed inhaled short-acting beta₂-agonist (SABA)

Preferred option: as-needed inhaled short-acting beta₂-agonist (SABA)

All children who experience wheezing episodes should be provided with inhaled SABA for relief of symptoms (Evidence D), although it is not effective in all children. See Box 6-7 (p.145) for choice of inhaler device. Use of SABA for the relief of symptoms on average more than twice a week over a one month period indicates the need for a trial of controller medication.

Other options

Oral bronchodilator therapy is not recommended due to its slower onset of action and higher rate of side-effects compared with inhaled SABA (Evidence D).

For children with intermittent viral-induced wheeze and no interval symptoms, particularly those with underlying atopy (positive mAPI) in whom inhaled SABA medication is not sufficient, intermittent high dose ICS may be considered^{499,636,637} (see *Management of worsening asthma and exacerbations*, p.146), but because of the risk of side-effects, this should only be considered if the physician is confident that the treatment will be used appropriately.

STEP 2: Initial controller treatment plus as-needed SABA

Preferred option: regular daily low dose ICS plus as-needed SABA

Regular daily, low dose ICS (Box 6-6, p.144) is recommended as the preferred initial treatment to control asthma in children 5 years and younger (Evidence A).^{630,638-640} This initial treatment should be given for at least 3 months to establish its effectiveness in achieving good asthma control.

Other options

In young children with persistent asthma, regular treatment with a leukotriene receptor antagonist (LTRA) modestly reduces symptoms and need for oral corticosteroids compared with placebo.⁶⁴¹ For young children with recurrent viral-induced wheezing, a recent review concluded that neither regular nor intermittent LTRA reduces OCS-requiring exacerbations (Evidence A).⁶⁴² For pre-school children with frequent viral-induced wheezing and interval asthma symptoms, as-needed (prn)⁶⁴³ or episodic ICS⁶⁴⁴ may be considered, but a trial of regular ICS should be undertaken first. The effect on exacerbation risk seems similar for regular and high dose episodic ICS.⁶⁴⁰ If good control is not achieved with a given therapy, trials of the alternative Step 2 therapies are recommended prior to moving to Step 3.

STEP 3: Additional controller treatment, plus as-needed SABA and consider specialist referral

If 3 months of initial therapy with a low dose ICS fails to control symptoms, or if exacerbations continue to occur, check the following *before any step up in treatment is considered*.

- Confirm that the symptoms are due to asthma rather than a concomitant or alternative condition (Box 6-3, p.136).
- Check and correct inhaler technique. Consider alternative delivery systems if indicated.
- Confirm good adherence with the prescribed dose.
- Enquire about risk factors such as allergen or tobacco smoke exposure (Box 6-4, p.138).

Preferred option: moderate dose ICS (double the 'low' daily dose)

Doubling the initial low dose of ICS may be the best option (Evidence C). Assess response after 3 months.

The child should be referred for expert assessment if symptom control remains poor and/or flare-ups persist, or if side-effects of treatment are observed or suspected.

Other options

Addition of a LTRA to low dose ICS may be considered, based on data from older children (Evidence D). The relative cost of different treatment options in some countries may be relevant to controller choices for children.

STEP 4: Continue controller treatment and refer for expert assessment

Preferred option: refer the child for expert advice and further investigation (Evidence D).

If doubling the initial dose of ICS fails to achieve and maintain good asthma control, carefully reassess inhaler technique and medication adherence as these are common problems in this age group. In addition, reassess and address control of environmental factors where relevant, and reconsider the asthma diagnosis.

Other options

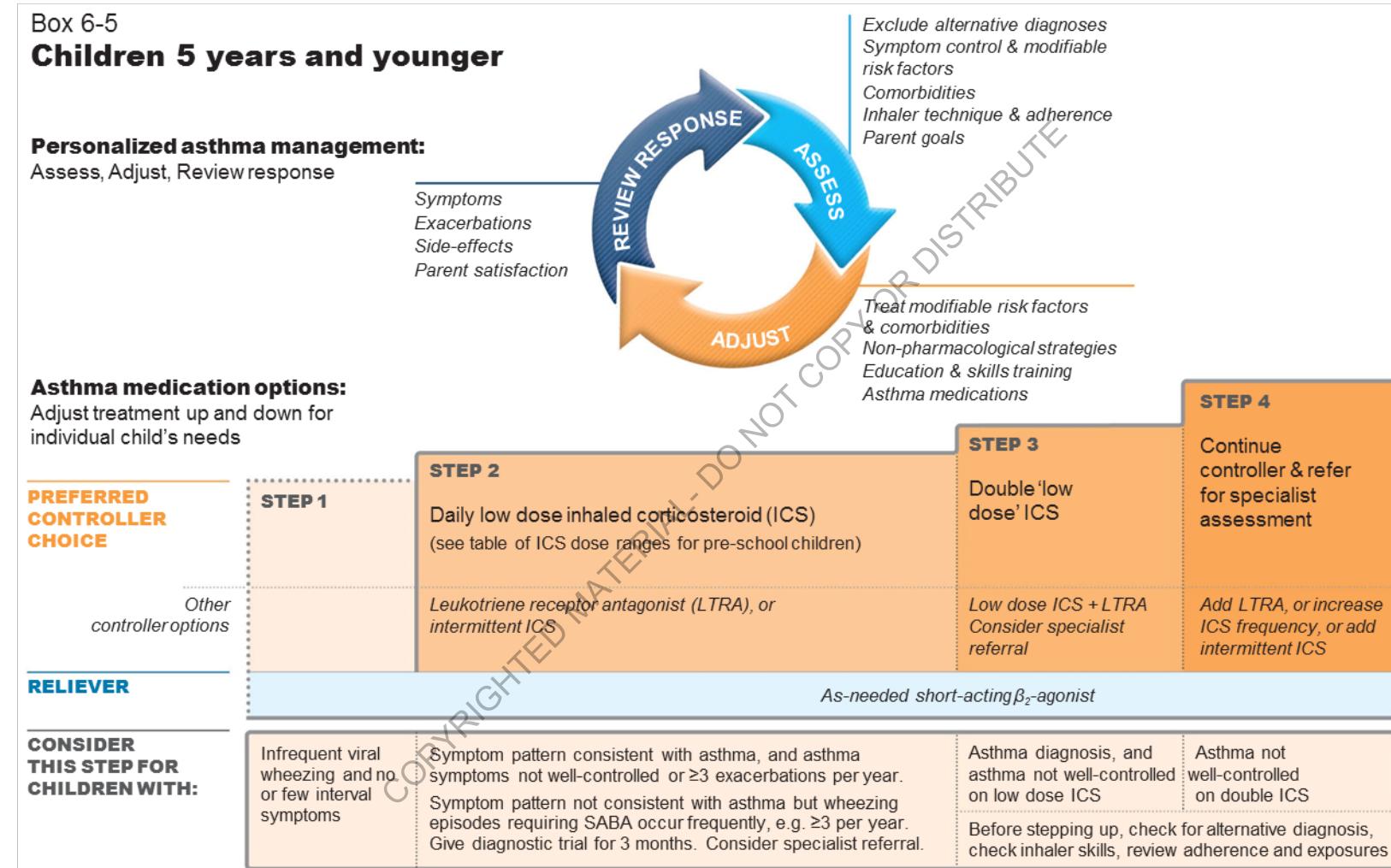
The best treatment for this population has not been established. If the diagnosis of asthma has been confirmed, options to consider, preferably with specialist advice, are:

- Further increase the dose of ICS (perhaps combined with more frequent dosing) for a few weeks until the control of the child's asthma improves (Evidence D). Monitor for side-effects.
- Add LTRA (data based on studies in older children, Evidence D)
- Add long acting beta agonist (LABA) in combination with ICS; data based on studies in children ≥ 4 years of age
- Add theophylline, or a low dose of oral corticosteroid (for a few weeks only) until asthma control improves (Evidence D).
- Add intermittent ICS to the regular daily ICS if exacerbations are the main problem (Evidence D).

The need for additional controller treatment should be re-evaluated at each visit and maintained for as short a period as possible, taking into account potential risks and benefits. Treatment goals and their feasibility should be re-considered and discussed with the child's family/carer; it may become necessary to accept a degree of persisting asthma symptoms to avoid excessive and harmful medication doses.

There are insufficient data about the efficacy and safety of inhaled combination ICS/long-acting beta₂-agonist (LABA) products in this age group to recommend their use.

Box 6-5. Personalized management of asthma in children 5 years and younger



ICS: inhaled corticosteroids; LTRA: leukotriene receptor antagonist; SABA: short-acting beta2-agonist

Box 6-6. Low daily doses of inhaled corticosteroids for children 5 years and younger

Low dose ICS provides most of the clinical benefit for most children with asthma. Higher doses are associated with an increased risk of local and systemic side-effects, which must be balanced against potential benefits.

This is not a table of equivalence, but of estimated clinical comparability, based on available studies and product information.

Drug	Low daily dose (mcg) (age-group with adequate safety and effectiveness data)
Beclomethasone dipropionate (HFA)	100 (ages \geq 5 years)
Budesonide nebulized	500 (ages \geq 1 year)
Fluticasone propionate (HFA)	50 (ages \geq 4 years)
Mometasone furoate	110 (ages \geq 4 years)
Budesonide pMDI + spacer	Not sufficiently studied in this age group
Ciclesonide	Not sufficiently studied in this age group
Triamcinolone acetonide	Not sufficiently studied in this age group

HFA: hydrofluoralkane propellant; pMDI: pressurized metered dose inhaler

A low daily dose is defined as the lowest approved dose for which safety and effectiveness have been adequately studied in this age group.

REVIEWING RESPONSE AND ADJUSTING TREATMENT

Assessment at every visit should include asthma symptom control and risk factors (Box 6-4, p.138), and side-effects. The child's height should be measured every year, or more often. Asthma-like symptoms remit in a substantial proportion of children of 5 years or younger,⁶⁴⁵⁻⁶⁴⁷ so the need for continued controller treatment should be regularly assessed (e.g. every 3–6 months) (Evidence D). If therapy is stepped-down or discontinued, schedule a follow-up visit 3–6 weeks later to check whether symptoms have recurred, as therapy may need to be stepped-up or reinstated (Evidence D).

Marked seasonal variations may be seen in symptoms and exacerbations in this age-group. For children with seasonal symptoms whose daily long-term controller treatment is to be discontinued (e.g. 4 weeks after their season ends), the parent/carer should be provided with a written asthma action plan detailing specific signs of worsening asthma, the medications that should be initiated to treat it, and when and how to contact medical care.

CHOICE OF INHALER DEVICE

Inhaled therapy constitutes the cornerstone of asthma treatment in children 5 years and younger. A pressurized metered dose inhaler (pMDI) with a valved spacer (with or without a face mask, depending on the child's age) is the preferred delivery system⁶⁴⁸ (Box 6-7, p.145) (Evidence A). This recommendation is based on studies with beta₂-agonists. The spacer device should have documented efficacy in young children. The dose delivered may vary considerably between spacers, so consider this if changing from one spacer to another.

The only possible inhalation technique in young children is tidal breathing. The optimal number of breaths required to empty the spacer depends on the child's tidal volume, and the dead space and volume of the spacer. Generally 5–10 breaths will be sufficient per actuation. The way a spacer is used can markedly affect the amount of drug delivered:

- Spacer size may affect the amount of drug available for inhalation in a complex way depending on the drug prescribed and the pMDI used. Young children can use spacers of all sizes, but theoretically a lower volume spacer (<350 mL) is advantageous in very young children.
- A single pMDI actuation should be delivered at a time, with the inhaler shaken in between. Multiple actuations into the spacer before inhalation may markedly reduce the amount of drug inhaled.

- Delay between actuating the pMDI into the spacer and inhalation may reduce the amount of drug available. This varies between spacers, but to maximize drug delivery, inhalation should start as soon as possible after actuation. If a health care provider or a carer is giving the medication to the child, they should actuate the pMDI only when the child is ready and the spacer is in the child's mouth.
- If a face mask is used it must be fitted tightly around the child's mouth and nose, to avoid loss of drug.
- Ensure that the valve is moving while the child is breathing through the spacer.
- Static charge may accumulate on some plastic spacers, attracting drug particles and reducing lung delivery. This charge can be reduced by washing the spacer with detergent (without rinsing) and allowing it to air dry, but it may re-accumulate over time. Spacers made of anti-static materials or metals are less subject to this problem. If a patient or health care provider carries a new plastic spacer for emergency use, it should be regularly washed with detergent (e.g. monthly) to reduce static charge.
- Nebulizers, the only viable alternative delivery systems in children, are reserved for the minority of children who cannot be taught effective use of a spacer device. If a nebulizer is used for delivery of ICS, it should be used with a mouthpiece to avoid the medication reaching the eyes.

Box 6-7. Choosing an inhaler device for children 5 years and younger

Age	Preferred device	Alternate device
0–3 years	Pressurized metered-dose inhaler plus dedicated spacer with face mask	Nebulizer with face mask
4–5 years	Pressurized metered-dose inhaler plus dedicated spacer with mouthpiece	Pressurized metered-dose inhaler plus dedicated spacer with face mask or nebulizer with mouthpiece or face mask

ASTHMA SELF-MANAGEMENT EDUCATION FOR CARERS OF YOUNG CHILDREN

Asthma self-management education should be provided to family members and carers of wheezy children 5 years and younger when wheeze is suspected to be caused by asthma. An educational program should contain:

- A basic explanation about asthma and the factors that influence it
- Training about correct inhalation technique
- Information on the importance of the child's adherence to the prescribed medication regimen
- A written asthma action plan.

Crucial to a successful asthma education program are a partnership between patient/carer and health care providers, with a high level of agreement regarding the goals of treatment for the child, and intensive follow-up (Evidence D).¹⁵

Written asthma action plans

Asthma action plans should be provided for the family/carers of all children with asthma, including those aged 5 years and younger (Evidence D). Action plans, developed through collaboration between an asthma educator, the health care provider and the family, have been shown to be of value in older children,⁶⁴⁹ although they have not been extensively studied in children of 5 years and younger. A written asthma action plan includes:

- A description of how the parent or carer can recognize when symptom control is deteriorating
- The medications to administer
- When and how to obtain medical care, including telephone numbers of services available for emergencies (e.g. doctors' offices, emergency rooms and hospitals, ambulance services and emergency pharmacies). Details of treatments that can be initiated at home are provided in the following section, *Part C: Management of worsening asthma and exacerbations in children 5 years and younger*, p.146.

PART C. MANAGEMENT OF WORSENING ASTHMA AND EXACERBATIONS IN CHILDREN 5 YEARS AND YOUNGER

KEY POINTS

- Early symptoms of exacerbations in young children may include increased symptoms; increased coughing, especially at night; lethargy or reduced exercise tolerance; impaired daily activities including feeding; and a poor response to reliever medication.
- Give a written asthma action plan to parents/carers of young children with asthma so they can recognize an impending severe attack, start treatment, and identify when urgent hospital treatment is required.
 - Initial treatment at home is with inhaled short-acting beta₂-agonist (SABA), with review after 1 hour or earlier.
 - Parents/carers should seek urgent medical care if the child is acutely distressed, lethargic, fails to respond to initial bronchodilator therapy, or is worsening, especially in children <1 year of age.
 - Medical attention should be sought on the same day if inhaled SABA is needed more often than 3-hourly or for more than 24 hours.
 - There is no compelling evidence to support parent-initiated oral corticosteroids.
- In children presenting to primary care or an acute care facility with an asthma exacerbation:
 - Assess severity of the exacerbation while initiating treatment with SABA (2–6 puffs every 20 minutes for first hour) and oxygen (to maintain saturation 94–98%).
 - Recommend immediate transfer to hospital if there is no response to inhaled SABA within 1–2 hours; if the child is unable to speak or drink or has subcostal retractions or cyanosis; if resources are lacking in the home; or if oxygen saturation is <92% on room air.
 - Consider oral prednisone/prednisolone 1–2 mg/kg/day for up to 5 days for children attending an Emergency Department or admitted to hospital, up to a maximum of 20 mg/day for 0–2 years, and 30 mg/day for 3–5 years; or dexamethasone 0.6mg/kg/day for 2 days.
- Children who have experienced an asthma exacerbation are at risk of further exacerbations. Follow up should be arranged within 1 week of an exacerbation to plan ongoing asthma management.

DIAGNOSIS OF EXACERBATIONS

A flare-up or exacerbation of asthma in children 5 years and younger is defined as an acute or sub-acute deterioration in symptom control that is sufficient to cause distress or risk to health, and necessitates a visit to a health care provider or requires treatment with systemic corticosteroids. They are sometimes called ‘episodes’.

Early symptoms of an exacerbation may include any of the following:

- Onset of symptoms of respiratory tract infection
- An acute or sub-acute increase in wheeze and shortness of breath
- An increase in coughing, especially while the child is asleep
- Lethargy or reduced exercise tolerance
- Impairment of daily activities, including feeding
- A poor response to reliever medication.

In a study of children aged 2–5 years, the combination of increased daytime cough, daytime wheeze, and night-time beta₂-agonist use was a strong predictor at a group level of an imminent exacerbation (1 day later). This combination predicted around 70% of exacerbations, with a low false positive rate of 14%. In contrast, no individual symptom was predictive of an imminent asthma exacerbation.⁶⁵⁰

Upper respiratory symptoms frequently precede the onset of an asthma exacerbation, indicating the important role of viral URTI in precipitating exacerbations in many, although not all, children with asthma. In a randomized controlled trial

of acetaminophen versus ibuprofen, given for pain or fever in children with mild persistent asthma, there was no evidence of a difference in the subsequent risk of flare-ups or poor symptom control.⁶³⁴

INITIAL HOME MANAGEMENT OF ASTHMA EXACERBATIONS

Initial management includes an action plan to enable the child's family members and carers to recognize worsening asthma and initiate treatment, recognize when it is severe, identify when urgent hospital treatment is necessary, and provide recommendations for follow up (Evidence D). The action plan should include specific information about medications and dosages and when and how to access medical care.

Need for urgent medical attention

Parents/carers should know that immediate medical attention should be sought if:

- The child is acutely distressed
- The child's symptoms are not relieved promptly by inhaled bronchodilator
- The period of relief after doses of SABA becomes progressively shorter
- A child younger than 1 year requires repeated inhaled SABA over several hours.

Initial treatment at home

Inhaled SABA via a mask or spacer, and review response

The parent/carer should initiate treatment with two puffs of inhaled SABA (200 mcg salbutamol or equivalent), given one puff at a time via a spacer device with or without a facemask (Evidence D). This may be repeated a further two times at 20 minute intervals, if needed. The child should be observed by the family/carer and, if improving, maintained in a restful and reassuring atmosphere for an hour or more. Medical attention should be sought urgently if any of the features listed above apply; or on the same day if more than 6 puffs of inhaled SABA are required for symptom relief within the first 2 hours, or if the child has not recovered after 24 hours.

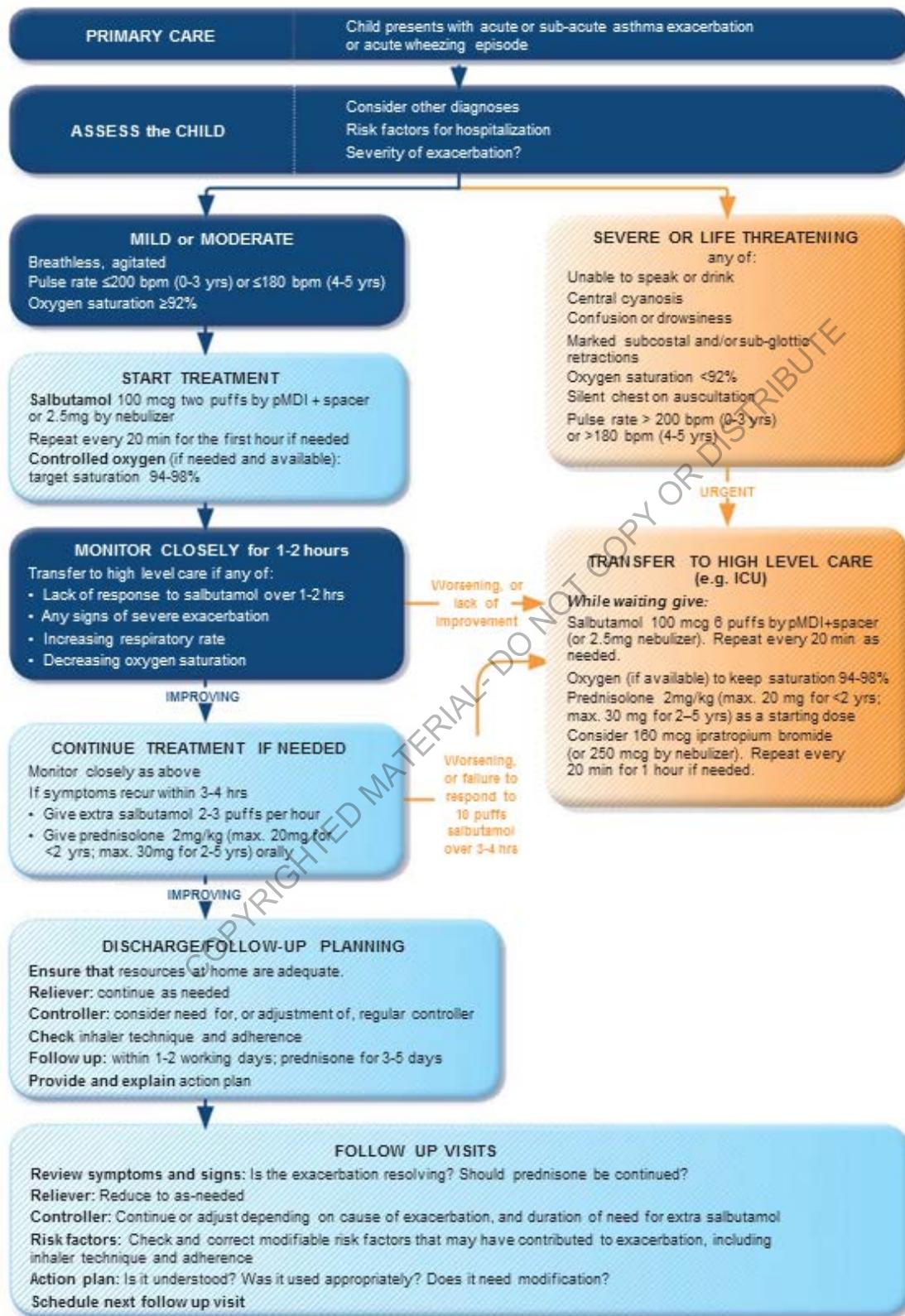
Family/carer-initiated corticosteroids

Although practiced in some parts of the world, the evidence to support the initiation of oral corticosteroid (OCS) treatment by family/carers in the home management of asthma exacerbations in children is weak.⁶⁵¹⁻⁶⁵⁵ Preemptive episodic high-dose episodic ICS may reduce exacerbations in children with intermittent viral triggered wheezing.⁶⁴⁰ However, because of the high potential for side-effects, especially if the treatment is continued inappropriately or is given frequently, family-administered high dose ICS should be considered only where the health care provider is confident that the medications will be used appropriately, and the child is closely monitored for side-effects (see p.150. Emergency treatment and initial pharmacotherapy).

Leukotriene receptor antagonists

In children aged 2–5 years with intermittent viral wheezing, one study found that a short course of an oral LTRA (for 7–20 days, commenced at the start of an URTI or the first sign of asthma symptoms) reduced symptoms, health care utilization and time off work for the carer.⁶⁵⁶ In contrast another study found no significant effect on episode-free days (primary outcome), OCS use, health care utilization, quality of life or hospitalization in children with or without a positive Asthma Predictive Index (API). However, activity limitation and a symptom trouble score were significantly improved, particularly in children with a positive API.⁶⁵⁷

Box 6-8. Primary care management of acute asthma or wheezing in children 5 years and younger



PRIMARY CARE OR HOSPITAL MANAGEMENT OF ACUTE ASTHMA EXACERBATIONS

Assessment of exacerbation severity

Conduct a brief history and examination concurrently with the initiation of therapy (Box 6-8, Box 6-9). The presence of any of the features of a severe exacerbation listed in Box 6-9 are an indication of the need for urgent treatment and immediate transfer to hospital (Evidence D). Oxygen saturation from pulse oximetry of <92% on presentation (before oxygen or bronchodilator treatment) is associated with high morbidity and likely need for hospitalization; saturation of 92–95% is also associated with higher risk.⁵¹⁶ Agitation, drowsiness and confusion are features of cerebral hypoxemia. A quiet chest on auscultation indicates minimal ventilation, insufficient to produce a wheeze.

