2025

Global Strategy for Asthma Management and Prevention

Updated 2025

Global Strategy for Asthma Management and Prevention (2025 update)

The reader acknowledges that this report is intended as an evidence-based asthma management strategy, for the use of healthcare providers 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 and national regulations and guidelines. GINA cannot be held liable or responsible for inappropriate health care associated with the use of this document, including any use which is not in accordance with applicable local or national regulations or guidelines.

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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 healthcare systems, and on society through loss of productivity in the workplace and, especially for pediatric asthma, disruption to the family.

The Global Initiative for Asthma has been working with healthcare providers, researchers, patients and public health officials around the world since 1993 to reduce asthma prevalence, morbidity and mortality. The Global Strategy for Asthma Management and Prevention (GINA Strategy Report) was first published in 1995, and has been updated annually since 2002 by the GINA Science Committee. It contains guidance for primary care practitioners, specialists and allied health professionals, based on the latest high-quality evidence available. More resources and supporting material are provided online at www.ginasthma.org.

GINA supports global efforts to achieve environmental sustainability in health care, while ensuring that our guidance reflects an optimal balance between clinical and environmental priorities, with a particular focus on patient safety. GINA also supports efforts to ensure global availability of, and access to, effective quality-assured medications, to reduce the burden of asthma mortality and morbidity. Since 2001, GINA has organized the annual World Asthma Day, a focus for local and national activities to raise awareness of asthma and educate families and healthcare providers about effective asthma care.

GINA is an independent organization funded solely through sale and licensing of its educational publications. Members of the GINA Board of Directors are drawn globally from leaders with an outstanding demonstrated commitment to asthma research, asthma clinical management, public health and patient advocacy. GINA Science Committee members are highly experienced asthma experts from around the world, who continually review and synthesize scientific evidence to provide guidance on asthma prevention, diagnosis and management. The GINA Dissemination Task Group is responsible for promoting GINA resources throughout the world. Members work with an international network of patient representatives and leaders in asthma care (GINA Advocates), to implement asthma education programs and support evidence-based care. GINA support staff comprise the Executive Director and Program Manager.

We acknowledge the superlative work of all who have contributed to the success of the GINA program. In particular, we recognize the outstanding long-term dedication of founding Scientific Director Dr Suzanne Hurd and the late Dr Claude Lenfant, founding Executive Director of GINA, in fostering GINA's development until their retirement in 2015. We mourn the loss of Professor Eric Bateman, who passed away in January 2025. Eric was a founding member of the GINA Science Committee, Chair of the Science Committee from 2004 to 2007, and Chair of the GINA Board from 2008 to 2011. While leading innovations in health care at the highest level, Eric also constantly reminded us of the burden and limited resources for people with respiratory diseases in low-middle-income countries. A tribute to Professor Bateman is available on the European Respiratory Society website. We acknowledge the invaluable commitment and skills of our current Executive Director Rebecca Decker, and Program Manager Kristi Rurey. We also thank all members of the Science Committee, who receive no honoraria or reimbursement for their many hours of work reviewing evidence and attending meetings, and the GINA Dissemination Working Group and GINA Advocates.

We hope you find this report to be a useful resource in the management of asthma and that it will help you work with each of your patients to provide the best personalized care,

Helen K Reddel, MBBS PhD

Chair, GINA Science Committee

Arzu Yorgancıoğlu, MD

Chair, GINA Board of Directors

Members of GINA committees (2024–2025)

GINA Science Committee

Helen K. Reddel, MBBS PhD (Chair)
Woolcock Institute of Medical Research
and Macquarie Medical School,
Macquarie University
Sydney, Australia

Leonard B. Bacharier, MD
Vanderbilt University Medical Center
Nashville, TN, USA

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

Matteo Bonini MD, PhD
Department of Public Health and Infectious Diseases,
Sapienza University of Rome, Italy
National Heart and Lung Institute (NHLI)
Imperial College London, UK

Arnaud Bourdin, MD, PhD
Department of Respiratory Diseases
University of Montpellier
Montpellier, France