Several clinical scoring systems such as PRAM (Preschool Respiratory Assessment Measure) and PASS (Pediatric Asthma Severity Score) have been developed for assessing the severity of acute asthma exacerbations in children.⁶⁵⁸

Box 6-9. Initial assessment of acute asthma exacerbations in children 5 years and younger

Symptoms	Mild	Severe*
Altered consciousness	No	Agitated, confused or drowsy
Oximetry on presentation (SaO_2) ^{**}	>95%	<92%
Speech [†]	Sentences	Words
Pulse rate	<100 beats/minute	>200 beats/minute (0–3 years) >180 beats/minute (4–5 years)
Central cyanosis	Absent	Likely to be present
Wheeze intensity	Variable	Chest may be quiet

*Any of these features indicates a severe asthma exacerbation. **Oximetry before treatment with oxygen or bronchodilator.

† The normal developmental capability of the child must be taken into account.

Indications for immediate transfer to hospital

Children with features of a severe exacerbation that fail to resolve within 1–2 hours despite repeated dosing with inhaled SABA, with or without OCS, must be referred to hospital for observation and further treatment (Evidence D). Other indications are respiratory arrest or impending arrest; lack of supervision in the home or doctor's office; and recurrence of signs of a severe exacerbation within 48 hours (particularly if treatment with OCS has already been given). In addition, early medical attention should be sought for children with a history of severe life-threatening exacerbations, and those less than 2 years of age as the risk of dehydration and respiratory fatigue is increased (Box 6-10, p.150).

Emergency treatment and initial pharmacotherapy

Oxygen

Treat hypoxemia urgently with oxygen by face mask to achieve and maintain percutaneous oxygen saturation 94–98% (Evidence A). To avoid hypoxemia during changes in treatment, children who are acutely distressed should be treated immediately with oxygen and SABA (2.5 mg of salbutamol or equivalent diluted in 3 mL of sterile normal saline) delivered by an oxygen-driven nebulizer (if available). This treatment should not be delayed, and may be given before the full assessment is completed. Transient hypoxemia due to ventilation/perfusion mismatch may occur during treatment with SABAs.

Box 6-10. Indications for immediate transfer to hospital for children 5 years and younger

Immediate transfer to hospital is indicated if a child ≤5 years with asthma has ANY of the following:

- At initial or subsequent assessment
 - Child is unable to speak or drink
 - Cyanosis
 - Subcostal retraction
 - Oxygen saturation <92% when breathing room air
 - Silent chest on auscultation
- Lack of response to initial bronchodilator treatment
 - Lack of response to 6 puffs of inhaled SABA (2 separate puffs, repeated 3 times) over 1–2 hours
 - Persisting tachypnoea* despite three administrations of inhaled SABA, even if the child shows other clinical signs of improvement
- Social environment that limits delivery of acute treatment, or parent/carer unable to manage acute asthma at home

During transfer to hospital, continue to give inhaled SABA, oxygen (if available) to maintain saturation 94–98%, and give systemic corticosteroids (see Box 6-8, p.148)

*Normal respiratory rates: <60 breaths/minute in children 0–2 months; <50 breaths/minute in children 2–12 months; <40 breaths/minute in children 1–5 years.

Bronchodilator therapy

The initial dose of SABA may be given by a pMDI with spacer and mask or mouthpiece or an air-driven nebulizer; or, if oxygen saturation is low, by an oxygen-driven nebulizer (as described above). For most children, pMDI plus spacer is favored as it is more efficient than a nebulizer for bronchodilator delivery⁶⁵⁹ (Evidence A). The initial dose of SABA is two puffs of salbutamol (100 mcg per puff) or equivalent, except in acute, severe asthma when six puffs should be given. When a nebulizer is used, a dose of 2.5 mg salbutamol solution is recommended. The frequency of dosing depends on the response observed over 1–2 hours (see below).

For children with moderate-severe exacerbations and a poor response to initial SABA, ipratropium bromide may be added, as 2 puffs of 80mcg (or 250mcg by nebulizer) every 20 minutes for 1 hour only.⁶⁵⁹

Magnesium sulfate

The role of magnesium sulfate is not established for children 5 years and younger, because there are few studies in this age group. Nebulized isotonic magnesium sulfate may be considered as an adjuvant to standard treatment with nebulized salbutamol and ipratropium in the first hour of treatment for children ≥2 years old with acute severe asthma (e.g. oxygen saturation <92%, Box 6-9, p.149), particularly those with symptoms lasting <6 hours.⁶⁶⁰ Intravenous magnesium sulfate in a single dose of 40–50 mg/kg (maximum 2 g) by slow infusion (20–60 minutes) has also been used.⁶⁶¹

Assessment of response and additional bronchodilator treatment

Children with a severe asthma exacerbation must be observed for at least 1 hour after initiation of treatment, at which time further treatment can be planned.

- *If symptoms persist after initial bronchodilator:* a further 2–6 puffs of salbutamol (depending on severity) may be given 20 minutes after the first dose and repeated at 20-minute intervals for an hour. Failure to respond at 1 hour, or earlier deterioration, should prompt urgent admission to hospital and a short-course of oral corticosteroids (Evidence D).
- *If symptoms have improved by 1 hour but recur within 3–4 hours:* the child may be given more frequent doses of bronchodilator (2–3 puffs each hour), and oral corticosteroids should be given. The child may need to remain in

the emergency room, or, if at home, should be observed by the family/carer and have ready access to emergency care. Children who fail to respond to 10 puffs of inhaled SABA within a 3–4 hour period should be referred to hospital (Evidence D).

- *If symptoms resolve rapidly after initial bronchodilator and do not recur for 1–2 hours:* no further treatment may be required. Further SABA may be given every 3–4 hours (up to a total of 10 puffs/24 hours) and, if symptoms persist beyond 1 day, other treatments including inhaled or oral corticosteroids are indicated (Evidence D), as outlined below.

Box 6-11. Initial management of asthma exacerbations in children 5 years and younger

Therapy	Dose and administration
Supplemental oxygen	Delivered by face mask (usually 1 L/minute) to maintain oxygen saturation 94–98%
Short-acting beta ₂ -agonist (SABA)	2–6 puffs of salbutamol by spacer, or 2.5 mg of salbutamol by nebulizer, every 20 minutes for first hour*, then reassess severity. If symptoms persist or recur, give an additional 2–3 puffs per hour. Admit to hospital if >10 puffs required in 3–4 hours.
Systemic corticosteroids	Give initial dose of oral prednisolone (1–2 mg/kg up to a maximum 20 mg for children <2 years old; 30 mg for children 2–5 years) OR, intravenous methylprednisolone 1 mg/kg 6-hourly on day 1
Additional options in the first hour of treatment	
Ipratropium bromide	For children with moderate-severe exacerbations, 2 puffs of ipratropium bromide 80mcg (or 250mcg by nebulizer) every 20 minutes for 1 hour only
Magnesium sulfate	Consider nebulized isotonic magnesium sulfate (150mg) 3 doses in the first hour of treatment for children aged ≥2 years with severe exacerbation (Box 6-9, p.149)

*If inhalation is not possible an intravenous bolus of terbutaline 2 mcg/kg may be given over 5 minutes, followed by continuous infusion of 5 mcg/kg/hour⁶⁶² (Evidence C). The child should be closely monitored, and the dose should be adjusted according to clinical improvement and side-effects. See below for additional and ongoing treatment, including controller therapy.

Additional treatment

When treatment in addition to SABA is required for an exacerbation, the options available for children in this age group include ICS; a short course of oral corticosteroid; and/or LTRA (see p.147). However, the clinical benefit of these interventions – particularly on endpoints such as hospitalizations and longer-term outcomes – has not been impressive.

Maintain current controller treatment (if prescribed)

Children who have been prescribed maintenance therapy with ICS, LTRA or both should continue to take the prescribed dose during and after an exacerbation (Evidence D).

Inhaled corticosteroids

For children not previously on ICS, an initial dose of ICS twice the low daily dose indicated in Box 6-6 (p.144) may be given and continued for a few weeks or months (Evidence D). Some studies have used high dose ICS (1600 mcg/day, preferably divided into four doses over the day and given for 5–10 days) as this may reduce the need for OCS.^{499,636,637,663,664} In one study of hospitalized pre-school children, adding nebulized budesonide to existing treatment (including OCS) reduced length of stay.⁶⁶⁵ However, the potential for side-effects with high dose ICS should be taken into account, especially if used repeatedly, and the child should be monitored closely. For those children already on ICS, doubling the dose was not effective in a small study of mild-moderate exacerbations in older children,⁶⁶⁶ and there are

no studies in children 5 years and younger; this approach should be reserved mainly for individual cases, and should always involve regular follow up (Evidence D).

Oral corticosteroids

For children with severe exacerbations, a dose of OCS equivalent to prednisolone 1–2 mg/kg/day, with a maximum of 20 mg/day for children under 2 years of age and 30 mg/day for children aged 2–5 years, is currently recommended (Evidence A),⁶⁶⁷ although several studies have failed to show any benefits when given earlier (e.g. by parents) during periods of worsening wheeze managed in an outpatient setting (Evidence D).^{651–654,668,669} A recent meta-analysis demonstrated a reduced risk of hospitalization when oral corticosteroids were administered in the emergency department, but no clear benefit in risk of hospitalization when given in the outpatient setting.⁶⁷⁰ A 3–5 day course is sufficient in most children and can be stopped abruptly (Evidence D).

In children discharged from the emergency department, an intramuscular corticosteroid may be an alternative to a course of OCS for preventing relapse.⁵³³ There is insufficient evidence to recommend intramuscular over oral corticosteroids.⁵³³

Regardless of treatment, the severity of the child's symptoms must be carefully monitored. The sooner therapy is started in relation to the onset of symptoms, the more likely it is that the impending exacerbation may be clinically attenuated or prevented.

Discharge and follow up after an exacerbation

Before discharge, the condition of the child should be stable (e.g. he/she should be out of bed and able to eat and drink without problems).

Children who have recently had an asthma exacerbation are at risk of further exacerbations and require follow up. The purpose is to ensure complete recovery, to establish the cause of the exacerbation, and, when necessary, to establish appropriate maintenance treatment and adherence (Evidence D).

Prior to discharge from the emergency department or hospital, family/carers should receive the following advice and information (all are Evidence D).

- Instruction on recognition of signs of recurrence and worsening of asthma. The factors that precipitated the exacerbation should be identified, and strategies for future avoidance of these factors implemented.
- A written, individualized action plan, including details of accessible emergency services.
- Careful review of inhaler technique.
- Further treatment advice explaining that:
 - SABAs should be used on an as-needed basis, but the daily requirement should be recorded to ensure it is being decreased over time to pre-exacerbation levels
 - ICS has been initiated where appropriate (at twice the low initial dose in Box 6-6 (p.144) for the first month after discharge, then adjusted as needed) or continued, for those previously prescribed controller medication.
- A supply of SABA and, where applicable, the remainder of the course of oral corticosteroid, ICS or LTRA.
- A follow-up appointment within 1–2 days and another within 1–2 months, depending on the clinical, social and practical context of the exacerbation

Chapter 7.

Primary prevention of asthma

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE

KEY POINTS

- The development and persistence of asthma are driven by gene–environment interactions. For children, a ‘window of opportunity’ to prevent asthma exists *in utero* and in early life, but intervention studies are limited.
- With regard to allergen avoidance strategies aimed at preventing asthma in children:
 - Strategies directed at a single allergen have not been effective in reducing the incidence of asthma
 - Multifaceted strategies may be effective, but the essential components have not been identified.
- Current recommendations for preventing asthma in children, based on high quality evidence or consensus, include:
 - Avoid exposure to environmental tobacco smoke during pregnancy and the first year of life
 - Encourage vaginal delivery
 - Advise breast-feeding for its general health benefits (not necessarily for asthma prevention)
 - Where possible, avoid use of paracetamol (acetaminophen) and broad-spectrum antibiotics during the first year of life.

FACTORS CONTRIBUTING TO THE DEVELOPMENT OF ASTHMA IN CHILDREN

Asthma is generally believed to be a heterogeneous disease whose inception and persistence is driven by gene–environment interactions. The most important of these interactions may occur in early life and even *in-utero*. There is consensus that a ‘window of opportunity’ exists during pregnancy and early in life when environmental factors may influence asthma development. Multiple environmental factors, both biological and sociological, may be important in the development of asthma. Data supporting the role of environmental risk factors for the development of asthma include a focus on: nutrition, allergens (both inhaled and ingested), pollutants (particularly environmental tobacco smoke), microbes, and psychosocial factors. Additional information about factors contributing to the development of asthma, including occupational asthma, is found in Appendix Chapter 2.

‘Primary prevention’ refers to preventing the onset of disease. This chapter focuses on primary prevention in children. See p.81 and review articles³⁶ for strategies for preventing occupational asthma.

FACTORS ASSOCIATED WITH INCREASED OR DECREASED RISK OF ASTHMA IN CHILDREN

Nutrition of mother and baby

Maternal diet

For some time, the mother’s diet during pregnancy has been a focus of concern relating to the development of allergy and asthma in the child. There is no firm evidence that ingestion of any specific foods during pregnancy increases the risk for asthma. However, a recent study of a pre-birth cohort observed that maternal intake of foods commonly considered allergenic (peanut and milk) was associated with a decrease in allergy and asthma in the offspring.⁶⁷¹ Similar data have been shown in a very large Danish National birth cohort, with an association between ingestion of peanuts, tree nuts and/or fish during pregnancy and a decreased risk of asthma in the offspring.^{672,673} Epidemiological studies and randomized controlled trials on maternal dietary intake of fish or long-chain polyunsaturated fatty acids during pregnancy showed no consistent effects on the risk of wheeze, asthma or atopy in the child.⁶⁷⁴⁻⁶⁷⁷ Dietary changes during pregnancy are therefore not recommended for prevention of allergies or asthma.

Maternal obesity and weight gain during pregnancy

Data suggest that maternal obesity and weight gain during pregnancy pose an increased risk for asthma in children. A recent meta-analysis⁶⁷⁸ showed that maternal obesity in pregnancy was associated with higher odds of ever asthma or wheeze or current asthma or wheeze; each 1 kg/m² increase in maternal BMI was associated with a 2% to 3% increase in the odd of childhood asthma. High gestational weight gain was associated with higher odds of ever asthma or wheeze. However, no recommendations can be made at present, as unguided weight loss in pregnancy should not be encouraged.

Breast-feeding

Despite the existence of many studies reporting a beneficial effect of breast-feeding on asthma prevention, results are conflicting,⁴⁰³ and caution should be taken in advising families that breast-feeding will prevent asthma.⁶⁷⁹ Breast-feeding decreases wheezing episodes in early life; however, it may not prevent development of persistent asthma (Evidence D). Regardless of its effect on development of asthma, breast-feeding should be encouraged for all of its other positive benefits (Evidence A).

Delayed introduction of solids

Beginning in the 1990s, many national pediatric agencies and societies recommended delay of introduction of solid food, especially for children at a high risk for developing allergy. Current guidelines do not recommend strict avoidance of high-risk foods,⁴⁰³ but carefully controlled, prospective studies are needed to conclusively resolve this controversy.

Dietary supplements for mothers and/or babies

Vitamin D

Intake of vitamin D may be through diet, dietary supplementation or sunlight. A systematic review of cohort, case control and cross-sectional studies concluded that maternal dietary intake of vitamin D, and of vitamin E, was associated with lower risk of wheezing illnesses in children.⁶⁸⁰ This was not confirmed in two randomized controlled trials of vitamin D supplementation in pregnancy, although a significant effect was not ruled out.^{681,682} When the results from these two trials were combined, there was a 25% reduction of risk of asthma/recurrent wheeze at ages 0-3 years.⁶⁸³ The effect was greatest among women who maintained 25(OH)vitamin D levels of at least 30ng/ml from the time of study entry through delivery, suggesting that sufficient levels of Vitamin D during early pregnancy may be important in decreasing risk for early life wheezing episodes.⁶⁸³

Fish oil and long-chain polyunsaturated fatty acids

Systematic reviews of cohort studies about maternal dietary intake of fish or seafood during pregnancy^{674,684} and of randomized controlled trials on maternal dietary intake of fish or long-chained polyunsaturated fatty acids during pregnancy⁶⁷⁴ showed no consistent effects on the risk of wheeze, asthma or atopy in the child. One recent study demonstrated decreased wheeze/asthma in pre-school children at high risk for asthma when mothers were given a high dose fish oil supplement in the third trimester;⁶⁸⁵ however 'fish oil' is not well defined, and the optimal dosing regimen has not been established.

Probiotics

A meta-analysis provided insufficient evidence to recommend probiotics for the prevention of allergic disease (asthma, rhinitis, eczema or food allergy).⁶⁸⁶

Inhalant allergens

Sensitization to indoor, inhaled aero-allergens is generally more important than sensitization to outdoor allergens for the presence of, and/or development of, asthma. While there appears to be a linear relationship between exposure and sensitization to house dust mite,^{687,688} the relationship for animal allergen appears to be more complex.⁴⁰³ Some studies have found that exposure to pet allergens is associated with increased risk of sensitization to these allergens,^{689,690} and of asthma and wheezing.^{691,692} By contrast, other studies have demonstrated a *decreased* risk of developing allergy with exposure to pets.^{693,694} A review of over 22,000 school-age children from 11 birth cohorts in Europe found no correlation between pets in the homes early in life and higher or lower prevalence of asthma in children.⁶⁹⁵ For children at risk of asthma, dampness, visible mold and mold odor in the home environment are associated with increased risk of developing asthma.⁶⁹⁶ Overall, there are insufficient data to recommend efforts to either reduce or increase pre-natal or early-life exposure to common sensitizing allergens, including pets, for the prevention of allergies and asthma.

Birth cohort studies provide some evidence for consideration. A meta-analysis found that studies of interventions focused on reducing exposure to a single allergen did not significantly affect asthma development, but that multifaceted

interventions such as in the Isle of Wight study,⁶⁹⁷ the Canadian Asthma Primary Prevention Study,⁶⁹⁸ and the Prevention of Asthma in Children study⁶⁹⁹ were associated with lower risk of asthma diagnosis in children younger than 5 years.⁷⁰⁰ Two multifaceted studies that followed children beyond 5 years of age demonstrated a significant protective effect both before and after the age of 5 years.^{697,701} The Isle of Wight study has shown a continuing positive benefit for early-life intervention through to 18 years of age;⁷⁰² however, exactly which components of the intervention were important and which specific mechanistic changes were induced remain elusive.

Treatment with grass SLIT for 3 years did not reduce the incidence of asthma diagnosis (primary outcome) in a large randomized double-blind placebo-controlled trial in children 5–12 years with grass-allergic rhinoconjunctivitis, but asthma symptoms and asthma medication use were reduced. At present, SLIT for children with grass allergic rhinoconjunctivitis is not recommended for asthma prevention.⁷⁰³ Additional studies are needed.

Pollutants

Maternal smoking during pregnancy is the most direct route of pre-natal environmental tobacco smoke exposure.⁷⁰⁴ A meta-analysis concluded that pre-natal smoking had its strongest effect on young children, whereas post-natal maternal smoking seemed relevant only to asthma development in older children.⁷⁰⁵ Exposure to outdoor pollutants, such as living near a main road, is associated with increased risk of asthma.^{706,707} Prenatal NO₂, SO₂, and PM10 exposures are associated with an increased risk of asthma in childhood,⁷⁰⁸ but it is difficult to separate pre- and post-natal exposure.

Microbial effects

The ‘hygiene hypothesis’, and the more recently coined ‘microflora hypothesis’ and ‘biodiversity hypothesis’,⁷⁰⁹ suggest that human interaction with microbiota may be beneficial in preventing asthma. For example, there is a lower risk of asthma among children raised on farms with exposure to stables and consumption of raw farm milk than among children of non-farmers.⁷¹⁰ The risk of asthma is also reduced in children whose bedrooms have high levels of bacterial-derived lipopolysaccharide endotoxin.^{711,712} Similarly, children in homes with ≥2 dogs or cats are less likely to be allergic than those in homes without dogs or cats.⁶⁹⁴ Exposure of an infant to the mother’s vaginal microflora through vaginal delivery may also be beneficial; the prevalence of asthma is higher in children born by cesarean section than those born vaginally.^{713,714} This may relate to differences in the infant gut microbiota according to their mode of delivery.⁷¹⁵

Respiratory syncytial virus infection is associated with subsequent recurrent wheeze, and preventative treatment of premature infants with monthly injections of the monoclonal antibody, palivizumab, (prescribed for prophylaxis of respiratory syncytial virus) is associated with a reduction in recurrent wheezing in the first year of life.⁷¹⁶ However, there is little evidence to suggest that this effect is sustained. Although the risk of parent-reported asthma with infrequent wheeze was reduced at 6 years, there was no impact on doctor-diagnosed asthma or lung function.⁷¹⁷ Thus, the long-term effect of palivizumab in the prevention of asthma remains uncertain.

Medications and other factors

Antibiotic use during pregnancy and in infants and toddlers has been associated with the development of asthma later in life,^{718–720} although not all studies have shown this association.⁷²¹ Intake of the analgesic, paracetamol (acetaminophen), may be associated with asthma in both children and adults,⁷²² although exposure during infancy may be confounded by use of paracetamol for respiratory tract infections.⁷²² Frequent use of paracetamol by pregnant women has been associated with asthma in their children.⁷²³ There is no evidence that vaccinations increase the risk of a child developing asthma.

Psychosocial factors

The social environment to which children are exposed may also contribute to the development and severity of asthma. Maternal distress during pregnancy⁷²⁴ or during the child’s early years⁷¹⁸ has been associated with an increased risk of the child developing asthma.

ADVICE ABOUT PRIMARY PREVENTION OF ASTHMA

Based on the results of cohort and observational studies,⁷²⁵ and a GRADE-based analysis for the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines,⁴⁰³ parents enquiring about how to reduce the risk of their children developing asthma can be provided with the advice summarized in Box 7-1.

Possibly the most important factor is the need to provide a positive, supportive environment for discussion that decreases stress, and which encourages families to make choices with which they feel comfortable.

Box 7-1. Advice about primary prevention of asthma in children 5 years and younger

Parents enquiring about how to reduce the risk of their child developing asthma can be provided with the following advice:

- Children should not be exposed to environmental tobacco smoke during pregnancy or after birth
- Vaginal delivery should be encouraged where possible
- Breast-feeding is advised, for reasons other than prevention of allergy and asthma
- The use of broad-spectrum antibiotics during the first year of life should be discouraged.

COPYRIGHTED MATERIAL-DO NOT COPY OR DISTRIBUTE

Chapter 8.

**Implementing asthma
management strategies
into health systems**

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE

KEY POINTS

- In order to improve asthma care and patient outcomes, evidence-based recommendations must not only be developed, but also disseminated and implemented at a national and local level, and integrated into clinical practice.
- Recommendations for implementing asthma care strategies are based on many successful programs worldwide.
- Implementation requires an evidence-based strategy involving professional groups and stakeholders, and should take into account local cultural and socioeconomic conditions.
- Cost-effectiveness of implementation programs should be assessed so a decision can be made to pursue or modify them.
- Local adaptation and implementation of asthma care strategies is aided by the use of tools developed for this purpose.

INTRODUCTION

Due to the exponential increase in medical research publications, practical syntheses are needed to guide policy makers and health care professionals in delivering evidence-based care. When asthma care is consistent with evidence-based recommendations, outcomes improve.^{151,726,727} The *Global Strategy for Asthma Management and Prevention* is a resource document for health care professionals to establish the main goals of asthma treatment and the actions required to ensure their fulfilment, as well as to facilitate the achievement of standards for quality asthma care.

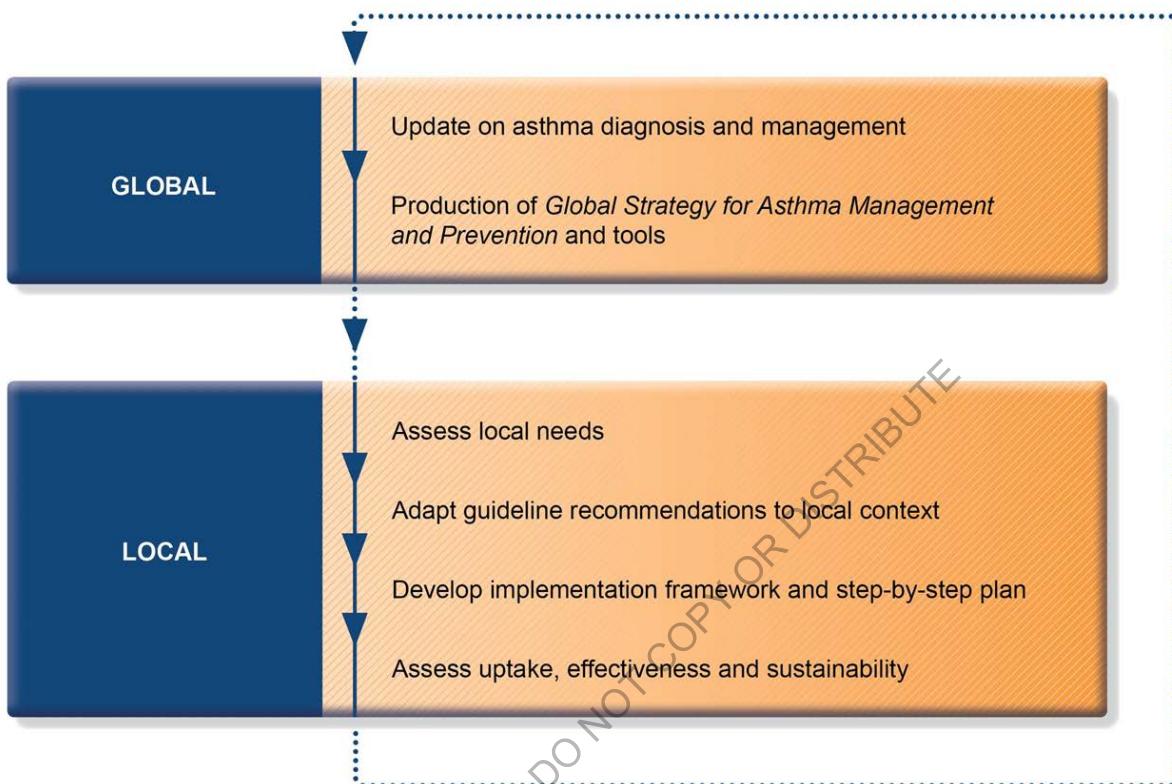
The recent adoption of rigorous methodologies such as GRADE² for the development of clinical practice recommendations, and the ADAPTE⁷²⁸ and similar approaches for assisting the adaptation of recommendations for local country and regional conditions, has assisted in reducing biased opinion as the basis for asthma programs worldwide. Adaptation of clinical practice recommendations to local conditions using the GRADE method is costly and often requires expertise that is not available locally; in addition, regular revision is required to remain abreast of developments, including drug availability and new evidence, and this is not easily achieved.⁷²⁹ Further, there is generally very limited high quality evidence addressing the many decision nodes in comprehensive clinical practice guidelines, particularly in developing countries.

ADAPTING AND IMPLEMENTING ASTHMA CLINICAL PRACTICE GUIDELINES

Implementation of asthma management strategies may be carried out at a national, regional or local level.⁷³⁰ Ideally, implementation should be a multidisciplinary effort involving many stakeholders, and using cost-effective methods of knowledge translation.⁷³⁰⁻⁷³² Each implementation initiative needs to consider the nature of the local health system and its resources (e.g. human, infrastructure, available treatments) (Box 8-1). Moreover, goals and implementation strategies will need to vary from country to country and within countries, based on economics, culture and the physical and social environment. Priority should be given to high-impact interventions.

Specific steps need to be followed before clinical practice recommendations can be embedded into local clinical practice and become the standard of care, particularly in low resource settings. The individual steps are summarized in Box 8-2, and a detailed description of the processes involved in each step can be found in the GINA Appendix Chapter 6, available online at www.ginasthma.org.

Box 8-1. Approach to implementation of the Global Strategy for Asthma Management and Prevention



Box 8-2. Essential elements required to implement a health-related strategy

Steps in implementing an asthma strategy into a health system

1. Develop a multidisciplinary working group
2. Assess the current status of asthma care delivery, care gaps and current needs
3. Select the material to be implemented, agree on main goals, identify key recommendations for diagnosis and treatment, and adapt them to the local context or environment
4. Identify barriers to, and facilitators of, implementation
5. Select an implementation framework and its component strategies
6. Develop a step-by-step implementation plan:
 - o Select target populations and evaluable outcomes
 - o Identify local resources to support implementation
 - o Set timelines
 - o Distribute tasks to members
 - o Evaluate outcomes
7. Continuously review progress and results to determine if the strategy requires modification

BARRIERS AND FACILITATORS

Many barriers to, and facilitators of, implementation procedures have been described.⁷³²⁻⁷³⁵ Some of the barriers to implementation of evidence-based asthma management relate to the delivery of care, while others relate to patients' attitudes (see Box 8-3, and examples in Appendix Chapter 6, Box 6-1). Cultural and economic barriers can particularly affect the application of recommendations.

Box 8-3. Examples of barriers to the implementation of evidence-based recommendations

Health care providers	Patients
Insufficient knowledge of recommendations	Low health literacy
Lack of agreement with recommendations or expectation that they will be effective	Insufficient understanding of asthma and its management
Resistance to change	Lack of agreement with recommendations
External barriers (organizational, health policies, financial constraints)	Cultural and economic barriers
Lack of time and resources	Peer influence
Medico-legal issues	Attitudes, beliefs, preferences, fears and misconceptions

EXAMPLES OF HIGH IMPACT IMPLEMENTATION INTERVENTIONS

Ideally, interventions should be applied at the level of both the patient and the health care provider and, where relevant, the health system. Studies of the most effective means of medical education show that it may be difficult to induce changes in clinical practice. Examples of highly effective interventions are shown in Box 8-4.

Box 8-4. Examples of high-impact interventions in asthma management

- Free ICS for patients with a recent hospital admission and/or severe asthma⁷³⁶
- Early treatment with ICS, guided self-management, reduction in exposure to tobacco smoke, improved access to asthma education¹⁵¹
- Self-inking stamp prompting assessment of asthma control and treatment strategies⁷³⁷
- Use of individualized written asthma action plans as part of self-management education³⁷⁹
- An evidence-based care process model for acute and chronic pediatric asthma management, implemented at multiple hospitals⁷³⁸

ICS: inhaled corticosteroids

EVALUATION OF THE IMPLEMENTATION PROCESS

An important part of the implementation process is to establish a means of evaluating the effectiveness of the program and any improvements in quality of care (see Appendix Chapter 6, Box A6-3). The Cochrane Effective Practice and Organization of Care Group (EPOC) offers suggestions on how to assess the effectiveness of interventions.⁷³⁹

Evaluation involves surveillance of traditional epidemiological parameters, such as morbidity and mortality, as well as specific audits of both process and outcome within different sectors of the health care system. Each country should determine its own minimum sets of data to audit health outcomes.

HOW CAN GINA HELP WITH IMPLEMENTATION?

GINA, through the work of its Dissemination and Implementation Committee, assists in the processes of adaptation and implementation of the recommendations in the *Global Strategy for Asthma Management and Prevention* report. The GINA report provides an annually-updated summary of evidence relevant to asthma diagnosis, management and prevention that may be used in the formulation and adaptation of local guidelines; where evidence is lacking, the GINA report provides approaches for consideration. A web-based implementation ‘toolkit’ will provide a template and guide to local adaptation and implementation of these recommendations, together with materials and advice from successful examples of asthma clinical practice guideline development and implementation in different settings.

Educational materials and tools based on the *Global Strategy for Asthma Management and Prevention* are available in several forms and can be found on the GINA Website (www.ginasthma.org).

COPYRIGHTED MATERIAL-DO NOT COPY OR DISTRIBUTE

COPYRIGHTED MATERIAL-DO NOT COPY OR DISTRIBUTE

REFERENCES

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE

REFERENCES

1. National Heart Lung and Blood Institute N. Global initiative for asthma. Global strategy for asthma management and prevention. NHBLI/WHO workshop. 1995:NIH Publication no. 95-3659.
2. Schunemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Sohly AA, Ernst A, Fahy BF, et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med* 2006;174:605-14.
3. Bel EH. Clinical phenotypes of asthma. *Curr Opin Pulm Med* 2004;10:44-50.
4. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, D'Agostino R, Jr., et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315-23.
5. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012;18:716-25.
6. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet* 2008;372:1107-19.
7. Levy ML, Quanjer PH, Booker R, Cooper BG, Holmes S, Small I, General Practice Airways Group. Diagnostic spirometry in primary care: Proposed standards for general practice compliant with American Thoracic Society and European Respiratory Society recommendations: a General Practice Airways Group (GPIAG) document, in association with the Association for Respiratory Technology & Physiology (ARTP) and Education for Health. *Prim Care Respir J* 2009;18:130-47.
8. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324-43.
9. Reddel H, Ware S, Marks G, Salome C, Jenkins C, Woolcock A. Differences between asthma exacerbations and poor asthma control [erratum in Lancet 1999;353:758]. *Lancet* 1999;353:364-9.
10. Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemiere C, Field SK, et al. Reevaluation of diagnosis in adults with physician-diagnosed asthma. *JAMA* 2017;317:269-79.
11. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
12. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948-68.
13. Tan WC, Vollmer WM, Lamprecht B, Mannino DM, Jithoo A, Nizankowska-Mogilnicka E, Mejza F, et al. Worldwide patterns of bronchodilator responsiveness: results from the Burden of Obstructive Lung Disease study. *Thorax* 2012;67:718-26.
14. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59-99.
15. Brouwer AF, Brand PL. Asthma education and monitoring: what has been shown to work. *Paediatr Respir Rev* 2008;9:193-9.
16. Parsons JP, Hallstrand TS, Mastronarde JG, Kaminsky DA, Rundell KW, Hull JH, Storms WW, et al. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 2013;187:1016-27.
17. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, et al. Guidelines for methacholine and exercise challenge testing-1999. *Am J Respir Crit Care Med* 2000;161:309-29.
18. Joos GF, O'Connor B, Anderson SD, Chung F, Cockcroft DW, Dahmen B, DiMaria G, et al. Indirect airway challenges. *Eur Respir J* 2003;21:1050-68.
19. Ramsdale EH, Morris MM, Roberts RS, Hargreave FE. Asymptomatic bronchial hyperresponsiveness in rhinitis. *J Allergy Clin Immunol* 1985;75:573-7.
20. van Haren EH, Lammers JW, Festen J, Heijerman HG, Groot CA, van Herwaarden CL. The effects of the inhaled corticosteroid budesonide on lung function and bronchial hyperresponsiveness in adult patients with cystic fibrosis. *Respir Med* 1995;89:209-14.

21. Joshi S, Powell T, Watkins WJ, Drayton M, Williams EM, Kotecha S. Exercise-induced bronchoconstriction in school-aged children who had chronic lung disease in infancy.[Erratum in J Pediatr. 2013 Jun;162(6):1298]. *J Pediatr* 2013;162:813-8.e1.
22. Ramsdale EH, Morris MM, Roberts RS, Hargreave FE. Bronchial responsiveness to methacholine in chronic bronchitis: relationship to airflow obstruction and cold air responsiveness. *Thorax* 1984;39:912-8.
23. Ahlstedt S, Murray CS. In vitro diagnosis of allergy: how to interpret IgE antibody results in clinical practice. *Prim Care Respir J* 2006;15:228-36.
24. Korevaar DA, Westerhof GA, Wang J, Cohen JF, Spijker R, Sterk PJ, Bel EH, et al. Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. *Lancet Respir Med* 2015;3:290-300.
25. Fahy JV. Type 2 inflammation in asthma--present in most, absent in many. *Nature Reviews Immunology* 2015;15:57-65.
26. American Thoracic Society, European Respiratory Society. ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005. *Am J Respir Crit Care Med* 2005;171:912-30.
27. Haccuria A, Michils A, Michiels S, Van Muylem A. Exhaled nitric oxide: a biomarker integrating both lung function and airway inflammation changes. *J Allergy Clin Immunol* 2014;134:554-9.
28. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, Olin A-C, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 2011;184:602-15.
29. Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, et al. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ* 2008;179:1121-31.
30. Lucas AE, Smeenk FW, Smeele IJ, van Schayck CP. Overtreatment with inhaled corticosteroids and diagnostic problems in primary care patients, an exploratory study. *Fam Pract* 2008;25:86-91.
31. Marklund B, Tunsater A, Bengtsson C. How often is the diagnosis bronchial asthma correct? *Fam Pract* 1999;16:112-6.
32. Montnemery P, Hansson L, Lanke J, Lindholm LH, Nyberg P, Lofdahl CG, Adelroth E. Accuracy of a first diagnosis of asthma in primary health care. *Fam Pract* 2002;19:365-8.
33. Gibson PG, Chang AB, Glasgow NJ, Holmes PW, Katelaris P, Kemp AS, Landau LI, et al. CICADA: Cough in Children and Adults: Diagnosis and Assessment. Australian cough guidelines summary statement. *Med J Aust* 2010;192:265-71.
34. Halvorsen T, Walsted ES, Bucca C, Bush A, Cantarella G, Friedrich G, Herth FJF, et al. Inducible laryngeal obstruction: an official joint European Respiratory Society and European Laryngological Society statement. *Eur Respir J* 2017;50.
35. Desai D, Brightling C. Cough due to asthma, cough-variant asthma and non-asthmatic eosinophilic bronchitis. *Otolaryngol Clin North Am* 2010;43:123-30.
36. Baur X, Sigsgaard T, Aasen TB, Burge PS, Heederik D, Henneberger P, Maestrelli P, et al. Guidelines for the management of work-related asthma.[Erratum appears in Eur Respir J. 2012 Jun;39(6):1553]. *Eur Respir J* 2012;39:529-45.
37. Tarlo SM, Malo JL. An official ATS proceedings: asthma in the workplace: the Third Jack Pepys Workshop on Asthma in the Workplace: answered and unanswered questions. *Proc Am Thorac Soc* 2009;6:339-49.
38. Levy ML, Nicholson PJ. Occupational asthma case finding: a role for primary care. *Br J Gen Pract* 2004;54:731-3.
39. Carlsen KH, Anderson SD, Bjermer L, Bonini S, Brusasco V, Canonica W, Cummiskey J, et al. Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: Part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. *Allergy* 2008;63:387-403.
40. Murphy VE, Gibson PG. Asthma in pregnancy. *Clin Chest Med* 2011;32:93-110, ix.
41. Adams RJ, Wilson DH, Appleton S, Taylor A, Dal Grande E, Chittleborough CR, Ruffin RE. Underdiagnosed asthma in South Australia. *Thorax* 2003;58:846-50.

42. Hsu J, Chen J, Mirabelli MC. Asthma Morbidity, Comorbidities, and Modifiable Factors Among Older Adults. *J Allergy Clin Immunol Pract* 2018;6:236-43.e7.
43. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, Calverley PM, et al. An Official American Thoracic Society Statement: Update on the Mechanisms, Assessment, and Management of Dyspnea. *Am J Respir Crit Care Med* 2012;185:435-52.
44. Januzzi JL, Jr., Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, Tung R, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol* 2005;95:948-54.
45. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management and Prevention of COPD Fontana, WI, USA 2019.
46. Hanania NA, Celli BR, Donohue JF, Martin UJ. Bronchodilator reversibility in COPD. *Chest* 2011;140:1055-63.
47. Alshabanat A, Zafari Z, Albanyan O, Dairi M, FitzGerald JM. Asthma and COPD Overlap Syndrome (ACOS): A Systematic Review and Meta Analysis. *PLoS One* 2015;10:e0136065.
48. Boulet LP. Asthma and obesity. *Clin Exp Allergy* 2013;43:8-21.
49. van Huisstede A, Castro Cabezas M, van de Geijn GJ, Mannaerts GH, Njo TL, Taube C, Hiemstra PS, et al. Underdiagnosis and overdiagnosis of asthma in the morbidly obese. *Respir Med* 2013;107:1356-64.
50. Levy ML, Fletcher M, Price DB, Hausen T, Halbert RJ, Yawn BP. International Primary Care Respiratory Group (IPCRG) Guidelines: diagnosis of respiratory diseases in primary care. *Prim Care Respir J* 2006;15:20-34.
51. English RG, Bachmann MO, Bateman ED, Zwarenstein MF, Fairall LR, Bheekie A, Majara BP, et al. Diagnostic accuracy of an integrated respiratory guideline in identifying patients with respiratory symptoms requiring screening for pulmonary tuberculosis: a cross-sectional study. *BMC Pulm Med* 2006;6:22.
52. Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings. WHO, 2010. at www.who.int/cardiovascular_diseases/publications/pen2010/en/.)
53. Ait-Khaled N, Enarson DA, Chiang C-Y, Marks G, K B. Management of asthma: a guide to the essentials of good clinical practice. Paris, France: International Union Against Tuberculosis and Lung Disease; 2008.
54. Barreto ML, Ribeiro-Silva Rde C, Malta DC, Oliveira-Campos M, Andreazzi MA, Cruz AA. Prevalence of asthma symptoms among adolescents in Brazil: National Adolescent School-based Health Survey (PeNSE 2012). *Revista Brasileira de Epidemiologia* 2014;17 Suppl 1:106-15.
55. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, Boulet LP. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012;12:204.
56. Jose BP, Camargos PA, Cruz Filho AA, Correa Rde A. Diagnostic accuracy of respiratory diseases in primary health units. *Rev Assoc Med Bras* 2014;60:599-612.
57. Burney P, Jithoo A, Kato B, Janson C, Mannino D, Nizankowska-Mogilnicka E, Studnicka M, et al. Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty--a BOLD analysis. *Thorax* 2014;69:465-73.
58. Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, Chanez P, et al. A new perspective on concepts of asthma severity and control. *Eur Respir J* 2008;32:545-54.
59. Aroni R, Goeman D, Stewart K, Thien F, Sawyer S, Abramson M, Douglass J. Enhancing validity: what counts as an asthma attack? *J Asthma* 2004;41:729-37.
60. McCoy K, Shade DM, Irvin CG, Mastronarde JG, Hanania NA, Castro M, Anthonisen NR. Predicting episodes of poor asthma control in treated patients with asthma. *J Allergy Clin Immunol* 2006;118:1226-33.
61. Meltzer EO, Busse WW, Wenzel SE, Belozeroff V, Weng HH, Feng J, Chon Y, et al. Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation. *J Allergy Clin Immunol* 2011;127:167-72.
62. Schatz M, Zeiger RS, Yang SJ, Chen W, Crawford W, Sajjan S, Allen-Ramey F. The relationship of asthma impairment determined by psychometric tools to future asthma exacerbations. *Chest* 2012;141:66-72.
63. O'Byrne PM, Reddel HK, Eriksson G, Ostlund O, Peterson S, Sears MR, Jenkins C, et al. Measuring asthma control: a comparison of three classification systems. *Eur Respir J* 2010;36:269-76.
64. Thomas M, Kay S, Pike J, Williams A, Rosenzweig JR, Hillyer EV, Price D. The Asthma Control Test (ACT) as a predictor of GINA guideline-defined asthma control: analysis of a multinational cross-sectional survey. *Prim Care Respir J* 2009;18:41-9.

65. LeMay KS, Armour CL, Reddel HK. Performance of a brief asthma control screening tool in community pharmacy: a cross-sectional and prospective longitudinal analysis. *Prim Care Respir J* 2014;23:79-84.
66. Ahmed S, Ernst P, Tamblyn R, Colman N. Validation of The 30 Second Asthma Test as a measure of asthma control. *Can Respir J* 2007;14:105-9.
67. Pinnoch H, Burton C, Campbell S, Gruffydd-Jones K, Hannon K, Hoskins G, Lester H, et al. Clinical implications of the Royal College of Physicians three questions in routine asthma care: a real-life validation study. *Prim Care Respir J* 2012;21:288-94.
68. Svedsater H, Jones R, Bosanquet N, Jacques L, Lay-Flurrie J, Leather DA, Vestbo J, et al. Patient-reported outcomes with initiation of fluticasone furoate/vilanterol versus continuing usual care in the Asthma Salford Lung Study. *Respir Med* 2018;141:198-206.
69. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.
70. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005;99:553-8.
71. Juniper EF, Bousquet J, Abetz L, Bateman ED, The GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006;100:616-21.
72. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59-65.
73. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol* 2009;124:719-23 e1.
74. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, Rosenzweig JC, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. *J Allergy Clin Immunol* 2007;119:817-25.
75. Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. *Eur Respir J* 2010;36:1410-6.
76. Nguyen JM, Holbrook JT, Wei CY, Gerald LB, Teague WG, Wise RA, American Lung Association Asthma Clinical Research C. Validation and psychometric properties of the Asthma Control Questionnaire among children. *J Allergy Clin Immunol* 2014;133:91-7.e1-6.
77. Chipps B, Zeiger RS, Murphy K, Mellon M, Schatz M, Kosinski M, Lampl K, et al. Longitudinal validation of the Test for Respiratory and Asthma Control in Kids in pediatric practices. *Pediatrics* 2011;127:e737-47.
78. Murphy KR, Zeiger RS, Kosinski M, Chipps B, Mellon M, Schatz M, Lampl K, et al. Test for respiratory and asthma control in kids (TRACK): a caregiver-completed questionnaire for preschool-aged children. *J Allergy Clin Immunol* 2009;123:833-9 e9.
79. Zeiger RS, Mellon M, Chipps B, Murphy KR, Schatz M, Kosinski M, Lampl K, et al. Test for Respiratory and Asthma Control in Kids (TRACK): clinically meaningful changes in score. *J Allergy Clin Immunol* 2011;128:983-8.
80. Wildfire JJ, Gergen PJ, Sorkness CA, Mitchell HE, Calatroni A, Kattan M, Szefler SJ, et al. Development and validation of the Composite Asthma Severity Index--an outcome measure for use in children and adolescents. *J Allergy Clin Immunol* 2012;129:694-701.
81. Haselkorn T, Fish JE, Zeiger RS, Szefler SJ, Miller DP, Chipps BE, Simons FER, et al. Consistently very poorly controlled asthma, as defined by the impairment domain of the Expert Panel Report 3 guidelines, increases risk for future severe asthma exacerbations in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol* 2009;124:895-902.e1-4.
82. Patel M, Pilcher J, Reddel HK, Pritchard A, Corin A, Helm C, Tofield C, et al. Metrics of salbutamol use as predictors of future adverse outcomes in asthma. *Clin Exp Allergy* 2013;43:1144-51.
83. Suissa S, Ernst P, Boivin JF, Horwitz RI, Habbick B, Cockcroft D, Blais L, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med* 1994;149:604-10.
84. Ernst P, Spitzer WO, Suissa S, Cockcroft D, Habbick B, Horwitz RI, Boivin JF, et al. Risk of fatal and near-fatal asthma in relation to inhaled corticosteroid use. *JAMA* 1992;268:3462-4.
85. Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, Serra M, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med* 2011;105:930-8.

86. Fitzpatrick S, Joks R, Silverberg JI. Obesity is associated with increased asthma severity and exacerbations, and increased serum immunoglobulin E in inner-city adults. *Clin Exp Allergy* 2012;42:747-59.
87. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, Castro M, et al. Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations. *Am J Respir Crit Care Med* 2017;195:302-13.
88. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, Zuberbier T, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;63 Suppl 86:8-160.
89. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, Fiocchi A, et al. ICON: food allergy. *J Allergy Clin Immunol* 2012;129:906-20.
90. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax* 2006;61:169-76.
91. Osborne ML, Pedula KL, O'Hollaren M, Ettinger KM, Stibolt T, Buist AS, Vollmer WM. Assessing future need for acute care in adult asthmatics: the Profile of Asthma Risk Study: a prospective health maintenance organization-based study. *Chest* 2007;132:1151-61.
92. Lim H, Kwon HJ, Lim JA, Choi JH, Ha M, Hwang SS, Choi WJ. Short-term Effect of Fine Particulate Matter on Children's Hospital Admissions and Emergency Department Visits for Asthma: A Systematic Review and Meta-analysis. *J Prev Med Public Health* 2016;49:205-19.
93. Zheng XY, Ding H, Jiang LN, Chen SW, Zheng JP, Qiu M, Zhou YX, et al. Association between air pollutants and asthma emergency room visits and hospital admissions in time series studies: A systematic review and meta-analysis. *PLoS One* 2015;10:e0138146.
94. Mazenq J, Dubus JC, Gaudart J, Charpin D, Viudes G, Noel G. City housing atmospheric pollutant impact on emergency visit for asthma: A classification and regression tree approach. *Respir Med* 2017;132:1-8.
95. Sturdy PM, Victor CR, Anderson HR, Bland JM, Butland BK, Harrison BD, Peckitt C, et al. Psychological, social and health behaviour risk factors for deaths certified as asthma: a national case-control study. *Thorax* 2002;57:1034-9.
96. Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann PJ, Dockery DW, Weiss ST. FEV1 is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol* 2001;107:61-7.
97. Ulrik CS. Peripheral eosinophil counts as a marker of disease activity in intrinsic and extrinsic asthma. *Clin Exp Allergy* 1995;25:820-7.
98. Pongracic JA, Krouse RZ, Babineau DC, Zoratti EM, Cohen RT, Wood RA, Khurana Hershey GK, et al. Distinguishing characteristics of difficult-to-control asthma in inner-city children and adolescents. *J Allergy Clin Immunol* 2016;138:1030-41.
99. Belda J, Giner J, Casan P, Sanchis J. Mild exacerbations and eosinophilic inflammation in patients with stable, well-controlled asthma after 1 year of follow-up. *Chest* 2001;119:1011-7.
100. Zeiger RS, Schatz M, Zhang F, Crawford WW, Kaplan MS, Roth RM, Chen W. Elevated exhaled nitric oxide is a clinical indicator of future uncontrolled asthma in asthmatic patients on inhaled corticosteroids. *J Allergy Clin Immunol* 2011;128:412-4.
101. Turner MO, Noertjojo K, Vedral S, Bai T, Crump S, FitzGerald JM. Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. *Am J Respir Crit Care Med* 1998;157:1804-9.
102. Miller MK, Lee JH, Miller DP, Wenzel SE. Recent asthma exacerbations: a key predictor of future exacerbations. *Respir Med* 2007;101:481-9.
103. den Dekker HT, Sonnenschein-van der Voort AMM, de Jongste JC, Anessi-Maesano I, Arshad SH, Barros H, Beardsmore CS, et al. Early growth characteristics and the risk of reduced lung function and asthma: A meta-analysis of 25,000 children. *J Allergy Clin Immunol* 2016;137:1026-35.
104. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194-200.
105. Ulrik CS. Outcome of asthma: longitudinal changes in lung function. *Eur Respir J* 1999;13:904-18.
106. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med* 2009;179:19-24.

107. Raissy HH, Kelly HW, Harkins M, Szeffler SJ. Inhaled corticosteroids in lung diseases. *Am J Respir Crit Care Med* 2013;187:798-803.
108. Foster JM, Aucott L, van der Werf RH, van der Meijden MJ, Schraa G, Postma DS, van der Molen T. Higher patient perceived side effects related to higher daily doses of inhaled corticosteroids in the community: a cross-sectional analysis. *Respir Med* 2006;100:1318-36.
109. Roland NJ, Bhalla RK, Earis J. The local side effects of inhaled corticosteroids: current understanding and review of the literature. *Chest* 2004;126:213-9.
110. Pedersen S. Do inhaled corticosteroids inhibit growth in children? *Am J Respir Crit Care Med* 2001;164:521-35.
111. Loke YK, Blanco P, Thavarajah M, Wilson AM. Impact of inhaled corticosteroids on growth in children with asthma: Systematic review and meta-analysis. *PLoS One* 2015;10:e0133428.
112. Wechsler ME, Kelley JM, Boyd IO, Dutille S, Marigowda G, Kirsch I, Israel E, et al. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. *N Engl J Med* 2011;365:119-26.
113. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL, Fiss E, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med* 2010;181:116-24.
114. Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF, Jr., Sorkness CA, Kraft M, et al. Long-acting beta₂-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285:2583-93.
115. Loymans RJ, Honkoop PJ, Termeer EH, Snoeck-Stroband JB, Assendelft WJ, Schermer TR, Chung KF, et al. Identifying patients at risk for severe exacerbations of asthma: development and external validation of a multivariable prediction model. *Thorax* 2016;71:838-46.
116. Kohansal R, Martinez-Camblor P, Agusti A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *Am J Respir Crit Care Med* 2009;180:3-10.
117. McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, Wise RA, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med* 2016;374:1842-52.
118. Kerstjens HA, Brand PL, de Jong PM, Koeter GH, Postma DS. Influence of treatment on peak expiratory flow and its relation to airway hyperresponsiveness and symptoms. The Dutch CNSLD Study Group. *Thorax* 1994;49:1109-15.
119. Brand PL, Duiverman EJ, Waalkens HJ, van Essen-Zandvliet EE, Kerrebijn KF. Peak flow variation in childhood asthma: correlation with symptoms, airways obstruction, and hyperresponsiveness during long-term treatment with inhaled corticosteroids. Dutch CNSLD Study Group. *Thorax* 1999;54:103-7.
120. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;170:836-44.
121. Jenkins CR, Thien FC, Wheatley JR, Reddel HK. Traditional and patient-centred outcomes with three classes of asthma medication. *Eur Respir J* 2005;26:36-44.
122. Li D, German D, Lulla S, Thomas RG, Wilson SR. Prospective study of hospitalization for asthma. A preliminary risk factor model. *Am J Respir Crit Care Med* 1995;151:647-55.
123. Kitch BT, Paltiel AD, Kuntz KM, Dockery DW, Schouten JP, Weiss ST, Fuhlbrigge AL. A single measure of FEV1 is associated with risk of asthma attacks in long-term follow-up. *Chest* 2004;126:1875-82.
124. Killian KJ, Watson R, Otis J, St Amand TA, O'Byrne PM. Symptom perception during acute bronchoconstriction. *Am J Respir Crit Care Med* 2000;162:490-6.
125. Rosi E, Standardi L, Binazzi B, Scano G. Perception of airway obstruction and airway inflammation in asthma: a review. *Lung* 2006;184:251-8.
126. Reddel HK, Jenkins CR, Marks GB, Ware SI, Xuan W, Salome CM, Badcock CA, et al. Optimal asthma control, starting with high doses of inhaled budesonide. *Eur Respir J* 2000;16:226-35.
127. Santanello NC, Davies G, Galant SP, Pedinoff A, Sveum R, Seltzer J, Seidenberg BC, et al. Validation of an asthma symptom diary for interventional studies. *Arch Dis Child* 1999;80:414-20.
128. Szeffler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, Craig TJ, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol* 2002;109:410-8.
129. Reddel HK, Marks GB, Jenkins CR. When can personal best peak flow be determined for asthma action plans? *Thorax* 2004;59:922-4.

130. Frey U, Brodbeck T, Majumdar A, Taylor DR, Town GI, Silverman M, Suki B. Risk of severe asthma episodes predicted from fluctuation analysis of airway function. *Nature* 2005;438:667-70.
131. Julius SM, Davenport KL, Davenport PW. Perception of intrinsic and extrinsic respiratory loads in children with life-threatening asthma. *Pediatr Pulmonol* 2002;34:425-33.
132. Kikuchi Y, Okabe S, Tamura G, Hida W, Homma M, Shirato K, Takishima T. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. *N Engl J Med* 1994;330:1329-34.
133. Magadle R, Berar-Yanay N, Weiner P. The risk of hospitalization and near-fatal and fatal asthma in relation to the perception of dyspnea. *Chest* 2002;121:329-33.
134. Nuijsink M, Hop WC, Jongste JC, Sterk PJ, Duiverman AE, Cato Study G. Perception of bronchoconstriction: a complementary disease marker in children with asthma. *J Asthma* 2013;50:560-4.
135. Jansen J, McCaffery KJ, Hayen A, Ma D, Reddel HK. Impact of graphic format on perception of change in biological data: implications for health monitoring in conditions such as asthma. *Prim Care Respir J* 2012;21:94-100.
136. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, et al. International ERS/ATS Guidelines on Definition, Evaluation and Treatment of Severe Asthma. *Eur Respir J* 2014;43:343-73.
137. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleeker ER, Brightling CE, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol* 2010;126:926-38.
138. Boulet L-P, Vervloet D, Magar Y, Foster JM. Adherence: the goal to control asthma. *Clin Chest Med* 2012;33:405-17.
139. Taylor YJ, Tapp H, Shade LE, Liu TL, Mowrer JL, Dulin MF. Impact of shared decision making on asthma quality of life and asthma control among children. *J Asthma* 2018;55:675-83.
140. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P, Bauman A, et al. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev* 2003;CD001117.
141. Guevara JP, Wolf FM, Grum CM, Clark NM. Effects of educational interventions for self management of asthma in children and adolescents: systematic review and meta-analysis. *BMJ* 2003;326:1308-9.
142. Wilson SR, Strub P, Buist AS, Knowles SB, Lavori PW, Lapidus J, Vollmer WM. Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. *Am J Respir Crit Care Med* 2010;181:566-77.
143. Cabana MD, Slish KK, Evans D, Mellins RB, Brown RW, Lin X, Kaciroti N, et al. Impact of physician asthma care education on patient outcomes. *Pediatrics* 2006;117:2149-57.
144. Partridge MR, Hill SR. Enhancing care for people with asthma: the role of communication, education, training and self-management. 1998 World Asthma Meeting Education and Delivery of Care Working Group. *Eur Respir J* 2000;16:333-48.
145. Maguire P, Pitceathly C. Key communication skills and how to acquire them. *BMJ* 2002;325:697-700.
146. Clark NM, Cabana MD, Nan B, Gong ZM, Slish KK, Birk NA, Kaciroti N. The clinician-patient partnership paradigm: outcomes associated with physician communication behavior. *Clin Pediatr (Phila)* 2008;47:49-57.
147. Rosas-Salazar C, Apter AJ, Canino G, Celedon JC. Health literacy and asthma. *J Allergy Clin Immunol* 2012;129:935-42.
148. Rosas-Salazar C, Ramratnam SK, Brehm JM, Han YY, Acosta-Perez E, Alvarez M, Colon-Semidey A, et al. Parental numeracy and asthma exacerbations in Puerto Rican children. *Chest* 2013;144:92-8.
149. Apter AJ, Wan F, Reisine S, Bender B, Rand C, Bogen DK, Bennett IM, et al. The association of health literacy with adherence and outcomes in moderate-severe asthma. *J Allergy Clin Immunol* 2013;132:321-7.
150. Poureslami I, Nimmon L, Doyle-Waters M, Rootman I, Schulzer M, Kuramoto L, Fitzgerald JM. Effectiveness of educational interventions on asthma self-management in Punjabi and Chinese asthma patients: a randomized controlled trial. *J Asthma* 2012;49:542-51.
151. Haahtela T, Tuomisto LE, Pietinalho A, Klaukka T, Erhola M, Kaila M, Nieminen MM, et al. A 10 year asthma programme in Finland: major change for the better. *Thorax* 2006;61:663-70.
152. Ait-Khaled N, Enarson DA, Bencharif N, Boulahdib F, Camara LM, Dagli E, Djankine TK, et al. Implementation of asthma guidelines in health centres of several developing countries. *Int J Tuberc Lung Dis* 2006;10:104-9.

153. Plaza V, Cobos A, Ignacio-Garcia JM, Molina J, Bergonon S, Garcia-Alonso F, Espinosa C. [Cost-effectiveness of an intervention based on the Global INitiative for Asthma (GINA) recommendations using a computerized clinical decision support system: a physicians randomized trial]. *Med Clin (Barc)* 2005;124:201-6.
154. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218-24.
155. Gibson PG, Powell H, Ducharme FM. Differential effects of maintenance long-acting beta-agonist and inhaled corticosteroid on asthma control and asthma exacerbations. *J Allergy Clin Immunol* 2007;119:344-50.
156. O'Byrne PM, Naya IP, Kallen A, Postma DS, Barnes PJ. Increasing doses of inhaled corticosteroids compared to adding long-acting inhaled beta₂-agonists in achieving asthma control. *Chest* 2008;134:1192-9.
157. Bateman ED, Reddel HK, Eriksson G, Peterson S, Ostlund O, Sears MR, Jenkins C, et al. Overall asthma control: the relationship between current control and future risk. *J Allergy Clin Immunol* 2010;125:600-8.
158. Petsky HL, Li A, Chang AB. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. *Cochrane Database Syst Rev* 2017;8:Cd005603.
159. Gibson PG. Using fractional exhaled nitric oxide to guide asthma therapy: design and methodological issues for ASthma TRreatment ALgorithm studies. *Clin Exp Allergy* 2009;39:478-90.
160. Petsky HL, Kew KM, Chang AB. Exhaled nitric oxide levels to guide treatment for children with asthma. *Cochrane Database Syst Rev* 2016;11:Cd011439.
161. Petsky HL, Kew KM, Turner C, Chang AB. Exhaled nitric oxide levels to guide treatment for adults with asthma. *Cochrane Database Syst Rev* 2016;9:Cd011440.
162. Roche N, Reddel HK, Agusti A, Bateman ED, Krishnan JA, Martin RJ, Papi A, et al. Integrating real-life studies in the global therapeutic research framework. *Lancet Respir Med* 2013;1:e29-e30.
163. Chung KF. New treatments for severe treatment-resistant asthma: targeting the right patient. *Lancet Respir Med* 2013;1:639-52.
164. Drazen JM. Asthma: the paradox of heterogeneity. *J Allergy Clin Immunol* 2012;129:1200-1.
165. Busse WW, Pedersen S, Pauwels RA, Tan WC, Chen YZ, Lamm CJ, O'Byrne PM. The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. *J Allergy Clin Immunol* 2008;121:1167-74.
166. Selroos O, Pietinalho A, Lofroos AB, Riska H. Effect of early vs late intervention with inhaled corticosteroids in asthma. *Chest* 1995;108:1228-34.
167. Selroos O. Effect of disease duration on dose-response of inhaled budesonide in asthma. *Respir Med* 2008;102:1065-72.
168. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, Tattersfield A. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;164(8 Pt 1):1392-7.
169. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, Ullman A, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;361:1071-6.
170. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332-6.
171. Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. *Thorax* 2002;57:880-4.
172. Reddel HK, Busse WW, Pedersen S, Tan WC, Chen YZ, Jorup C, Lythgoe D, et al. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. *Lancet* 2017;389:157-66.
173. El Baou C, Di Santostefano RL, Alfonso-Cristancho R, Suarez EA, Stempel D, Everard ML, Barnes N. Effect of inhaled corticosteroid particle size on asthma efficacy and safety outcomes: a systematic literature review and meta-analysis. *BMC Pulm Med* 2017;17:31.
174. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, Jorup C, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018;378:1865-76.
175. Dusser D, Montani D, Chanez P, de Blic J, Delacourt C, Deschildre A, Devillier P, et al. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. *Allergy* 2007;62:591-604.

176. Barnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. *Respir Care* 2015;60.
177. Sobieraj DM, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, Blake KV, et al. Association of inhaled corticosteroids and long-acting beta-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: A systematic review and meta-analysis. *JAMA* 2018;319:1485-96.
178. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, Jorup C, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med* 2018;378:1877-87.
179. Lazarinis N, Jørgensen L, Ekström T, Bjermer L, Dahlén B, Pullerits T, Hedlin G, et al. Combination of budesonide/formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction. *Thorax* 2014;69:130-6.
180. Papi A, Canonica GW, Maestrelli P, Paggiaro PL, Olivieri D, Pozzi E, Crimi N, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007;356:2040-52.
181. Martinez FD, Chinchilli VM, Morgan WJ, Boehmer SJ, Lemanske RF, Jr., Mauger DT, Strunk RC, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet* 2011;377:650-7.
182. Calhoun WJ, Ameredes BT, King TS, Icitovic N, Bleeker ER, Castro M, Cherniack RM, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. *JAMA* 2012;308:987-97.
183. Anonymous. Using beta 2-stimulants in asthma. *Drug Ther Bull* 1997;35:1-4.
184. Reddel HK, Ampon RD, Sawyer SM, Peters MJ. Risks associated with managing asthma without a preventer: urgent healthcare, poor asthma control and over-the-counter reliever use in a cross-sectional population survey. *BMJ open* 2017;7:e016688.
185. Haahtela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Selroos O, Sovijarvi A, et al. Comparison of a β_2 -agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325:388-92.
186. Welsh EJ, Cates CJ. Formoterol versus short-acting beta-agonists as relief medication for adults and children with asthma. *Cochrane Database Syst Rev* 2010;CD008418.
187. Adams NP, Bestall JB, Malouf R, Lasserson TJ, Jones PW. Inhaled beclomethasone versus placebo for chronic asthma. *Cochrane Database Syst Rev* 2005;CD002738.
188. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database Syst Rev* 2012;5:CD002314.
189. Philip G, Nayak AS, Berger WE, Leynadier F, Vrijens F, Dass SB, Reiss TF. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. *Curr Med Res Opin* 2004;20:1549-58.
190. Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ. A comparison of topical budesonide and oral montelukast in seasonal allergic rhinitis and asthma. *Clin Exp Allergy* 2001;31:616-24.
191. Ni Chroinin M, Greenstone I, Lasserson TJ, Ducharme FM. Addition of inhaled long-acting beta₂-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naïve adults and children. *Cochrane Database Syst Rev* 2009;CD005307.
192. Dahl R, Larsen BB, Venge P. Effect of long-term treatment with inhaled budesonide or theophylline on lung function, airway reactivity and asthma symptoms. *Respir Med* 2002;96:432-8.
193. Rivington RN, Boulet LP, Cote J, Kreisman H, Small DI, Alexander M, Day A, et al. Efficacy of Uniphyll, salbutamol, and their combination in asthmatic patients on high-dose inhaled steroids. *Am J Respir Crit Care Med* 1995;151:325-32.
194. American Lung Association Asthma Clinical Research Centers. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. *Am J Respir Crit Care Med* 2007;175:235-42.
195. Tsiu SJ, Self TH, Burns R. Theophylline toxicity: update. *Ann Allergy* 1990;64:241-57.
196. Guevara JP, Ducharme FM, Keren R, Nihtianova S, Zorc J. Inhaled corticosteroids versus sodium cromoglycate in children and adults with asthma. *Cochrane Database Syst Rev* 2006;CD003558.
197. Sridhar AV, McKean M. Nedocromil sodium for chronic asthma in children. *Cochrane Database Syst Rev* 2006;CD004108.

198. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta₂-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Cochrane Database Syst Rev 2010;CD005535.
199. Peters SP, Bleeker ER, Canonica GW, Park YB, Ramirez R, Hollis S, Fjallbrant H, et al. Serious Asthma Events with Budesonide plus Formoterol vs. Budesonide Alone. *N Engl J Med* 2016;375:850-60.
200. Stempel DA, Raphiou IH, Kral KM, Yeakey AM, Emmett AH, Prazma CM, Buaron KS, et al. Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone. *N Engl J Med* 2016;374:1822-30.
201. Woodcock A, Vestbo J, Bakerly ND, New J, Gibson JM, McCorkindale S, Jones R, et al. Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial. *Lancet* 2017;390:2247-55.
202. Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. Cochrane Database Syst Rev 2013;4:CD007313.
203. Kew KM, Karner C, Mindus SM, Ferrara G. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. Cochrane Database Syst Rev 2013;12:CD009019.
204. Papi A, Corradi M, Pigeon-Francisco C, Baronio R, Siergiejko Z, Petruzzelli S, Fabbri LM, et al. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. *Lancet Respir Med* 2013;1:23-31.
205. Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, Holt S, et al. Efficacy and safety of maintenance and reliever combination budesonide/formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013;1:32-42.
206. Bateman ED, Harrison TW, Quirce S, Reddel HK, Buhl R, Humbert M, Jenkins CR, et al. Overall asthma control achieved with budesonide/formoterol maintenance and reliever therapy for patients on different treatment steps. *Respir Res* 2011;12:38.
207. Jorup C, Lythgoe D, Bisgaard H. Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma. *Eur Respir J* 2018;51.
208. Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, Ljorring C, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: A randomized clinical trial. *Jama* 2016;315:1715-25.
209. Mosbech H, Deckermann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP, Malcus I, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014;134:568-75.e7.
210. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta₂-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. Cochrane Database Syst Rev 2010;CD005533.
211. Powell H, Gibson PG. Inhaled corticosteroid doses in asthma: an evidence-based approach. *Med J Aust* 2003;178:223-5.
212. Chauhan BF, Ducharme FM. Addition to inhaled corticosteroids of long-acting beta₂-agonists versus anti-leukotrienes for chronic asthma. Cochrane Database Syst Rev 2014;1:CD003137.
213. Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high- dose inhaled budesonide for moderate asthma. *N Engl J Med* 1997;337:1412-8.
214. Ni Chroinin M, Lasserson TJ, Greenstone I, Ducharme FM. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev 2009;CD007949.
215. Vaessen-Verberne AA, van den Berg NJ, van Nierop JC, Brackel HJ, Gerrits GP, Hop WC, Duiverman EJ. Combination therapy salmeterol/fluticasone versus doubling dose of fluticasone in children with asthma. *Am J Respir Crit Care Med* 2010;182:1221-7.
216. Stempel DA, Szeffler SJ, Pedersen S, Zeiger RS, Yeakey AM, Lee LA, Liu AH, et al. Safety of Adding Salmeterol to Fluticasone Propionate in Children with Asthma. *N Engl J Med* 2016;375:840-9.

217. Bisgaard H, Le Roux P, Bjamer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest* 2006;130:1733-43.
218. Rodrigo GJ, Neffen H. Efficacy and safety of tiotropium in school-age children with moderate-to-severe symptomatic asthma: A systematic review. *Pediatr Allergy Immunol* 2017;28:573-8.
219. Kew KM, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta₂-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. *Cochrane Database Syst Rev* 2016;Cd011721.
220. Sobieraj DM, Baker WL, Nguyen E, Weeda ER, Coleman CI, White CM, Lazarus SC, et al. Association of inhaled corticosteroids and long-acting muscarinic antagonists with asthma control in patients with uncontrolled, persistent asthma: A systematic review and meta-analysis. *JAMA* 2018;319:1473-84.
221. Malo JL, Cartier A, Ghezzo H, Trudeau C, Morris J, Jennings B. Comparison of four-times-a-day and twice-a-day dosing regimens in subjects requiring 1200 micrograms or less of budesonide to control mild to moderate asthma. *Respir Med* 1995;89:537-43.
222. Toogood JH, Baskerville JC, Jennings B, Lefcoe NM, Johansson SA. Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. *J Allergy Clin Immunol* 1982;70:288-98.
223. Lofdahl CG, Reiss TF, Leff JA, Israel E, Noonan MJ, Finn AF, Seidenberg BC, et al. Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. *BMJ* 1999;319:87-90.
224. Price DB, Hernandez D, Magyar P, Fiterman J, Beeh KM, James IG, Konstantopoulos S, et al. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003;58:211-6.
225. Vaquerizo MJ, Casan P, Castillo J, Perpina M, Sanchis J, Sobradillo V, Valencia A, et al. Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. *Thorax* 2003;58:204-10.
226. Virchow JC, Prasse A, Naya I, Summerton L, Harris A. Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosteroids. *Am J Respir Crit Care Med* 2000;162:578-85.
227. Tamaoki J, Kondo M, Sakai N, Nakata J, Takemura H, Nagai A, Takizawa T, et al. Leukotriene antagonist prevents exacerbation of asthma during reduction of high-dose inhaled corticosteroid. The Tokyo Joshi-I dai Asthma Research Group. *Am J Respir Crit Care Med* 1997;155:1235-40.
228. Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997;337:1405-11.
229. Broersen LH, Pereira AM, Jorgensen JO, Dekkers OM. Adrenal insufficiency in corticosteroids use: Systematic review and meta-analysis. *J Clin Endocrinol Metab* 2015;100:2171-80.
230. Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, Jenkins C, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;390:659-68.
231. Brusselle GG, Vanderstichele C, Jordens P, Deman R, Slabbynck H, Ringoet V, Verleden G, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax* 2013;68:322-9.
232. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev* 2014;1:CD003559.
233. Rodrigo GJ, Neffen H. Systematic review on the use of omalizumab for the treatment of asthmatic children and adolescents. *Pediatr Allergy Immunol* 2015;26:551-6.
234. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973-84.
235. Pavord ID, Korn S, Howarth P, Bleeker ER, Buhl R, Keene ON, Ortega H, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.
236. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, Murphy K, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015;3:355-66.

237. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, Barker P, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. *N Engl J Med* 2017;376:2448-58.
238. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev* 2017;9: Cd010834.
239. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, Busse WW, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *The New England journal of medicine* 2018;378:2486-96.
240. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, Pirozzi G, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting b2agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *The Lancet* 2016;388:31-44.
241. Chupp G, Laviolette M, Cohn L, McEvoy C, Bansal S, Shifren A, Khatri S, et al. Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies. *Eur Respir J* 2017;50.
242. Walsh LJ, Wong CA, Oborne J, Cooper S, Lewis SA, Pringle M, Hubbard R, et al. Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. *Thorax* 2001;56:279-84.
243. Lefebvre P, Duh MS, Lafeuille M-H, Gozalo L, Desai U, Robitaille M-N, Albers F, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol* 2015;136:1488-95.
244. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, Curtis JR, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res* 2010;62:1515-26.
245. Bateman ED, Bousquet J, Keech ML, Busse WW, Clark TJ, Pedersen SE. The correlation between asthma control and health status: the GOAL study. *Eur Respir J* 2007;29:56-62.
246. Sont JK. How do we monitor asthma control? *Allergy* 1999;54 Suppl 49:68-73.
247. Mintz M, Gilsenan AW, Bui CL, Ziemiecki R, Stanford RH, Lincourt W, Ortega H. Assessment of asthma control in primary care. *Curr Med Res Opin* 2009;25:2523-31.
248. Schatz M, Rachelefsky G, Krishnan JA. Follow-up after acute asthma episodes: what improves future outcomes? *Proc Am Thorac Soc* 2009;6:386-93.
249. Thomas A, Lemanske RF, Jr., Jackson DJ. Approaches to stepping up and stepping down care in asthmatic patients. *J Allergy Clin Immunol* 2011;128:915-24.
250. Boulet LP. Perception of the role and potential side effects of inhaled corticosteroids among asthmatic patients. *Chest* 1998;113:587-92.
251. Leuppi JD, Salome CM, Jenkins CR, Anderson SD, Xuan W, Marks GB, Koskela H, et al. Predictive markers of asthma exacerbation during stepwise dose reduction of inhaled corticosteroids. *Am J Respir Crit Care Med* 2001;163:406-12.
252. Usmani OS, Kemppinen A, Gardener E, Thomas V, Konduru PR, Callan C, McLoughlin A, et al. A Randomized Pragmatic Trial of Changing to and Stepping Down Fluticasone/Formoterol in Asthma. *J Allergy Clin Immunol Pract* 2017;5:1378-87.e5.
253. Rogers L, Sugar EA, Blake K, Castro M, Dimango E, Hanania NA, Happel KL, et al. Step-Down Therapy for Asthma Well Controlled on Inhaled Corticosteroid and Long-Acting Beta-Agonist: A Randomized Clinical Trial. *J Allergy Clin Immunol Pract* 2018;6:633-43.e1.
254. FitzGerald JM, Boulet LP, Follows RM. The CONCEPT trial: a 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. *Clin Ther* 2005;27:393-406.
255. Rank MA, Hagan JB, Park MA, Podjasek JC, Samant SA, Volcheck GW, Erwin PJ, et al. The risk of asthma exacerbation after stopping low-dose inhaled corticosteroids: a systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol* 2013;131:724-9.
256. Hagan JB, Samant SA, Volcheck GW, Li JT, Hagan CR, Erwin PJ, Rank MA. The risk of asthma exacerbation after reducing inhaled corticosteroids: a systematic review and meta-analysis of randomized controlled trials. *Allergy* 2014;69:510-6.
257. Ahmad S, Kew KM, Normansell R. Stopping long-acting beta2-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids. *Cochrane Database Syst Rev* 2015: Cd011306.

258. Masoli M, Weatherall M, Holt S, Beasley R. Budesonide once versus twice-daily administration: meta-analysis. *Respirology* 2004;9:528-34.
259. Boulet LP, Drollmann A, Magyar P, Timar M, Knight A, Engelstatter R, Fabbri L. Comparative efficacy of once-daily ciclesonide and budesonide in the treatment of persistent asthma. *Respir Med* 2006;100:785-94.
260. Rank MA, Gionfriddo MR, Pongdee T, Volcheck GW, Li JT, Hagan CR, Erwin PJ, et al. Stepping down from inhaled corticosteroids with leukotriene inhibitors in asthma: a systematic review and meta-analysis. *Allergy Asthma Proc* 2015;36:200-5.
261. Gionfriddo MR, Hagan JB, Hagan CR, Volcheck GW, Castaneda-Guarderas A, Rank MA. Stepping down inhaled corticosteroids from scheduled to as needed in stable asthma: Systematic review and meta-analysis. *Allergy Asthma Proc* 2015;36:262-7.
262. Rice JL, Diette GB, Suarez-Cuervo C, Brigham EP, Lin SY, Ramanathan M, Jr., Robinson KA, et al. Allergen-specific immunotherapy in the treatment of pediatric asthma: A systematic review. *Pediatrics* 2018;141.
263. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010;CD001186.
264. Tao L, Shi B, Shi G, Wan H. Efficacy of sublingual immunotherapy for allergic asthma: retrospective meta-analysis of randomized, double-blind and placebo-controlled trials. *Clin Respir J* 2014;8:192-205.
265. Calamita Z, Saconato H, Pela AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. *Allergy* 2006;61:1162-72.
266. Lin SY, Erekosima N, Kim JM, Ramanathan M, Suarez-Cuervo C, Chelladurai Y, Ward D, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA* 2013;309:1278-88.
267. Normansell R, Kew KM, Bridgman A. Sublingual immunotherapy for asthma. *Cochrane Database Syst Rev* 2015.
268. Marogna M, Spadolini I, Massolo A, Berra D, Zanon P, Chiodini E, Canonica GW, et al. Long-term comparison of sublingual immunotherapy vs inhaled budesonide in patients with mild persistent asthma due to grass pollen. *Ann Allergy Asthma Immunol* 2009;102:69-75.
269. Baena-Cagnani CE, Larenas-Linnemann D, Teijeiro A, Canonica GW, Passalacqua G. Will sublingual immunotherapy offer benefit for asthma? *Curr Allergy Asthma Rep* 2013.
270. Burks AW, Calderon MA, Casale T, Cox L, Demoly P, Jutel M, Nelson H, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol* 2013;131:1288-96.e3.
271. Dretzke J, Meadows A, Novielli N, Huissoon A, Fry-Smith A, Meads C. Subcutaneous and sublingual immunotherapy for seasonal allergic rhinitis: a systematic review and indirect comparison. *J Allergy Clin Immunol* 2013;131:1361-6.
272. Cates CJ, Rowe BH. Vaccines for preventing influenza in people with asthma. *Cochrane Database Syst Rev* 2013;2:CD000364.
273. Vasileiou E, Sheikh A, Butler C, El Ferkh K, von Wissmann B, McMenamin J, Ritchie L, et al. Effectiveness of Influenza Vaccines in Asthma: A Systematic Review and Meta-Analysis. *Clin Infect Dis* 2017;65:1388-95.
274. Talbot TR, Hartert TV, Mitchel E, Halasa NB, Arbogast PG, Poehling KA, Schaffner W, et al. Asthma as a risk factor for invasive pneumococcal disease. *N Engl J Med* 2005;352:2082-90.
275. Sheikh A, Alves B, Dhami S. Pneumococcal vaccine for asthma. *Cochrane Database Syst Rev* 2002;CD002165.
276. Wechsler ME, Laviolette M, Rubin AS, Fiterman J, Lapa ESJR, Shah PL, Fiss E, et al. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. *J Allergy Clin Immunol* 2013;132:1295-302.e3.
277. Global Initiative for Asthma. Difficult-to-treat and severe asthma in adolescent and adult patients - Diagnosis and Management. A GINA Pocket Guide for Health Professionals V2.0. Fontana, WI, USA: GINA; 2019.
278. Cassim R, Russell MA, Lodge CJ, Lowe AJ, Koplin JJ, Dharmage SC. The role of circulating 25 hydroxyvitamin D in asthma: a systematic review. *Allergy* 2015;70:339-54.
279. Jolliffe DA, Greenberg L, Hooper RL, Griffiths CJ, Camargo CA, Jr., Kerley CP, Jensen ME, et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. *Lancet Respir Med* 2017;5:881-90.

280. Riverin BD, Maguire JL, Li P. Vitamin D supplementation for childhood asthma: A systematic review and meta-analysis. *PLoS One* 2015;10:e0136841.
281. Pojsupap S, Iliriani K, Sampaio TZ, O'Hearn K, Kovesi T, Menon K, McNally JD. Efficacy of high-dose vitamin D in pediatric asthma: a systematic review and meta-analysis. *J Asthma* 2015;52:382-90.
282. Castro M, King TS, Kunselman SJ, Cabana MD, Denlinger L, Holguin F, Kazani SD, et al. Effect of vitamin D3 on asthma treatment failures in adults with symptomatic asthma and lower vitamin D levels: the VIDA randomized clinical trial. *Jama* 2014;311:2083-91.
283. Lazarus SC, Chinchilli VM, Rollings NJ, Boushey HA, Cherniack R, Craig TJ, Deykin A, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med* 2007;175:783-90.
284. Chaudhuri R, Livingston E, McMahon AD, Lafferty J, Fraser I, Spears M, McSharry CP, et al. Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. *Am J Respir Crit Care Med* 2006;174:127-33.
285. Rayens MK, Burkhardt PV, Zhang M, Lee S, Moser DK, Mannino D, Hahn EJ. Reduction in asthma-related emergency department visits after implementation of a smoke-free law. *J Allergy Clin Immunol* 2008;122:537-41.
286. Global Initiative for Asthma. Global strategy for asthma management and prevention. Updated 2017. Vancouver, USA GINA; 2017.
287. Carson KV, Chandratilleke MG, Picot J, Brinn MP, Esterman AJ, Smith BJ. Physical training for asthma. *Cochrane Database Syst Rev* 2013;9:CD001116.
288. Toennesen LL, Meteran H, Hostrup M, Wium Geiker NR, Jensen CB, Porsbjerg C, Astrup A, et al. Effects of Exercise and Diet in Nonobese Asthma Patients-A Randomized Controlled Trial. *J Allergy Clin Immunol Pract* 2018;6:803-11.
289. Beggs S, Foong YC, Le HC, Noor D, Wood-Baker R, Walters JA. Swimming training for asthma in children and adolescents aged 18 years and under. *Cochrane Database Syst Rev* 2013;4:CD009607.
290. Kogevinas M, Zock JP, Jarvis D, Kromhout H, Lilienberg L, Plana E, Radon K, et al. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). *Lancet* 2007;370:336-41.
291. Szczeklik A, Nizankowska E, Dupлага M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J* 2000;16:432-6.
292. Covar RA, Macomber BA, Szefler SJ. Medications as asthma triggers. *Immunol Allergy Clin North Am* 2005;25:169-90.
293. Olenchock BA, Fonarow GG, Pan W, Hernandez A, Cannon CP. Current use of beta blockers in patients with reactive airway disease who are hospitalized with acute coronary syndromes. *Am J Cardiol* 2009;103:295-300.
294. Morales DR, Jackson C, Lipworth BJ, Donnan PT, Guthrie B. Adverse respiratory effect of acute beta-blocker exposure in asthma: a systematic review and meta-analysis of randomized controlled trials. *Chest* 2014;145:779-86.
295. Gotzsche PC, Johansen HK. House dust mite control measures for asthma. *Cochrane Database Syst Rev* 2008;CD001187.
296. Leas BF, D'Anci KE, Apter AJ, Bryant-Stephens T, Lynch MP, Kaczmarek JL, Umscheid CA. Effectiveness of indoor allergen reduction in asthma management: A systematic review. *J Allergy Clin Immunol* 2018;141:1854-69.
297. Sheffer AL. Allergen avoidance to reduce asthma-related morbidity. *N Engl J Med* 2004;351:1134-6.
298. Platts-Mills TA. Allergen avoidance in the treatment of asthma and rhinitis. *N Engl J Med* 2003;349:207-8.
299. Rabito FA, Carlson JC, He H, Werthmann D, Schal C. A single intervention for cockroach control reduces cockroach exposure and asthma morbidity in children. *J Allergy Clin Immunol* 2017;140:565-70.
300. Crocker DD, Kinyota S, Dumitru GG, Ligon CB, Herman EJ, Ferdinand JM, Hopkins DP, et al. Effectiveness of home-based, multi-trigger, multicomponent interventions with an environmental focus for reducing asthma morbidity: a community guide systematic review. *Am J Prev Med* 2011;41:S5-32.
301. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R, 3rd, Stout J, et al. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 2004;351:1068-80.
302. Murray CS, Foden P, Sumner H, Shepley E, Custovic A, Simpson A. Preventing Severe Asthma Exacerbations in Children. A Randomized Trial of Mite-Impermeable Bedcovers. *Am J Respir Crit Care Med* 2017;196:150-8.

303. Custovic A, Green R, Taggart SC, Smith A, Pickering CA, Chapman MD, Woodcock A. Domestic allergens in public places. II: Dog (Can f1) and cockroach (Bla g 2) allergens in dust and mite, cat, dog and cockroach allergens in the air in public buildings. *Clin Exp Allergy* 1996;26:1246-52.
304. Almqvist C, Larsson PH, Egmar AC, Hedren M, Malmberg P, Wickman M. School as a risk environment for children allergic to cats and a site for transfer of cat allergen to homes. *J Allergy Clin Immunol* 1999;103:1012-7.
305. Shirai T, Matsui T, Suzuki K, Chida K. Effect of pet removal on pet allergic asthma. *Chest* 2005;127:1565-71.
306. Wood RA, Chapman MD, Adkinson NF, Jr., Eggleston PA. The effect of cat removal on allergen content in household-dust samples. *J Allergy Clin Immunol* 1989;83:730-4.
307. Erwin EA, Woodfolk JA, Custis N, Platts-Mills TA. Animal danders. *Immunol Allergy Clin North Am* 2003;23:469-81.
308. Phipatanakul W, Matsui E, Portnoy J, Williams PB, Barnes C, Kennedy K, Bernstein D, et al. Environmental assessment and exposure reduction of rodents: a practice parameter. *Ann Allergy Asthma Immunol* 2012;109:375-87.
309. Matsui EC, Perzanowski M, Peng RD, Wise RA, Balcer-Whaley S, Newman M, Cunningham A, et al. Effect of an Integrated Pest Management Intervention on Asthma Symptoms Among Mouse-Sensitized Children and Adolescents With Asthma: A Randomized Clinical Trial. *Jama* 2017;317:1027-36.
310. Custovic A, Wijk RG. The effectiveness of measures to change the indoor environment in the treatment of allergic rhinitis and asthma: ARIA update (in collaboration with GA(2)LEN). *Allergy* 2005;60:1112-5.
311. Eggleston PA, Wood RA, Rand C, Nixon WJ, Chen PH, Lukk P. Removal of cockroach allergen from inner-city homes. *J Allergy Clin Immunol* 1999;104:842-6.
312. Denning DW, O'Driscoll B R, Hogaboam CM, Bowyer P, Niven RM. The link between fungi and severe asthma: a summary of the evidence. *Eur Respir J* 2006;27:615-26.
313. Hirsch T, Hering M, Burkner K, Hirsch D, Leupold W, Kerkmann ML, Kuhlisch E, et al. House-dust-mite allergen concentrations (Der f 1) and mold spores in apartment bedrooms before and after installation of insulated windows and central heating systems. *Allergy* 2000;55:79-83.
314. Wood LG, Garg ML, Smart JM, Scott HA, Barker D, Gibson PG. Manipulating antioxidant intake in asthma: a randomized controlled trial. *Am J Clin Nutr* 2012;96:534-43.
315. Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respir Med* 2007;101:2240-7.
316. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med* 2006;100:648-57.
317. Saint-Pierre P, Bourdin A, Chanez P, Daures JP, Godard P. Are overweight asthmatics more difficult to control? *Allergy* 2006;61:79-84.
318. Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DY. Body mass and glucocorticoid response in asthma. *Am J Respir Crit Care Med* 2008;178:682-7.
319. Adeniyi FB, Young T. Weight loss interventions for chronic asthma. *Cochrane Database Syst Rev* 2012;7:CD009339.
320. Moreira A, Bonini M, Garcia-Larsen V, Bonini S, Del Giacco SR, Agache I, Fonseca J, et al. Weight loss interventions in asthma: EAACI Evidence-Based Clinical Practice Guideline (Part I). *Allergy* 2013;68:425-39.
321. Boulet LP, Turcotte H, Martin J, Poirier P. Effect of bariatric surgery on airway response and lung function in obese subjects with asthma. *Respir Med* 2012;106:651-60.
322. Dixon AE, Pratley RE, Forgione PM, Kaminsky DA, Whittaker-Leclair LA, Griffes LA, Garudathri J, et al. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *J Allergy Clin Immunol* 2011;128:508-15 e1-2.
323. Scott HA, Gibson PG, Garg ML, Pretto JJ, Morgan PJ, Callister R, Wood LG. Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial. *Clin Exp Allergy* 2013;43:36-49.
324. Freitas PD, Ferreira PG, Silva AG, Stelmach R, Carvalho-Pinto RM, Fernandes FL, Mancini MC, et al. The Role of Exercise in a Weight-Loss Program on Clinical Control in Obese Adults with Asthma. A Randomized Controlled Trial. *Am J Respir Crit Care Med* 2017;195:32-42.

325. Freitas DA, Holloway EA, Bruno SS, Chaves GS, Fregonezi GA, Mendonca KP. Breathing exercises for adults with asthma. *Cochrane Database Syst Rev* 2013;10:CD001277.
326. Bruton A, Lee A, Yardley L, Raftery J, Arden-Close E, Kirby S, Zhu S, et al. Physiotherapy breathing retraining for asthma: a randomised controlled trial. *Lancet Respir Med* 2018;6:19-28.
327. Slader CA, Reddel HK, Spencer LM, Belousova EG, Armour CL, Bosnic-Anticevich SZ, Thien FC, et al. Double blind randomised controlled trial of two different breathing techniques in the management of asthma. *Thorax* 2006;61:651-6.
328. Upham JW, Holt PG. Environment and development of atopy. *Curr Opin Allergy Clin Immunol* 2005;5:167-72.
329. Howden-Chapman P, Pierse N, Nicholls S, Gillespie-Bennett J, Viggers H, Cunningham M, Phipps R, et al. Effects of improved home heating on asthma in community dwelling children: randomised controlled trial. *BMJ* 2008;337:a1411.
330. Tibosch MM, Verhaak CM, Merkus PJ. Psychological characteristics associated with the onset and course of asthma in children and adolescents: a systematic review of longitudinal effects. *Patient Educ Couns* 2011;82:11-9.
331. Rietveld S, van Beest I, Everaerd W. Stress-induced breathlessness in asthma. *Psychol Med* 1999;29:1359-66.
332. Sandberg S, Paton JY, Ahola S, McCann DC, McGuinness D, Hillary CR, Oja H. The role of acute and chronic stress in asthma attacks in children. *Lancet* 2000;356:982-7.
333. Lehrer PM, Isenberg S, Hochron SM. Asthma and emotion: a review. *J Asthma* 1993;30:5-21.
334. Nouwen A, Freeston MH, Labbe R, Boulet LP. Psychological factors associated with emergency room visits among asthmatic patients. *Behav Modif* 1999;23:217-33.
335. Newson R, Strachan D, Archibald E, Emberlin J, Hardaker P, Collier C. Acute asthma epidemics, weather and pollen in England, 1987-1994. *Eur Respir J* 1998;11:694-701.
336. Li Y, Wang W, Wang J, Zhang X, Lin W, Yang Y. Impact of air pollution control measures and weather conditions on asthma during the 2008 Summer Olympic Games in Beijing. *Int J Biometeorol* 2011;55:547-54.
337. Taylor SL, Bush RK, Selner JC, Nordlee JA, Wiener MB, Holden K, Koepke JW, et al. Sensitivity to sulfited foods among sulfite-sensitive subjects with asthma. *J Allergy Clin Immunol* 1988;81:1159-67.
338. Ahmed S, Steed L, Harris K, Taylor SJC, Pinnock H. Interventions to enhance the adoption of asthma self-management behaviour in the South Asian and African American population: a systematic review. *NPJ primary care respiratory medicine* 2018;28:5.
339. Fink JB, Rubin BK. Problems with inhaler use: a call for improved clinician and patient education. *Respir Care* 2005;50:1360-74; discussion 74-5.
340. Klijn SL, Hiligsmann M, Evers S, Roman-Rodriguez M, van der Molen T, van Boven JFM. Effectiveness and success factors of educational inhaler technique interventions in asthma & COPD patients: a systematic review. *NPJ primary care respiratory medicine* 2017;27:24.
341. Newman SP. Spacer devices for metered dose inhalers. *Clin Pharmacokinet* 2004;43:349-60.
342. Basheti IA, Reddel HK, Armour CL, Bosnic-Anticevich SZ. Improved asthma outcomes with a simple inhaler technique intervention by community pharmacists. *J Allergy Clin Immunol* 2007;119:1537-8.
343. Giraud V, Allaert FA, Roche N. Inhaler technique and asthma: feasibility and acceptability of training by pharmacists. *Respir Med* 2011;105:1815-22.
344. van der Palen J, Klein JJ, Kerkhoff AH, van Herwaarden CL, Seydel ER. Evaluation of the long-term effectiveness of three instruction modes for inhaling medicines. *Patient Educ Couns* 1997;32:S87-95.
345. Armour CL, Reddel HK, LeMay KS, Saini B, Smith LD, Bosnic-Anticevich SZ, Song YJC, et al. Feasibility and effectiveness of an evidence-based asthma service in Australian community pharmacies: a pragmatic cluster randomized trial. *J Asthma* 2013;50:302-9.
346. Kuethe MC, Vaessen-Verberne AA, Elbers RG, Van Aalderen WM. Nurse versus physician-led care for the management of asthma. *Cochrane Database Syst Rev* 2013;2: Cd009296.
347. Crompton GK, Barnes PJ, Broeders M, Corrigan C, Corbett L, Dekhuijzen R, Dubus JC, et al. The need to improve inhalation technique in Europe: a report from the Aerosol Drug Management Improvement Team. *Respir Med* 2006;100:1479-94.

348. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC, Coker-Schwimmer EJ, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Ann Intern Med* 2012;157:785-95.
349. Chan AH, Harrison J, Black PN, Mitchell EA, Foster JM. Using electronic monitoring devices to measure inhaler adherence: a practical guide for clinicians. *The Journal of Allergy & Clinical Immunology in Practice* 2015;3:335-49.e1-5.
350. Cohen JL, Mann DM, Wisnivesky JP, Home R, Leventhal H, Musumeci-Szabo TJ, Halm EA. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. *Ann Allergy Asthma Immunol* 2009;103:325-31.
351. Poureslami IM, Rootman I, Balka E, Devarakonda R, Hatch J, FitzGerald JM. A systematic review of asthma and health literacy: a cultural-ethnic perspective in Canada. *MedGenMed* 2007;9:40.
352. Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Crotty K. Low health literacy and health outcomes: an updated systematic review. *Ann Intern Med* 2011;155:97-107.
353. Zeni MB. Systematic review of health literacy in Cochrane database studies on paediatric asthma educational interventions: searching beyond rigorous design. *Int J Evid Based Healthc* 2012;10:3-8.
354. Partridge MR, Dal Negro RW, Olivieri D. Understanding patients with asthma and COPD: insights from a European study. *Prim Care Respir J* 2011;20:315-23, 17 p following 23.
355. Foster JM, Usherwood T, Smith L, Sawyer SM, Xuan W, Rand CS, Reddel HK. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. *J Allergy Clin Immunol* 2014;134:1260-8.
356. Chan AH, Stewart AW, Harrison J, Camargo CA, Jr., Black PN, Mitchell EA. The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. *Lancet Respir Med* 2015;3:210-9.
357. Morton RW, Elphick HE, Rigby AS, Daw WJ, King DA, Smith LJ, Everard ML. STAAR: a randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma. *Thorax* 2017;72:347-54.
358. Otsuki M, Eakin MN, Rand CS, Butz AM, Hsu VD, Zuckerman IH, Ogborn J, et al. Adherence feedback to improve asthma outcomes among inner-city children: a randomized trial. *Pediatrics* 2009;124:1513-21.
359. Williams LK, Peterson EL, Wells K, Campbell J, Wang M, Chowdhry VK, Walsh M, et al. A cluster-randomized trial to provide clinicians inhaled corticosteroid adherence information for their patients with asthma. *J Allergy Clin Immunol* 2010;126:225-31, 31 e1-4.
360. Bender BG, Cvietusa PJ, Goodrich GK, Lowe R, Nuances HA, Rand C, Shetterly S, et al. Pragmatic trial of health care technologies to improve adherence to pediatric asthma treatment: a randomized clinical trial. *JAMA pediatrics* 2015;169:317-23.
361. Halterman JS, Fagnano M, Tajon RS, Tremblay P, Wang H, Butz A, Perry TT, et al. Effect of the School-Based Telemedicine Enhanced Asthma Management (SB-TEAM) Program on Asthma Morbidity: A Randomized Clinical Trial. *JAMA pediatrics* 2018;172:e174938.
362. Normansell R, Kew KM, Stovold E. Interventions to improve adherence to inhaled steroids for asthma. *Cochrane Database Syst Rev* 2017;4:Cd012226.
363. Foster JM, Smith L, Bosnic-Anticevich SZ, Usherwood T, Sawyer SM, Rand CS, Reddel HK. Identifying patient-specific beliefs and behaviours for conversations about adherence in asthma. *Intern Med J* 2012;42:e136-44.
364. Ulrik CS, Backer V, Soes-Petersen U, Lange P, Harving H, Plaschke PP. The patient's perspective: adherence or non-adherence to asthma controller therapy? *J Asthma* 2006;43:701-4.
365. Price D, Robertson A, Bullen K, Rand C, Horne R, Staudinger H. Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study. *BMC Pulm Med* 2010;10:1.
366. Kew KM, Carr R, Crossingham I. Lay-led and peer support interventions for adolescents with asthma. *Cochrane Database Syst Rev* 2017;4:Cd012331.
367. Clark NM, Shah S, Dodge JA, Thomas LJ, Andridge RR, Little RJ. An evaluation of asthma interventions for preteen students. *J Sch Health* 2010;80:80-7.
368. Gibson PG, Powell H, Coughlan J, Wilson AJ, Hensley MJ, Abramson M, Bauman A, et al. Limited (information only) patient education programs for adults with asthma. *Cochrane Database Syst Rev* 2002;CD001005.

369. Houts PS, Bachrach R, Witmer JT, Tringali CA, Bucher JA, Localio RA. Using pictographs to enhance recall of spoken medical instructions. *Patient Educ Couns* 1998;35:83-8.
370. Meade CD, McKinney WP, Barnas GP. Educating patients with limited literacy skills: the effectiveness of printed and videotaped materials about colon cancer. *Am J Public Health* 1994;84:119-21.
371. Manfrin A, Tinelli M, Thomas T, Krska J. A cluster randomised control trial to evaluate the effectiveness and cost-effectiveness of the Italian medicines use review (I-MUR) for asthma patients. *BMC Health Serv Res* 2017;17:300.
372. Campbell JD, Brooks M, Hosokawa P, Robinson J, Song L, Krieger J. Community health worker home visits for medicaid-enrolled children with asthma: Effects on asthma outcomes and costs. *Am J Public Health* 2015;105:2366-72.
373. Partridge MR, Caress AL, Brown C, Hennings J, Luker K, Woodcock A, Campbell M. Can lay people deliver asthma self-management education as effectively as primary care based practice nurses? *Thorax* 2008;63:778-83.
374. Pinnock H, Parke HL, Panagioti M, Daines L, Pearce G, Epiphanou E, Bower P, et al. Systematic meta-review of supported self-management for asthma: a healthcare perspective. *BMC Med* 2017;15:64.
375. Boyd M, Lasserson TJ, McKean MC, Gibson PG, Ducharme FM, Haby M. Interventions for educating children who are at risk of asthma-related emergency department attendance. *Cochrane Database Syst Rev* 2009;CD001290.
376. Powell H, Gibson PG. Options for self-management education for adults with asthma. *Cochrane Database Syst Rev* 2003;CD004107.
377. McLean S, Chandler D, Nurmatov U, Liu J, Pagliari C, Car J, Sheikh A. Telehealthcare for asthma. *Cochrane Database Syst Rev* 2010;CD007717.
378. Fishwick D, D'Souza W, Beasley R. The asthma self-management plan system of care: what does it mean, how is it done, does it work, what models are available, what do patients want and who needs it? *Patient Educ Couns* 1997;32:S21-33.
379. Gibson PG, Powell H. Written action plans for asthma: an evidence-based review of the key components. *Thorax* 2004;59:94-9.
380. Holt S, Masoli M, Beasley R. The use of the self-management plan system of care in adult asthma. *Primary care respiratory journal : journal of the General Practice Airways Group* 2004;13:19-27.
381. Roberts NJ, Evans G, Blenkhorn P, Partridge MR. Development of an electronic pictorial asthma action plan and its use in primary care. *Patient Educ Couns* 2010;80:141-6.
382. Ring N, Malcolm C, Wyke S, Macgillivray S, Dixon D, Hoskins G, Pinnock H, et al. Promoting the use of Personal Asthma Action Plans: a systematic review. *Prim Care Respir J* 2007;16:271-83.
383. Halterman JS, Fisher S, Conn KM, Fagnano M, Lynch K, Marky A, Szilagyi PG. Improved preventive care for asthma: a randomized trial of clinician prompting in pediatric offices. *Arch Pediatr Adolesc Med* 2006;160:1018-25.
384. Boulet LP. Influence of comorbid conditions on asthma. *Eur Respir J* 2009;33:897-906.
385. Chan WW, Chiou E, Obstein KL, Tignor AS, Whitlock TL. The efficacy of proton pump inhibitors for the treatment of asthma in adults: a meta-analysis. *Arch Intern Med* 2011;171:620-9.
386. Mastronarde JG, Anthonisen NR, Castro M, Holbrook JT, Leone FT, Teague WG, Wise RA. Efficacy of esomeprazole for treatment of poorly controlled asthma. *N Engl J Med* 2009;360:1487-99.
387. Kiljander TO, Harding SM, Field SK, Stein MR, Nelson HS, Ekelund J, Illueca M, et al. Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2006;173:1091-7.
388. Sopo SM, Radzik D, Calvani M. Does treatment with proton pump inhibitors for gastroesophageal reflux disease (GERD) improve asthma symptoms in children with asthma and GERD? A systematic review. *J Investig Allergol Clin Immunol* 2009;19:1-5.
389. Holbrook JT, Wise RA, Gold BD, Blake K, Brown ED, Castro M, Dozor AJ, et al. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. *JAMA* 2012;307:373-81.
390. Goodwin RD, Jacobi F, Thefeld W. Mental disorders and asthma in the community. *Arch Gen Psychiatry* 2003;60:1125-30.
391. Lavoie KL, Cartier A, Labrecque M, Bacon SL, Lemiere C, Malo JL, Lacoste G, et al. Are psychiatric disorders associated with worse asthma control and quality of life in asthma patients? *Respir Med* 2005;99:1249-57.
392. Ahmedani BK, Peterson EL, Wells KE, Williams LK. Examining the relationship between depression and asthma exacerbations in a prospective follow-up study. *Psychosom Med* 2013;75:305-10.

393. Yorke J, Fleming SL, Shuldhham C. Psychological interventions for adults with asthma. Cochrane Database Syst Rev 2009.
394. Parry GD, Cooper CL, Moore JM, Yadegarfar G, Campbell MJ, Esmonde L, Morice AH, et al. Cognitive behavioural intervention for adults with anxiety complications of asthma: prospective randomised trial. *Respir Med* 2012;106:802-10.
395. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol* 2007;119:1016-8.
396. Pumphrey RSH, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. *J Allergy Clin Immunol* 2007;119:1018-9.
397. Liu AH, Jaramillo R, Sicherer SH, Wood RA, Bock SA, Burks AW, Massing M, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 2010;126:798-806.e13.
398. Bousquet J, Schunemann HJ, Samolinski B, Demoly P, Baena-Cagnani CE, Bachert C, Bonini S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs. *J Allergy Clin Immunol* 2012;130:1049-62.
399. Cruz AA, Popov T, Pawankar R, Annesi-Maesano I, Fokkens W, Kemp J, Ohta K, et al. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. *Allergy* 2007;62 Suppl 84:1-41.
400. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Allobid I, Baroody F, Cohen N, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinol* 2012;50:1-12.
401. Tan BK, Chandra RK, Pollak J, Kato A, Conley DB, Peters AT, Grammer LC, et al. Incidence and associated premorbid diagnoses of patients with chronic rhinosinusitis. *J Allergy Clin Immunol* 2013;131:1350-60.
402. Hamilos DL. Chronic rhinosinusitis: epidemiology and medical management. *J Allergy Clin Immunol* 2011;128:693-707.
403. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, van Wijk RG, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;126:466-76.
404. Corren J, Manning BE, Thompson SF, Hennessy S, Strom BL. Rhinitis therapy and the prevention of hospital care for asthma: a case-control study. *J Allergy Clin Immunol* 2004;113:415-9.
405. Lohia S, Schlosser RJ, Soler ZM. Impact of intranasal corticosteroids on asthma outcomes in allergic rhinitis: a meta-analysis. *Allergy* 2013;68:569-79.
406. Dixon AE, Castro M, Cohen RI, Gerald LB, Holbrook JT, Irvin CG, Mohapatra S, et al. Efficacy of nasal mometasone for the treatment of chronic sinonasal disease in patients with inadequately controlled asthma. *J Allergy Clin Immunol* 2015;135:701-9.e5.
407. Souza-Machado C, Souza-Machado A, Franco R, Ponte EV, Barreto ML, Rodrigues LC, Bousquet J, et al. Rapid reduction in hospitalisations after an intervention to manage severe asthma. *Eur Respir J* 2010;35:515-21.
408. Franco R, Nascimento HF, Cruz AA, Santos AC, Souza-Machado C, Ponte EV, Souza-Machado A, et al. The economic impact of severe asthma to low-income families. *Allergy* 2009;64:478-83.
409. Bahadori K, Quon BS, Doyle-Waters MM, Marra C, Fitzgerald JM. A systematic review of economic evaluations of therapy in asthma. *J Asthma Allergy* 2010;3:33-42.
410. Fairall L, Bateman E, Cornick R, Faris G, Timmerman V, Folb N, Bachmann M, et al. Innovating to improve primary care in less developed countries: towards a global model. *BMJ Innovations* 2015.
411. Patton GC, Viner R. Pubertal transitions in health. *Lancet* 2007;369:1130-9.
412. Michaud P-A, Suris JC, Viner R. The adolescent with a chronic condition : epidemiology, developmental issues and health care provision. Geneva: WHO; 2007.
413. Carlsen KH, Anderson SD, Bjermer L, Bonini S, Brusasco V, Canonica W, Cummiskey J, et al. Treatment of exercise-induced asthma, respiratory and allergic disorders in sports and the relationship to doping: Part II of the report from the Joint Task Force of European Respiratory Society (ERS) and European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA(2)LEN. *Allergy* 2008;63:492-505.
414. Gluck JC, Gluck PA. The effect of pregnancy on the course of asthma. *Immunol Allergy Clin North Am* 2006;26:63-80.

415. Murphy VE, Powell H, Wark PA, Gibson PG. A prospective study of respiratory viral infection in pregnant women with and without asthma. *Chest* 2013;144:420-7.
416. Lim A, Stewart K, Konig K, George J. Systematic review of the safety of regular preventive asthma medications during pregnancy. *Ann Pharmacother* 2011;45:931-45.
417. Wendel PJ, Ramin SM, Barnett-Hamm C, Rowe TF, Cunningham FG. Asthma treatment in pregnancy: a randomized controlled study. *Am J Obstet Gynecol* 1996;175:150-4.
418. Schatz M, Leibman C. Inhaled corticosteroid use and outcomes in pregnancy. *Annals of Allergy, Asthma & Immunology* 2005;95:234-8.
419. Powell H, Murphy VE, Taylor DR, Hensley MJ, McCaffery K, Giles W, Clifton VL, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet* 2011;378:983-90.
420. Lim AS, Stewart K, Abramson MJ, Ryan K, George J. Asthma during pregnancy: the experiences, concerns and views of pregnant women with asthma. *J Asthma* 2012;49:474-9.
421. National Heart Lung and Blood Institute, National Asthma Education and Prevention Program Asthma and Pregnancy Working Group. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. *J Allergy Clin Immunol* 2005;115:34-46.
422. Lim AS, Stewart K, Abramson MJ, Walker SP, Smith CL, George J. Multidisciplinary Approach to Management of Maternal Asthma (MAMMA): a randomized controlled trial. *Chest* 2014;145:1046-54.
423. Nelson-Piercy C. Asthma in pregnancy. *Thorax* 2001;56:325-8.
424. Sanchez-Ramos JL, Pereira-Vega AR, Alvarado-Gomez F, Maldonado-Perez JA, Svanes C, Gomez-Real F. Risk factors for premenstrual asthma: a systematic review and meta-analysis. *Expert Rev Respir Med* 2017;11:57-72.
425. Reed CE. Asthma in the elderly: diagnosis and management. *J Allergy Clin Immunol* 2010;126:681-7.
426. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet* 2010;376:803-13.
427. Slavin RG, Haselkorn T, Lee JH, Zheng B, Deniz Y, Wenzel SE, Group TS. Asthma in older adults: observations from the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) study. *Ann Allergy Asthma Immunol* 2006;96:406-14.
428. Vincken W, Dekhuijzen PR, Barnes P, on behalf of the ADMIT Working Group. The ADMIT series - Issues in inhalation therapy. 4) How to choose inhaler devices for the treatment of COPD. *Prim Care Respir J* 2010;19:10-20.
429. Smetana GW, Lawrence VA, Cornell JE. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. *Ann Intern Med* 2006;144:581-95.
430. Woods BD, Sladen RN. Perioperative considerations for the patient with asthma and bronchospasm. *Br J Anaesth* 2009;103 Suppl 1:i57-65.
431. Wakim JH, Sledge KC. Anesthetic implications for patients receiving exogenous corticosteroids. *AANA Journal* 2006;74:133-9.
432. Stevenson DD. Diagnosis, prevention, and treatment of adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs. *J Allergy Clin Immunol* 1984;74:617-22.
433. Szczeklik A, Sanak M, Nizankowska-Mogilnicka E, Kielbasa B. Aspirin intolerance and the cyclooxygenase-leukotriene pathways. *Curr Opin Pulm Med* 2004;10:51-6.
434. Mascia K, Haselkorn T, Deniz YM, Miller DP, Bleeker ER, Borish L, Group TS. Aspirin sensitivity and severity of asthma: evidence for irreversible airway obstruction in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2005;116:970-5.
435. Morales DR, Guthrie B, Lipworth BJ, Jackson C, Donnan PT, Santiago VH. NSAID-exacerbated respiratory disease: a meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. *Allergy* 2015;70:828-35.
436. Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: A meta-analysis of the literature. *J Allergy Clin Immunol* 2015;135:676-81.e1.
437. Nizankowska E, Bestynska-Krypel A, Cmiel A, Szczeklik A. Oral and bronchial provocation tests with aspirin for diagnosis of aspirin-induced asthma. *Eur Respir J* 2000;15:863-9.
438. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis and management. *J Allergy Clin Immunol* 1999;104:5-13.

439. Milewski M, Mastalerz L, Nizankowska E, Szczechlik A. Nasal provocation test with lysine-aspirin for diagnosis of aspirin-sensitive asthma. *J Allergy Clin Immunol* 1998;101:581-6.
440. El Miedany Y, Youssef S, Ahmed I, El Gaafary M. Safety of etoricoxib, a specific cyclooxygenase-2 inhibitor, in asthmatic patients with aspirin-exacerbated respiratory disease. *Annals of Allergy, Asthma & Immunology* 2006;97:105-9.
441. Morales DR, Lipworth BJ, Guthrie B, Jackson C, Donnan PT, Santiago VH. Safety risks for patients with aspirin-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: Meta-analysis of controlled clinical trials. *J Allergy Clin Immunol* 2014;134:40-5.
442. Dahlen SE, Malmstrom K, Nizankowska E, Dahlen B, Kuna P, Kowalski M, Lumry WR, et al. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med* 2002;165:9-14.
443. Pleskow WW, Stevenson DD, Mathison DA, Simon RA, Schatz M, Zeiger RS. Aspirin desensitization in aspirin-sensitive asthmatic patients: clinical manifestations and characterization of the refractory period. *J Allergy Clin Immunol* 1982;69:11-9.
444. Swierczynska-Krepa M, Sanak M, Bochenek G, Strek P, Cmiel A, Gielicz A, Plutecka H, et al. Aspirin desensitization in patients with aspirin-induced and aspirin-tolerant asthma: a double-blind study. *J Allergy Clin Immunol* 2014;134:883-90.
445. Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, Moss R, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy* 2013;43:850-73.
446. Agarwal R, Sehgal IS, Dhooria S, Aggarwal AN. Developments in the diagnosis and treatment of allergic bronchopulmonary aspergillosis. *Expert Rev Respir Med* 2016;10:1317-34.
447. Agarwal R, Dhooria S, Singh Sehgal I, Aggarwal AN, Garg M, Saikia B, Behera D, et al. A Randomized Trial of Itraconazole vs Prednisolone in Acute-Stage Allergic Bronchopulmonary Aspergillosis Complicating Asthma. *Chest* 2018;153:656-64.
448. Voskamp AL, Gillman A, Symons K, Sandrini A, Rolland JM, O'Hehir RE, Douglass JA. Clinical efficacy and immunologic effects of omalizumab in allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract* 2015;3:192-9.
449. Hekking PP, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015;135:896-902.
450. Foster JM, McDonald VM, Guo M, Reddel Helen K. "I have lost in every facet of my life": the hidden burden of severe asthma. *Eur Respir J* 2017;50:1700765.
451. Waljee AK, Rogers MA, Lin P, Singal AG, Stein JD, Marks RM, Ayanian JZ, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ* 2017;357:j1415.
452. O'Neill S, Sweeney J, Patterson CC, Menzies-Gow A, Niven R, Mansur AH, Bucknall C, et al. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. *Thorax* 2015;70:376-8.
453. Sadatsafavi M, Lynd L, Marra C, Carleton B, Tan WC, Sullivan S, FitzGerald JM. Direct health care costs associated with asthma in British Columbia. *Can Respir J* 2010;17:74-80.
454. Hashimoto S, Bel EH. Current treatment of severe asthma. *Clin Exp Allergy* 2012;42:693-705.
455. Hancox RJ, Cowan JO, Flannery EM, Herbison GP, McLachlan CR, Taylor DR. Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled beta-agonist treatment. *Respir Med* 2000;94:767-71.
456. Stanford RH, Shah MB, D'Souza AO, Dhamane AD, Schatz M. Short-acting β-agonist use and its ability to predict future asthma-related outcomes. *Annals of Allergy, Asthma & Immunology* 2012;109:403-7.
457. Basheti IA, Armour CL, Bosnic-Anticevich SZ, Reddel HK. Evaluation of a novel educational strategy, including inhaler-based reminder labels, to improve asthma inhaler technique. *Patient Educ Couns* 2008;72:26-33.
458. Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. *N Engl J Med* 2017;377:965-76.
459. Clark VL, Gibson PG, Genn G, Hiles SA, Pavord ID, McDonald VM. Multidimensional assessment of severe asthma: A systematic review and meta-analysis. *Respirology* 2017;22:1262-75.
460. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med* 2009;180:817-22.

461. McNicholl DM, Stevenson M, McGarvey LP, Heaney LG. The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma. *Am J Respir Crit Care Med* 2012;186:1102-8.
462. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, Rosen KE, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med* 2011;154:573-82.
463. Brusselle G, Michils A, Louis R, Dupont L, Van de Maele B, Delobbe A, Pilette C, et al. "Real-life" effectiveness of omalizumab in patients with severe persistent allergic asthma: The PERSIST study. *Respir Med* 2009;103:1633-42.
464. Humbert M, Taille C, Mala L, Le Gros V, Just J, Molimard M. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. *Eur Respir J* 2018;51.
465. Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy DF, Lal P, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013;187:804-11.
466. Casale TB, Chipps BE, Rosen K, Trzaskoma B, Haselkorn T, Omachi TA, Greenberg S, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. *Allergy* 2018;73:490-7.
467. Busse WW. Are peripheral blood eosinophil counts a guideline for omalizumab treatment? STELLAIR says no! *Eur Respir J* 2018;51:1800730.
468. Gevaert P, Van Bruaene N, Catteart T, Van Steen K, Van Zele T, Acke F, De Ruyck N, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol* 2011;128:989-95.e8.
469. Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleeker ER, Brightling CE, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med* 2016;4:549-56.
470. Brusselle G, Germinaro M, Weiss S, Zangrilli J. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. *Pulm Pharmacol Ther* 2017;43:39-45.
471. FitzGerald JM, Bleeker ER, Menzies-Gow A, Zangrilli JG, Hirsch I, Metcalfe P, Newbold P, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med* 2018;6:51-64.
472. Simpson EL, Akinlade B, Ardeleanu M. Two Phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2017;376:1090-1.
473. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, Hellings P, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: A randomized clinical trial. *Jama* 2016;315:469-79.
474. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, Zhu H, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018;378:2475-85.
475. Hashimoto S, Brinke AT, Roldaan AC, van Veen IH, Moller GM, Sont JK, Weersink EJ, et al. Internet-based tapering of oral corticosteroids in severe asthma: a pragmatic randomised controlled trial. *Thorax* 2011;66:514-20.
476. Haldar P, Brightling CE, Singapuri A, Hargadon B, Gupta S, Monteiro W, Bradding P, et al. Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. *J Allergy Clin Immunol* 2014;133:921-3.
477. Ledford D, Busse W, Trzaskoma B, Omachi TA, Rosen K, Chipps BE, Luskin AT, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol* 2017;140:162-9.e2.
478. Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. Effect of outdoor air pollution on asthma exacerbations in children and adults: Systematic review and multilevel meta-analysis. *PLoS One* 2017;12:e0174050.
479. Ramnath VR, Clark S, Camargo CA, Jr. Multicenter study of clinical features of sudden-onset versus slower-onset asthma exacerbations requiring hospitalization. *Respir Care* 2007;52:1013-20.
480. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. *J Allergy Clin Immunol* 2010;125:1178-87.
481. Erbas B, Jazayeri M, Lambert KA, Katelaris CH, Prendergast LA, Tham R, Parrodi MJ, et al. Outdoor pollen is a trigger of child and adolescent asthma emergency department presentations: A systematic review and meta-analysis. *Allergy* 2018;73:1632-41.
482. Anto JM, Sunyer J, Reed CE, Sabria J, Martinez F, Morell F, Codina R, et al. Preventing asthma epidemics due to soybeans by dust-control measures. *N Engl J Med* 1993;329:1760-3.

483. Pike KC, Akhbari M, Kneale D, Harris KM. Interventions for autumn exacerbations of asthma in children. Cochrane Database Syst Rev 2018;3: Cd012393.
484. Williams LK, Peterson EL, Wells K, Ahmedani BK, Kumar R, Burchard EG, Chowdhry VK, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. J Allergy Clin Immunol 2011;128:1185-91.e2.
485. Andrew E, Nehme Z, Bernard S, Abramson MJ, Newbigin E, Piper B, Dunlop J, et al. Stormy weather: a retrospective analysis of demand for emergency medical services during epidemic thunderstorm asthma. BMJ 2017;359:j5636.
486. Alvarez GG, Schulzer M, Jung D, Fitzgerald JM. A systematic review of risk factors associated with near-fatal and fatal asthma. Can Respir J 2005;12:265-70.
487. Suissa S, Blais L, Ernst P. Patterns of increasing beta-agonist use and the risk of fatal or near-fatal asthma. Eur Respir J 1994;7:1602-9.
488. Roberts G, Patel N, Levi-Schaffer F, Habibi P, Lack G. Food allergy as a risk factor for life-threatening asthma in childhood: a case-controlled study. J Allergy Clin Immunol 2003;112:168-74.
489. Blaiss MS, Nathan RA, Stoloff SW, Meltzer EO, Murphy KR, Doherty DE. Patient and physician asthma deterioration terminology: results from the 2009 Asthma Insight and Management survey. Allergy Asthma Proc 2012;33:47-53.
490. Vincent SD, Toelle BG, Aroni RA, Jenkins CR, Reddel HK. "Exasperations" of asthma. A qualitative study of patient language about worsening asthma. Med J Aust 2006;184:451-4.
491. Fitzgerald JM, Grunfeld A. Status asthmaticus. In: Lichtenstein LM, Fauci AS, eds. Current therapy in allergy, immunology, and rheumatology. 5th edition. St. Louis, MO: Mosby; 1996:p. 63-7.
492. Chan-Yeung M, Chang JH, Manfreda J, Ferguson A, Becker A. Changes in peak flow, symptom score, and the use of medications during acute exacerbations of asthma. Am J Respir Crit Care Med 1996;154:889-93.
493. Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, Carlsheimer A. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respir Med 2007;101:2437-46.
494. Buhl R, Kuna P, Peters MJ, Andersson TL, Naya IP, Peterson S, Rabe KF. The effect of budesonide/formoterol maintenance and reliever therapy on the risk of severe asthma exacerbations following episodes of high reliever use: an exploratory analysis of two randomised, controlled studies with comparisons to standard therapy. Respir Res 2012;13:59.
495. Quon BS, Fitzgerald JM, Lemiere C, Shahidi N, Ducharme FM. Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. Cochrane Database Syst Rev 2010:CD007524.
496. Fitzgerald JM, Becker A, Sears MR, Mink S, Chung K, Lee J. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. Thorax 2004;59:550-6.
497. Harrison TW, Oborne J, Newton S, Tattersfield AE. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. Lancet 2004;363:271-5.
498. Reddel HK, Barnes DJ. Pharmacological strategies for self-management of asthma exacerbations. Eur Respir J 2006;28:182-99.
499. Ducharme FM, Lemire C, Noya FJ, Davis GM, Alos N, Leblond H, Savdie C, et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. N Engl J Med 2009;360:339-53.
500. Oborne J, Mortimer K, Hubbard RB, Tattersfield AE, Harrison TW. Quadrupling the dose of inhaled corticosteroid to prevent asthma exacerbations: a randomized, double-blind, placebo-controlled, parallel-group clinical trial. Am J Respir Crit Care Med 2009;180:598-602.
501. McKeever T, Mortimer K, Wilson A, Walker S, Brightling C, Skeggs A, Pavord I, et al. Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations. N Engl J Med 2018;378:902-10.
502. Jackson DJ, Bacharier LB, Mauger DT, Boehmer S, Beigelman A, Chmiel JF, Fitzpatrick AM, et al. Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations. N Engl J Med 2018;378:891-901.
503. Richards RN. Side effects of short-term oral corticosteroids. J Cutan Med Surg 2008;12:77-81.
504. Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev 2013.
505. Selroos O. Dry-powder inhalers in acute asthma. Ther Deliv 2014;5:69-81.

506. Newman KB, Milne S, Hamilton C, Hall K. A comparison of albuterol administered by metered-dose inhaler and spacer with albuterol by nebulizer in adults presenting to an urban emergency department with acute asthma. *Chest* 2002;121:1036-41.
507. Chien JW, Ciuffo R, Novak R, Skowronski M, Nelson J, Coreno A, McFadden ER, Jr. Uncontrolled oxygen administration and respiratory failure in acute asthma. *Chest* 2000;117:728-33.
508. Rodrigo GJ, Rodriguez Verde M, Peregalli V, Rodrigo C. Effects of short-term 28% and 100% oxygen on PaCO₂ and peak expiratory flow rate in acute asthma: a randomized trial. *Chest* 2003;124:1312-7.
509. Perrin K, Wijesinghe M, Healy B, Wadsworth K, Bowditch R, Bibby S, Baker T, et al. Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. *Thorax* 2011;66:937-41.
510. Hasegawa T, Ishihara K, Takakura S, Fujii H, Nishimura T, Okazaki M, Katakami N, et al. Duration of systemic corticosteroids in the treatment of asthma exacerbation: a randomized study. *Intern Med* 2000;39:794-7.
511. Jones AM, Munavvar M, Vail A, Aldridge RE, Hopkinson L, Rayner C, O'Driscoll BR. Prospective, placebo-controlled trial of 5 vs 10 days of oral prednisolone in acute adult asthma. *Respir Med* 2002;96:950-4.
512. Normansell R, Sayer B, Waterson S, Dennett EJ, Del Forno M, Dunleavy A. Antibiotics for exacerbations of asthma. *Cochrane Database Syst Rev* 2018;6:CD002741.
513. Leatherman J. Mechanical ventilation for severe asthma. *Chest* 2015;147:1671-80.
514. Shim CS, Williams MH, Jr. Evaluation of the severity of asthma: patients versus physicians. *Am J Med* 1980;68:11-3.
515. Atta JA, Nunes MP, Fonseca-Guedes CH, Avena LA, Borgiani MT, Fiorenza RF, Martins MA. Patient and physician evaluation of the severity of acute asthma exacerbations. *Braz J Med Biol Res* 2004;37:1321-30.
516. Geelhoed GC, Landau LI, Le Souef PN. Evaluation of SaO₂ as a predictor of outcome in 280 children presenting with acute asthma. *Ann Emerg Med* 1994;23:1236-41.
517. Nowak RM, Tomlanovich MC, Sarkar DD, Kvale PA, Anderson JA. Arterial blood gases and pulmonary function testing in acute bronchial asthma. Predicting patient outcomes. *JAMA* 1983;249:2043-6.
518. Carruthers DM, Harrison BD. Arterial blood gas analysis or oxygen saturation in the assessment of acute asthma? *Thorax* 1995;50:186-8.
519. White CS, Cole RP, Lubetsky HW, Austin JH. Acute asthma. Admission chest radiography in hospitalized adult patients. *Chest* 1991;100:14-6.
520. Roback MG, Dreitlein DA. Chest radiograph in the evaluation of first time wheezing episodes: review of current clinical practice and efficacy. *Pediatr Emerg Care* 1998;14:181-4.
521. Cates C, FitzGerald JM, O'Byrne PM. Asthma. *Clin Evidence* 2000;3:686-700.
522. Rodrigo GJ, Rodrigo C. Continuous vs intermittent beta-agonists in the treatment of acute adult asthma: a systematic review with meta-analysis. *Chest* 2002;122:160-5.
523. Camargo CA, Jr., Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. *Cochrane Database Syst Rev* 2003;CD001115.
524. Bradding P, Rushby I, Scullion J, Morgan MD. As-required versus regular nebulized salbutamol for the treatment of acute severe asthma. *Eur Respir J* 1999;13:290-4.
525. Travers AH, Milan SJ, Jones AP, Camargo CA, Jr., Rowe BH. Addition of intravenous beta(2)-agonists to inhaled beta(2)-agonists for acute asthma. *Cochrane Database Syst Rev* 2012;12:CD010179.
526. Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients. *Cochrane Database Syst Rev* 2000;2.
527. Rowe BH, Spooner CH, Ducharme FM, Bretzlaaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev* 2007;CD000195.
528. Edmonds ML, Milan SJ, Camargo CA, Jr., Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. *Cochrane Database Syst Rev* 2012;12:CD002308.
529. Ratto D, Alfaro C, Sipsey J, Glovsky MM, Sharma OP. Are intravenous corticosteroids required in status asthmaticus? *JAMA* 1988;260:527-9.
530. Harrison BD, Stokes TC, Hart GJ, Vaughan DA, Ali NJ, Robinson AA. Need for intravenous hydrocortisone in addition to oral prednisolone in patients admitted to hospital with severe asthma without ventilatory failure. *Lancet* 1986;1:181-4.

531. Gries DM, Moffitt DR, Pulos E, Carter ER. A single dose of intramuscularly administered dexamethasone acetate is as effective as oral prednisone to treat asthma exacerbations in young children. *J Pediatr* 2000;136:298-303.
532. Krishnan JA, Riekert KA, McCoy JV, Stewart DY, Schmidt S, Chanmugam A, Hill P, et al. Corticosteroid use after hospital discharge among high-risk adults with asthma. *Am J Respir Crit Care Med* 2004;170:1281-5.
533. Kirkland SW, Cross E, Campbell S, Villa-Roel C, Rowe BH. Intramuscular versus oral corticosteroids to reduce relapses following discharge from the emergency department for acute asthma. *Cochrane Database Syst Rev* 2018;6: Cd012629.
534. Kayani S, Shannon DC. Adverse behavioral effects of treatment for acute exacerbation of asthma in children: a comparison of two doses of oral steroids. *Chest* 2002;122:624-8.
535. Cronin JJ, McCoy S, Kennedy U, An Fhaili SN, Wakai A, Hayden J, Crispino G, et al. A Randomized Trial of Single-Dose Oral Dexamethasone Versus Multidose Prednisolone for Acute Exacerbations of Asthma in Children Who Attend the Emergency Department. *Ann Emerg Med* 2016;67:593-601.e3.
536. Keeney GE, Gray MP, Morrison AK, Levas MN, Kessler EA, Hill GD, Gorelick MH, et al. Dexamethasone for acute asthma exacerbations in children: a meta-analysis. *Pediatrics* 2014;133:493-9.
537. Kravitz J, Dominici P, Ufberg J, Fisher J, Giraldo P. Two days of dexamethasone versus 5 days of prednisone in the treatment of acute asthma: a randomized controlled trial. *Ann Emerg Med* 2011;58:200-4.
538. O'Driscoll BR, Kalra S, Wilson M, Pickering CA, Carroll KB, Woodcock AA. Double-blind trial of steroid tapering in acute asthma. *Lancet* 1993;341:324-7.
539. Lederle FA, Pluhar RE, Joseph AM, Niewoehner DE. Tapering of corticosteroid therapy following exacerbation of asthma. A randomized, double-blind, placebo-controlled trial. *Arch Intern Med* 1987;147:2201-3.
540. Edmonds ML, Milan SJ, Brenner BE, Camargo CA, Jr., Rowe BH. Inhaled steroids for acute asthma following emergency department discharge. *Cochrane Database Syst Rev* 2012;12:CD002316.
541. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax* 2005;60:740-6.
542. Griffiths B, Ducharme FM. Combined inhaled anticholinergics and short-acting beta₂-agonists for initial treatment of acute asthma in children. *Cochrane Database Syst Rev* 2013;8:CD000060.
543. Kirkland SW, Vandenberghe C, Voaklander B, Nikel T, Campbell S, Rowe BH. Combined inhaled beta-agonist and anticholinergic agents for emergency management in adults with asthma. *Cochrane Database Syst Rev* 2017;1: Cd001284.
544. Vezina K, Chauhan BF, Ducharme FM. Inhaled anticholinergics and short-acting beta(2)-agonists versus short-acting beta₂-agonists alone for children with acute asthma in hospital. *Cochrane Database Syst Rev* 2014;7: Cd010283.
545. Nair P, Milan SJ, Rowe BH. Addition of intravenous aminophylline to inhaled beta(2)-agonists in adults with acute asthma. *Cochrane Database Syst Rev* 2012;12: CD002742.
546. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo CA, Jr. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. *Cochrane Database Syst Rev* 2000;2.
547. FitzGerald JM. Magnesium sulfate is effective for severe acute asthma treated in the emergency department. *West J Med* 2000;172:96.
548. Gallegos-Solorzano MC, Perez-Padilla R, Hernandez-Zenteno RJ. Usefulness of inhaled magnesium sulfate in the coadjvant management of severe asthma crisis in an emergency department. *Pulm Pharmacol Ther* 2010;23:432-7.
549. Goodacre S, Cohen J, Bradburn M, Gray A, Benger J, Coats T. Intravenous or nebulised magnesium sulphate versus standard therapy for severe acute asthma (3Mg trial): a double-blind, randomised controlled trial. *Lancet Respir Med* 2013;1:293-300.
550. Griffiths B, Kew KM. Intravenous magnesium sulfate for treating children with acute asthma in the emergency department. *Cochrane Database Syst Rev* 2016;4: Cd011050.
551. Knightly R, Milan SJ, Hughes R, Knopp-Sihota JA, Rowe BH, Normansell R, Powell C. Inhaled magnesium sulfate in the treatment of acute asthma. *Cochrane Database Syst Rev* 2017;11: Cd003898.
552. Turker S, Dogru M, Yildiz F, Yilmaz SB. The effect of nebulised magnesium sulphate in the management of childhood moderate asthma exacerbations as adjuvant treatment. *Allergol Immunopathol (Madr)* 2017;45:115-20.
553. Rodrigo GJ, Castro-Rodriguez JA. Heliox-driven beta₂-agonists nebulization for children and adults with acute asthma: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2014;112:29-34.

554. Ramsay CF, Pearson D, Mildenhall S, Wilson AM. Oral montelukast in acute asthma exacerbations: a randomised, double-blind, placebo-controlled trial. *Thorax* 2011;66:7-11.
555. Watts K, Chavasse RJ. Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children. *Cochrane Database Syst Rev* 2012;5:Cd006100.
556. Balanag VM, Yunus F, Yang PC, Jorup C. Efficacy and safety of budesonide/formoterol compared with salbutamol in the treatment of acute asthma. *Pulm Pharmacol Ther* 2006;19:139-47.
557. Peters JI, Shelledy DC, Jones AP, Jr., Lawson RW, Davis CP, LeGrand TS. A randomized, placebo-controlled study to evaluate the role of salmeterol in the in-hospital management of asthma. *Chest* 2000;118:313-20.
558. Joseph KS, Blais L, Ernst P, Suissa S. Increased morbidity and mortality related to asthma among asthmatic patients who use major tranquillisers. *BMJ* 1996;312:79-82.
559. FitzGerald JM, Macklem P. Fatal asthma. *Annu Rev Med* 1996;47:161-8.
560. Lim WJ, Mohammed Akram R, Carson KV, Mysore S, Labiszewski NA, Wedzicha JA, Rowe BH, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. *Cochrane Database Syst Rev* 2012;12:CD004360.
561. Kelly A-M, Kerr D, Powell C. Is severity assessment after one hour of treatment better for predicting the need for admission in acute asthma? *Respir Med* 2004;98:777-81.
562. Wilson MM, Irwin RS, Connolly AE, Linden C, Manno MM. A prospective evaluation of the 1-hour decision point for admission versus discharge in acute asthma. *J Intensive Care Med* 2003;18:275-85.
563. Grunfeld A, FitzGerald J. Discharge considerations for adult asthmatic patients treated in emergency departments. *Can Respir J* 1996;3:322 - 7.
564. Pollack CV, Jr., Pollack ES, Baren JM, Smith SR, Woodruff PG, Clark S, Camargo CA, et al. A prospective multicenter study of patient factors associated with hospital admission from the emergency department among children with acute asthma. *Arch Pediatr Adolesc Med* 2002;156:934-40.
565. Rowe BH, Villa-Roel C, Abu-Laban RB, Stenstrom R, Mackey D, Stiell IG, Campbell S, et al. Admissions to Canadian hospitals for acute asthma: a prospective, multicentre study. *Can Respir J* 2010;17:25-30.
566. Weber EJ, Silverman RA, Callaham ML, Pollack CV, Woodruff PG, Clark S, Camargo CA, Jr. A prospective multicenter study of factors associated with hospital admission among adults with acute asthma. *Am J Med* 2002;113:371-8.
567. Cowie RL, Revitt SG, Underwood MF, Field SK. The effect of a peak flow-based action plan in the prevention of exacerbations of asthma. *Chest* 1997;112:1534-8.
568. Ducharme FM, Zemek RL, Chalut D, McGillivray D, Noya FJ, Resendes S, Khomenko L, et al. Written action plan in pediatric emergency room improves asthma prescribing, adherence, and control. *Am J Respir Crit Care Med* 2011;183:195-203.
569. Vonk JM, Jongepier H, Panhuisen CIM, Schouten JP, Bleeker ER, Postma DS. Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. *Thorax* 2003;58:322-7.
570. Lange P, Celli B, Agusti A, Boje Jensen G, Divo M, Faner R, Guerra S, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med* 2015;373:111-22.
571. Guerra S, Sherrill DL, Kurzius-Spencer M, Venker C, Halonen M, Quan SF, Martinez FD. The course of persistent airflow limitation in subjects with and without asthma. *Respir Med* 2008;102:1473-82.
572. Silva GE, Sherrill DL, Guerra S, Barbee RA. Asthma as a risk factor for COPD in a longitudinal study. *Chest* 2004;126:59-65.
573. van Schayck CP, Levy ML, Chen JC, Isonaka S, Halbert RJ. Coordinated diagnostic approach for adult obstructive lung disease in primary care. *Prim Care Respir J* 2004;13:218-21.
574. Zeki AA, Schivo M, Chan A, Albertson TE, Louie S. The asthma-COPD overlap syndrome: a common clinical problem in the elderly. *J Allergy* 2011;2011:861926.
575. Abramson MJ, Schattner RL, Sulaiman ND, Del Colle EA, Aroni R, Thien F. Accuracy of asthma and COPD diagnosis in Australian general practice: a mixed methods study. *Prim Care Respir J* 2012;21:167-73.
576. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax* 2009;64:728-35.

577. Mannino DM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. *Arch Intern Med* 2000;160:1683-9.
578. Marsh SE, Travers J, Weatherall M, Williams MV, Aldington S, Shirtcliffe PM, Hansell AL, et al. Proportional classifications of COPD phenotypes. *Thorax* 2008;63:761-7.
579. Shirtcliffe P, Marsh S, Travers J, Weatherall M, Beasley R. Childhood asthma and GOLD-defined chronic obstructive pulmonary disease. *Intern Med J* 2012;42:83-8.
580. Louie S, Zeki AA, Schivo M, Chan AL, Yoneda KY, Avdalovic M, Morrissey BM, et al. The asthma-chronic obstructive pulmonary disease overlap syndrome: pharmacotherapeutic considerations. *Expert Rev Clin Pharmacol* 2013;6:197-219.
581. Miravitlles M, Soler-Cataluna JJ, Calle M, Soriano JB. Treatment of COPD by clinical phenotypes: putting old evidence into clinical practice. *Eur Respir J* 2013;41:1252-6.
582. Soler-Cataluna JJ, Cosio B, Izquierdo JL, Lopez-Campos JL, Marin JM, Aguero R, Baloira A, et al. Consensus document on the overlap phenotype COPD-asthma in COPD. *Arch Bronconeumol* 2012;48:331-7.
583. Kauppi P, Kupiainen H, Lindqvist A, Tammilehto L, Kilpelainen M, Kinnula VL, Haahtela T, et al. Overlap syndrome of asthma and COPD predicts low quality of life. *J Asthma* 2011;48:279-85.
584. Andersen H, Lampela P, Nevanlinna A, Saynajakangas O, Keistinen T. High hospital burden in overlap syndrome of asthma and COPD. *Clin Respir J* 2013;7:342-6.
585. Weatherall M, Travers J, Shirtcliffe PM, Marsh SE, Williams MV, Nowitz MR, Aldington S, et al. Distinct clinical phenotypes of airways disease defined by cluster analysis. *Eur Respir J* 2009;34:812-8.
586. Inoue H, Nagase T, Morita S, Yoshida A, Jinnai T, Ichinose M. Prevalence and characteristics of asthma-COPD overlap syndrome identified by a stepwise approach. *Int J Chron Obstruct Pulmon Dis* 2017;12:1803-10.
587. McDonald VM, Simpson JL, Higgins I, Gibson PG. Multidimensional assessment of older people with asthma and COPD: clinical management and health status. *Age Ageing* 2011;40:42-9.
588. Soriano JB, Davis KJ, Coleman B, Visick G, Mannino D, Pride NB. The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. *Chest* 2003;124:474-81.
589. Carolan BJ, Sutherland ER. Clinical phenotypes of chronic obstructive pulmonary disease and asthma: recent advances. *J Allergy Clin Immunol* 2013;131:627-34.
590. Hardin M, Silverman EK, Barr RG, Hansel NN, Schroeder JD, Make BJ, Crapo JD, et al. The clinical features of the overlap between COPD and asthma. *Respir Res* 2011;12:127.
591. Wardlaw AJ, Silverman M, Siva R, Pavord ID, Green R. Multi-dimensional phenotyping: towards a new taxonomy for airway disease. *Clin Exp Allergy* 2005;35:1254-62.
592. Brightling CE, Monteiro W, Ward R, Parker D, Morgan MD, Wardlaw AJ, Pavord ID. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2000;356:1480-5.
593. Pizzichini E, Pizzichini MM, Gibson P, Parameswaran K, Gleich GJ, Berman L, Dolovich J, et al. Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. *Am J Respir Crit Care Med* 1998;158:1511-7.
594. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med* 2015;3:435-42.
595. Global Initiative for Asthma. Global strategy for asthma management and prevention. Updated 2018. Fontana, WI, USA: GINA; 2018.
596. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management and Prevention of COPD Fontana, WI, USA 2018.
597. Halbert RJ, Isonaka S. International Primary Care Respiratory Group (IPCRG) Guidelines: integrating diagnostic guidelines for managing chronic respiratory diseases in primary care. *Prim Care Respir J* 2006;15:13-9.
598. Price DB, Tinkelman DG, Halbert RJ, Nordyke RJ, Isonaka S, Nonikov D, Juniper EF, et al. Symptom-based questionnaire for identifying COPD in smokers. *Respiration* 2006;73:285-95.

599. Thiadens HA, de Bock GH, Dekker FW, Huysman JA, van Houwelingen JC, Springer MP, Postma DS. Identifying asthma and chronic obstructive pulmonary disease in patients with persistent cough presenting to general practitioners: descriptive study. *BMJ* 1998;316:1286-90.
600. Tinkelman DG, Price DB, Nordyke RJ, Halbert RJ, Isonaka S, Nonikov D, Juniper EF, et al. Symptom-based questionnaire for differentiating COPD and asthma. *Respiration* 2006;73:296-305.
601. Van Schayck CP, Loozen JM, Wagena E, Akkermans RP, Wesseling GJ. Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. *BMJ* 2002;324:1370.
602. Gershon AS, Campitelli MA, Croxford R, et al. Combination long-acting β -agonists and inhaled corticosteroids compared with long-acting β -agonists alone in older adults with chronic obstructive pulmonary disease. *JAMA* 2014;312:1114-21.
603. Travers J, Marsh S, Caldwell B, Williams M, Aldington S, Weatherall M, Shirtcliffe P, et al. External validity of randomized controlled trials in COPD. *Respir Med* 2007;101:1313-20.
604. Travers J, Marsh S, Williams M, Weatherall M, Caldwell B, Shirtcliffe P, Aldington S, et al. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? *Thorax* 2007;62:219-23.
605. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59:469-78.
606. Simpson CR, Sheikh A. Trends in the epidemiology of asthma in England: a national study of 333,294 patients. *J R Soc Med* 2010;103:98-106.
607. Bisgaard H, Szeffler S. Prevalence of asthma-like symptoms in young children. *Pediatr Pulmonol* 2007;42:723-8.
608. Kuehni CE, Strippoli MP, Low N, Brooke AM, Silverman M. Wheeze and asthma prevalence and related health-service use in white and south Asian pre-schoolchildren in the United Kingdom. *Clin Exp Allergy* 2007;37:1738-46.
609. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332:133-8.
610. Sly PD, Boner AL, Bjorksten B, Bush A, Custovic A, Eigenmann PA, Gern JE, et al. Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008;372:1100-6.
611. Heikkinen T, Jarvinen A. The common cold. *Lancet* 2003;361:51-9.
612. Caudri D, Wijga A, CM AS, Hoekstra M, Postma DS, Koppelman GH, Brunekreef B, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *J Allergy Clin Immunol* 2009;124:903-10 e1-7.
613. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, de Blic J, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008;32:1096-110.
614. Belgrave DCM, Simpson A, Semic-Jusufagic A, Murray CS, Buchan I, Pickles A, Custovic A. Joint modeling of parentally reported and physician-confirmed wheeze identifies children with persistent troublesome wheezing. *J Allergy Clin Immunol* 2013;132:575-83.e12.
615. Savenije OE, Kerkhof M, Koppelman GH, Postma DS. Predicting who will have asthma at school age among preschool children. *J Allergy Clin Immunol* 2012;130:325-31.
616. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, Strachan DP, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008;63:974-80.
617. Spycher BD, Silverman M, Brooke AM, Minder CE, Kuehni CE. Distinguishing phenotypes of childhood wheeze and cough using latent class analysis. *Eur Respir J* 2008;31:974-81.
618. Schultz A, Devadason SG, Savenije OE, Sly PD, Le Souef PN, Brand PL. The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. *Acta Paediatr* 2010;99:56-60.
619. Doherty G, Bush A. Diagnosing respiratory problems in young children. *Practitioner* 2007;251:20, 2-5.
620. Pedersen S. Preschool asthma--not so easy to diagnose. *Prim Care Respir J* 2007;16:4-6.
621. Brand PL, Caudri D, Eber E, Gaillard EA, Garcia-Marcos L, Hedlin G, Henderson J, et al. Classification and pharmacological treatment of preschool wheezing: changes since 2008. *Eur Respir J* 2014;43:1172-7.

622. Saglani S, McKenzie SA, Bush A, Payne DN. A video questionnaire identifies upper airway abnormalities in preschool children with reported wheeze. *Arch Dis Child* 2005;90:961-4.
623. Mellis C. Respiratory noises: how useful are they clinically? *Pediatr Clin North Am* 2009;56:1-17, ix.
624. Oren E, Rother J, Stern DA, Morgan WJ, Halonen M, Wright AL. Cough during infancy and subsequent childhood asthma. *Clin Exp Allergy* 2015;45:1439-46.
625. Azad MB, Chan-Yeung M, Chan ES, Dytnerki AM, Kozyrskyj AL, Ramsey C, Becker AB. Wheezing Patterns in Early Childhood and the Risk of Respiratory and Allergic Disease in Adolescence. *JAMA pediatrics* 2016;170:393-5.
626. Van Der Heijden HH, Brouwer ML, Hoekstra F, Van Der Pol P, Merkus PJ. Reference values of exhaled nitric oxide in healthy children 1-5 years using off-line tidal breathing. *Pediatr Pulmonol* 2014;49:291-5.
627. Singer F, Luchsinger I, Inci D, Knauer N, Latzin P, Wildhaber JH, Moeller A. Exhaled nitric oxide in symptomatic children at preschool age predicts later asthma. *Allergy* 2013;68:531-8.
628. Caudri D, Wijga AH, Hoekstra MO, Kerkhof M, Koppelman GH, Brunekreef B, Smit HA, et al. Prediction of asthma in symptomatic preschool children using exhaled nitric oxide, Rint and specific IgE. *Thorax* 2010;65:801-7.
629. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6.
630. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szeffler SJ, Bacharier LB, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985-97.
631. Chang TS, Lemanske RF, Jr., Guilbert TW, Gern JE, Coen MH, Evans MD, Gangnon RE, et al. Evaluation of the modified asthma predictive index in high-risk preschool children. *J Allergy Clin Immunol Pract* 2013;1.
632. Murray CS, Poletti G, Kebadze T, Morris J, Woodcock A, Johnston SL, Custovic A. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006;61:376-82.
633. Bisgaard H, Allen D, Milanowski J, Kalev I, Willits L, Davies P. Twelve-month safety and efficacy of inhaled fluticasone propionate in children aged 1 to 3 years with recurrent wheezing. *Pediatrics* 2004;113:e87-94.
634. Fitzpatrick AM, Jackson DJ, Mauger DT, Boehmer SJ, Phipatanakul W, Sheehan WJ, Moy JN, et al. Individualized therapy for persistent asthma in young children. *J Allergy Clin Immunol* 2016;138:1608-18.e12.
635. Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, Raissy HH, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012;367:904-12.
636. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;354:1998-2005.
637. Wilson NM, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. *Arch Dis Child* 1990;65:407-10.
638. Nielsen KG, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2- to 5-year-old asthmatic children. *Am J Respir Crit Care Med* 2000;162:1500-6.
639. Szeffler SJ, Baker JW, Uryniak T, Goldman M, Silkoff PE. Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. *J Allergy Clin Immunol* 2007;120:1043-50.
640. Kaiser SV, Huynh T, Bacharier LB, Rosenthal JL, Bakel LA, Parkin PC, Cabana MD. Preventing Exacerbations in Preschoolers With Recurrent Wheeze: A Meta-analysis. *Pediatrics* 2016;137.
641. Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N, Michele TM, et al. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics* 2001;108:E48.
642. Brodlie M, Gupta A, Rodriguez-Martinez CE, Castro-Rodriguez JA, Ducharme FM, McKean MC. Leukotriene receptor antagonists as maintenance and intermittent therapy for episodic viral wheeze in children. *Cochrane Database Syst Rev* 2015;Cd008202.
643. Papi A, Nicolini G, Baraldi E, Boner AL, Cutrera R, Rossi GA, Fabbri LM. Regular vs prn nebulized treatment in wheeze preschool children. *Allergy* 2009;64:1463-71.
644. Zeiger RS, Mauger D, Bacharier LB, Guilbert TW, Martinez FD, Lemanske RF, Jr., Strunk RC, et al. Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med* 2011;365:1990-2001.
645. Piippo-Savolainen E, Remes S, Kannisto S, Korhonen K, Korppi M. Asthma and lung function 20 years after wheezing in infancy: results from a prospective follow-up study. *Arch Pediatr Adolesc Med* 2004;158:1070-6.

646. Wennergren G, Hansson S, Engstrom I, Jodal U, Amark M, Brolin I, Juto P. Characteristics and prognosis of hospital-treated obstructive bronchitis in children aged less than two years. *Acta Paediatr* 1992;81:40-5.
647. Goksor E, Amark M, Alm B, Gustafsson PM, Wennergren G. Asthma symptoms in early childhood--what happens then? *Acta Paediatr* 2006;95:471-8.
648. Castro-Rodriguez JA, Rodrigo GJ. Beta-agonists through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: a systematic review with meta-analysis. *J Pediatr* 2004;145:172-7.
649. Zemek RL, Bhogal SK, Ducharme FM. Systematic review of randomized controlled trials examining written action plans in children: what is the plan? *Arch Pediatr Adolesc Med* 2008;162:157-63.
650. Swern AS, Tozzi CA, Knorr B, Bisgaard H. Predicting an asthma exacerbation in children 2 to 5 years of age. *Ann Allergy Asthma Immunol* 2008;101:626-30.
651. Brunette MG, Lands L, Thibodeau LP. Childhood asthma: prevention of attacks with short-term corticosteroid treatment of upper respiratory tract infection. *Pediatrics* 1988;81:624-9.
652. Fox GF, Marsh MJ, Milner AD. Treatment of recurrent acute wheezing episodes in infancy with oral salbutamol and prednisolone. *Eur J Pediatr* 1996;155:512-6.
653. Grant CC, Duggan AK, DeAngelis C. Independent parental administration of prednisone in acute asthma: a double-blind, placebo-controlled, crossover study. *Pediatrics* 1995;96:224-9.
654. Oommen A, Lambert PC, Grigg J. Efficacy of a short course of parent-initiated oral prednisolone for viral wheeze in children aged 1-5 years: randomised controlled trial. *Lancet* 2003;362:1433-8.
655. Vuillermin P, South M, Robertson C. Parent-initiated oral corticosteroid therapy for intermittent wheezing illnesses in children. *Cochrane Database Syst Rev* 2006;CD005311.
656. Robertson CF, Price D, Henry R, Mellis C, Glasgow N, Fitzgerald D, Lee AJ, et al. Short-course montelukast for intermittent asthma in children: a randomized controlled trial. *Am J Respir Crit Care Med* 2007;175:323-9.
657. Bacharier LB, Phillips BR, Zeiger RS, Szeffler SJ, Martinez FD, Lemanske RF, Jr., Sorkness CA, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008;122:1127-35 e8.
658. Gouin S, Robidas I, Gravel J, Guimont C, Chalut D, Amre D. Prospective evaluation of two clinical scores for acute asthma in children 18 months to 7 years of age. *Acad Emerg Med* 2010;17:598-603.
659. Pollock M, Sinha IP, Hartling L, Rowe BH, Schreiber S, Fernandes RM. Inhaled short-acting bronchodilators for managing emergency childhood asthma: an overview of reviews. *Allergy* 2017;72:183-200.
660. Powell C, Kolamunnage-Dona R, Lowe J, Boland A, Petrou S, Doull I, Hood K, et al. Magnesium sulphate in acute severe asthma in children (MAGNETIC): a randomised, placebo-controlled trial. *Lancet Respir Med* 2013;1:301-8.
661. Pruukkonen H, Tapiainen T, Kallio M, Dunder T, Pokka T, Uhari M, Renko M. Intravenous magnesium sulfate for acute wheezing in young children: a randomised double-blind trial. *Eur Respir J* 2018;51.
662. Fuglsang G, Pedersen S, Borgstrom L. Dose-response relationships of intravenously administered terbutaline in children with asthma. *J Pediatr* 1989;114:315-20.
663. Connett G, Lenney W. Prevention of viral induced asthma attacks using inhaled budesonide. *Arch Dis Child* 1993;68:85-7.
664. Svedmyr J, Nyberg E, Thunqvist P, Asbrink-Nilsson E, Hedlin G. Prophylactic intermittent treatment with inhaled corticosteroids of asthma exacerbations due to airway infections in toddlers. *Acta Paediatr* 1999;88:42-7.
665. Razi CH, Akelma AZ, Harmanci K, Kocak M, Kuras Can Y. The addition of inhaled budesonide to standard therapy shortens the length of stay in hospital for asthmatic preschool children: A randomized, double-blind, placebo-controlled trial. *Int Arch Allergy Immunol* 2015;166:297-303.
666. Garrett J, Williams S, Wong C, Holdaway D. Treatment of acute asthmatic exacerbations with an increased dose of inhaled steroid. *Arch Dis Child* 1998;79:12-7.
667. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev* 2001;CD002178.
668. Panickar J, Lakhapaul M, Lambert PC, Kenia P, Stephenson T, Smyth A, Grigg J. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009;360:329-38.

669. Webb MS, Henry RL, Milner AD. Oral corticosteroids for wheezing attacks under 18 months. *Arch Dis Child* 1986;61:15-9.
670. Castro-Rodriguez JA, Beckhaus AA, Forno E. Efficacy of oral corticosteroids in the treatment of acute wheezing episodes in asthmatic preschoolers: Systematic review with meta-analysis. *Pediatr Pulmonol* 2016;51:868-76.
671. Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, Workman L, Sordillo JE, Camargo CA, Jr., Gillman MW, et al. Peanut, milk, and wheat intake during pregnancy is associated with reduced allergy and asthma in children. *J Allergy Clin Immunol* 2014;133:1373-82.
672. Maslova E, Granstrom C, Hansen S, Petersen SB, Strom M, Willett WC, Olsen SF. Peanut and tree nut consumption during pregnancy and allergic disease in children—should mothers decrease their intake? Longitudinal evidence from the Danish National Birth Cohort. *J Allergy Clin Immunol* 2012;130:724-32.
673. Maslova E, Strom M, Oken E, Campos H, Lange C, Gold D, Olsen SF. Fish intake during pregnancy and the risk of child asthma and allergic rhinitis - longitudinal evidence from the Danish National Birth Cohort. *Br J Nutr* 2013;110:1313-25.
674. Best KP, Gold M, Kennedy D, Martin J, Makrides M. Omega-3 long-chain PUFA intake during pregnancy and allergic disease outcomes in the offspring: a systematic review and meta-analysis of observational studies and randomized controlled trials. *Am J Clin Nutr* 2016;103:128-43.
675. Best KP, Sullivan T, Palmer D, Gold M, Kennedy DJ, Martin J, Makrides M. Prenatal Fish Oil Supplementation and Allergy: 6-Year Follow-up of a Randomized Controlled Trial. *Pediatrics* 2016;137.
676. Hansen S, Strom M, Maslova E, Dahl R, Hoffmann HJ, Rytter D, Bech BH, et al. Fish oil supplementation during pregnancy and allergic respiratory disease in the adult offspring. *J Allergy Clin Immunol* 2017;139:104-11.e4.
677. Best KP, Sullivan TR, Palmer DJ, Gold M, Martin J, Kennedy D, Makrides M. Prenatal omega-3 LCPUFA and symptoms of allergic disease and sensitization throughout early childhood - a longitudinal analysis of long-term follow-up of a randomized controlled trial. *The World Allergy Organization journal* 2018;11:10.
678. Forno E, Young OM, Kumar R, Simhan H, Celedon JC. Maternal obesity in pregnancy, gestational weight gain, and risk of childhood asthma. *Pediatrics* 2014;134:e535-46.
679. Chan-Yeung M, Becker A. Primary prevention of childhood asthma and allergic disorders. *Curr Opin Allergy Clin Immunol* 2006;6:146-51.
680. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. *J Allergy Clin Immunol* 2011;127:724-33.e1-30.
681. Chawes BL, Bonnelykke K, Stokholm J, Vissing NH, Bjarnadottir E, Schoos AM, Wolsk HM, et al. Effect of vitamin D3 supplementation during pregnancy on risk of persistent wheeze in the offspring: A randomized clinical trial. *Jama* 2016;315:353-61.
682. Litonjua AA, Carey VJ, Laranjo N, Harshfield BJ, McElrath TF, O'Connor GT, Sandel M, et al. Effect of prenatal supplementation with Vitamin D on asthma or recurrent wheezing in offspring by age 3 years: The VDAART randomized clinical trial. *Jama* 2016;315:362-70.
683. Wolsk HM, Harshfield BJ, Laranjo N, Carey VJ, O'Connor G, Sandel M, Strunk RC, et al. Vitamin D supplementation in pregnancy, prenatal 25(OH)D levels, race, and subsequent asthma or recurrent wheeze in offspring: Secondary analyses from the Vitamin D Antenatal Asthma Reduction Trial. *J Allergy Clin Immunol* 2017;140:1423-9.e5.
684. Stratakis N, Roumeliotaki T, Oken E, Ballester F, Barros H, Basterrechea M, Cordier S, et al. Fish and seafood consumption during pregnancy and the risk of asthma and allergic rhinitis in childhood: a pooled analysis of 18 European and US birth cohorts. *Int J Epidemiol* 2017;46:1465-77.
685. Bisgaard H, Stokholm J, Chawes BL, Vissing NH, Bjarnadottir E, Schoos AM, Wolsk HM, et al. Fish Oil-Derived Fatty Acids in Pregnancy and Wheeze and Asthma in Offspring. *N Engl J Med* 2016;375:2530-9.
686. Azad MB, Coneys JG, Kozyrskyj AL, Field CJ, Ramsey CD, Becker AB, Friesen C, et al. Probiotic supplementation during pregnancy or infancy for the prevention of asthma and wheeze: systematic review and meta-analysis. *BMJ* 2013;347:f6471.
687. Celedon JC, Milton DK, Ramsey CD, Litonjua AA, Ryan L, Platts-Mills TAE, Gold DR. Exposure to dust mite allergen and endotoxin in early life and asthma and atopy in childhood. *J Allergy Clin Immunol* 2007;120:144-9.
688. Lodge CJ, Lowe AJ, Gurrin LC, Hill DJ, Hosking CS, Khalafzai RU, Hopper JL, et al. House dust mite sensitization in toddlers predicts current wheeze at age 12 years. *J Allergy Clin Immunol* 2011;128:782-8.e9.

689. Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A, NAC Manchester Asthma Study Group. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomised trial. *Lancet* 2001;358:188-93.
690. Perzanowski MS, Chew GL, Divjan A, Johnson A, Goldstein IF, Garfinkel RS, Hoepner LA, et al. Cat ownership is a risk factor for the development of anti-cat IgE but not current wheeze at age 5 years in an inner-city cohort. *J Allergy Clin Immunol* 2008;121:1047-52.
691. Melen E, Wickman M, Nordvall SL, van Hage-Hamsten M, Lindfors A. Influence of early and current environmental exposure factors on sensitization and outcome of asthma in pre-school children. *Allergy* 2001;56:646-52.
692. Takkouche B, Gonzalez-Barcala FJ, Etminan M, Fitzgerald M. Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis. *Allergy* 2008;63:857-64.
693. Bufford JD, Gern JE. Early exposure to pets: good or bad? *Current Allergy & Asthma Reports* 2007;7:375-82.
694. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. *JAMA* 2002;288:963-72.
695. Lodrup Carlsen KC, Roll S, Carlsen KH, Mowinkel P, Wijga AH, Brunekreef B, Torrent M, et al. Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts. *PLoS One* 2012;7:e43214.
696. Quansah R, Jaakkola MS, Hugg TT, Heikkinen SA, Jaakkola JJ. Residential dampness and molds and the risk of developing asthma: a systematic review and meta-analysis. *PLoS ONE [Electronic Resource]* 2012;7:e47526.
697. Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. *Thorax* 2003;58:489-93.
698. Becker A, Watson W, Ferguson A, Dimich-Ward H, Chan-Yeung M. The Canadian asthma primary prevention study: outcomes at 2 years of age. *J Allergy Clin Immunol* 2004;113:650-6.
699. Schonberger HJAM, Dompeling E, Knottnerus JA, Maas T, Muris JWM, van Weel C, van Schayck CP. The PREVASC study: the clinical effect of a multifaceted educational intervention to prevent childhood asthma. *Eur Respir J* 2005;25:660-70.
700. van Schayck OCP, Maas T, Kaper J, Knottnerus AJA, Sheikh A. Is there any role for allergen avoidance in the primary prevention of childhood asthma? *J Allergy Clin Immunol* 2007;119:1323-8.
701. Chan-Yeung M, Ferguson A, Watson W, Dimich-Ward H, Rousseau R, Lilley M, Dybuncio A, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005;116:49-55.
702. Scott M, Roberts G, Kurukulaaratchy RJ, Matthews S, Nove A, Arshad SH. Multifaceted allergen avoidance during infancy reduces asthma during childhood with the effect persisting until age 18 years. *Thorax* 2012;67:1046-51.
703. Valovirta E, Petersen TH, Piotrowska T, Laursen MK, Andersen JS, Sorensen HF, Klink R. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. *J Allergy Clin Immunol* 2018;141:529-38.e13.
704. Wongtrakool C, Wang N, Hyde DM, Roman J, Spindel ER. Prenatal nicotine exposure alters lung function and airway geometry through α 7 nicotinic receptors. *Am J Respir Cell Mol Biol* 2012;46:695-702.
705. Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, Britton JR, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics* 2012;129:735-44.
706. Bowatte G, Lodge C, Lowe AJ, Erbas B, Perret J, Abramson MJ, Matheson M, et al. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. *Allergy* 2015;70:245-56.
707. Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Nieuwenhuijsen M. Exposure to traffic-related air pollution and risk of development of childhood asthma: A systematic review and meta-analysis. *Environ Int* 2017;100:1-31.
708. Hehua Z, Qing C, Shanyan G, Qijun W, Yuhong Z. The impact of prenatal exposure to air pollution on childhood wheezing and asthma: A systematic review. *Environ Res* 2017;159:519-30.
709. Haahtela T, Holgate S, Pawankar R, Akdis CA, Benjaponpitak S, Caraballo L, Demain J, et al. The biodiversity hypothesis and allergic disease: world allergy organization position statement. *World Allergy Org J* 2013;6:3.
710. Riedler J, Braun-Fahrlander C, Eder W, Schreuer M, Waser M, Maisch S, Carr D, et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 2001;358:1129-33.

711. Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, Maisch S, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002;347:869-77.
712. Karvonen AM, Hyvarinen A, Gehring U, Korppi M, Doeke G, Riedler J, Braun-Fahrlander C, et al. Exposure to microbial agents in house dust and wheezing, atopic dermatitis and atopic sensitization in early childhood: a birth cohort study in rural areas. *Clin Exp Allergy* 2012;42:1246-56.
713. Huang L, Chen Q, Zhao Y, Wang W, Fang F, Bao Y. Is elective cesarean section associated with a higher risk of asthma? A meta-analysis. *J Asthma* 2015;52:16-25.
714. Keag OE, Norman JE, Stock SJ. Long-term risks and benefits associated with cesarean delivery for mother, baby, and subsequent pregnancies: Systematic review and meta-analysis. *PLoS Med* 2018;15:e1002494.
715. Azad MB, Konya T, Maughan H, Guttman DS, Field CJ, Chari RS, Sears MR, et al. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. *CMAJ* 2013;185:385-94.
716. Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen JLL, Bont L, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med* 2013;368:1791-9.
717. Scheltema NM, Nibbelke EE, Pouw J, Blanken MO, Rovers MM, Naaktgeboren CA, Mazur NI, et al. Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. *Lancet Respir Med* 2018;6:257-64.
718. Kozyrskyj AL, Mai XM, McGrath P, Hayglass KT, Becker AB, Macneil B. Continued exposure to maternal distress in early life is associated with an increased risk of childhood asthma. *Am J Respir Crit Care Med* 2008;177:142-7.
719. Marra F, Marra CA, Richardson K, Lynd LD, Kozyrskyj A, Patrick DM, Bowie WR, et al. Antibiotic use in children is associated with increased risk of asthma. *Pediatrics* 2009;123:1003-10.
720. Stensballe LG, Simonsen J, Jensen SM, Bonnelykke K, Bisgaard H. Use of antibiotics during pregnancy increases the risk of asthma in early childhood. *J Pediatr* 2013;162:832-8.e3.
721. Celedon JC, Fuhlbrigge A, Rifas-Shiman S, Weiss ST, Finkelstein JA. Antibiotic use in the first year of life and asthma in early childhood. *Clin Exp Allergy* 2004;34:1011-6.
722. Cheebo M, Lodge CJ, Dharmage SC, Simpson JA, Matheson M, Heinrich J, Lowe AJ. Paracetamol exposure in pregnancy and early childhood and development of childhood asthma: a systematic review and meta-analysis. *Arch Dis Child* 2015;100:81-9.
723. Eyers S, Weatherall M, Jefferies S, Beasley R. Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. *Clin Exp Allergy* 2011;41:482-9.
724. Flanigan C, Sheikh A, DunnGalvin A, Brew BK, Almqvist C, Nwaru BI. Prenatal maternal psychosocial stress and offspring's asthma and allergic disease: A systematic review and meta-analysis. *Clin Exp Allergy* 2018;48:403-14.
725. Beasley R, Semprini A, Mitchell EA. Risk factors for asthma: is prevention possible? *Lancet* 2015;386:1075-85.
726. Burgers J, Eccles M. Clinical guidelines as a tool for implementing change in patient care. Oxford: Butterworth-Heinemann; 2005.
727. Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. *BMJ* 1999;318:527-30.
728. ADAPTE Framework. Available from <http://www.adapte.org>. 2012.
729. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, Fervers B, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010;182:E839-42.
730. Boulet LP, FitzGerald JM, Levy ML, Cruz AA, Pedersen S, Haahela T, Bateman ED. A guide to the translation of the Global Initiative for Asthma (GINA) strategy into improved care. *Eur Respir J* 2012;39:1220-9.
731. Davis DA, Taylor-Vaisey A. Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. *CMAJ* 1997;157:408-16.
732. Harrison MB, Legare F, Graham ID, Fervers B. Adapting clinical practice guidelines to local context and assessing barriers to their use. *CMAJ* 2010;182:E78-84.
733. Partridge MR. Translating research into practice: how are guidelines implemented? *Eur Respir J Suppl* 2003;39:23s-9s.
734. Baiardini I, Braido F, Bonini M, Compalati E, Canonica GW. Why do doctors and patients not follow guidelines? *Curr Opin Allergy Clin Immunol* 2009;9:228-33.

735. Boulet LP, Becker A, Bowie D, Hernandez P, McIvor A, Rouleau M, Bourbeau J, et al. Implementing practice guidelines: a workshop on guidelines dissemination and implementation with a focus on asthma and COPD. *Can Respir J* 2006;13 Suppl A:5-47.
736. Franco R, Santos AC, do Nascimento HF, Souza-Machado C, Ponte E, Souza-Machado A, Loureiro S, et al. Cost-effectiveness analysis of a state funded programme for control of severe asthma. *BMC Public Health* 2007;7:82.
737. Renzi PM, Ghezzo H, Goulet S, Dorval E, Thivierge RL. Paper stamp checklist tool enhances asthma guidelines knowledge and implementation by primary care physicians. *Can Respir J* 2006;13:193-7.
738. Nkoy F, Fassl B, Stone B, Uchida DA, Johnson J, Reynolds C, Valentine K, et al. Improving pediatric asthma care and outcomes across multiple hospitals. *Pediatrics* 2015;136:e1602-10.
739. Cochrane Effective Practice and Organisation of Care Group (EPOC). Available at <http://epoc.cochrane.org>. 2013.

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE

COPYRIGHTED MATERIAL-DO NOT COPY OR DISTRIBUTE

Visit the GINA website at www.ginasthma.org
© 2019 Global Initiative for Asthma