Christopher Brightling, FMedSci, PhD
Leicester NIHR Biomedical Research Centre,
University of Leicester
Leicester, UK

Guy Brusselle, MD, PhD
Department of Respiratory Medicine
Ghent University Hospital
Ghent, Belgium
Departments of Epidemiology and Respiratory
Medicine, Erasmus Medical Centre Rotterdam
Rotterdam, The Netherlands

Roland Buhl, MD PhD
Mainz University Hospital
Mainz, Germany

Jeffrey M. Drazen, MD
Harvard Medical School
Boston, MA, USA

Francine M. Ducharme, MD
Departments of Pediatrics and of
Social and Preventive Medicine,
Sainte-Justine University Health Centre,
University of Montreal
Montreal, Quebec, Canada

Liesbeth Duijts, MD MSc PhD
Department of Pediatrics, Erasmus MC,
University Medical Center
Rotterdam, The Netherlands

Louise Fleming, MBChB MD
Imperial College Healthcare NHS Trust
Imperial College, London
London, United Kingdom

Hiromasa Inoue, MD
Kagoshima University
Kagoshima, Japan

Alan Kaplan, MD
Family Physician Airways Group of Canada
Markham, Ontario, Canada

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

Refiloe Masekela MBBCh, PhD
Department of Paediatrics and
Child Health, University of KwaZulu Natal
Durban, South Africa

Paulo Pitrez, MD, PhD
Hospital Santa Casa de Porto Alegre
Universidade Federal de Ciências da Saúde de Porto
Alegre (UFCSPA)
Porto Alegre, Brazil

Sundeep Salvi MD, PhD
Pulmocare Research and Education (PURE)
Foundation
Symbiosis International University,
Pune, India

Aziz Sheikh, BSc, MBBS, MSc, MD
University of Oxford
Oxford, United Kingdom

Min Zhang, MD
Department of Respiratory and Critical Care Medicine
Shanghai General Hospital
Shanghai Jiao Tong University School of Medicine
Shanghai, China

†Deceased January 2025

GINA Board of Directors

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

Keith Allan, CBiol, MRSB
Patient Partner
University Hospitals of Leicester
Leicester, UK

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

Guy Brusselle, MD, PhD
Department of Respiratory Medicine
Ghent University Hospital
Ghent, Belgium
Departments of Epidemiology and Respiratory Medicine, Erasmus Medical Centre Rotterdam
Rotterdam, The Netherlands

Muhwa Jeremiah Chakaya, MD
Research and Public Health Unit,
Respiratory Society of Kenya
Kenyatta University
Nairobi, Kenya

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

Hiromasa Inoue, MD
Kagoshima University
Kagoshima, Japan

Jerry A. Krishnan, MD PhD
Breathe Chicago Center
University of Illinois Chicago
Chicago, IL, USA

Mark L. Levy, MD
Locum GP
London, UK

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

†Deceased January 2025

GINA Dissemination Group

Mark L. Levy, MD (Chair)
Locum GP
London, UK

Keith Allan, CBiol, MRSB
Patient Partner
University Hospitals of Leicester
Leicester, UK

Hiromasa Inoue, MD
Kagoshima University
Kagoshima, Japan

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

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

Disclosures for members of GINA committees can be found at www.ginasthma.org

GINA Program

Rebecca Decker, BS, MSJ

Kristi Rurey, AS

Editorial assistance

Charu Grover, PhD

Jenni Harman, BVSc, BA

Graphics assistance

Kate Chisnall

Information design for severe asthma decision tree

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

Abbreviations

ABPA	Allergic bronchopulmonary aspergillosis
ACE	Angiotensin-converting enzyme
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test (see also cACT)
AERD	Aspirin-exacerbated respiratory disease
AIR	Anti-inflammatory reliever (see Box 4-1, p.70)
ANCA	Antineutrophil cytoplasmic antibody
Anti-IL4Rα	Anti-interleukin 4 receptor alpha (monoclonal antibody)
Anti-IL5	Anti-interleukin 5 (monoclonal antibody)
Anti-IL5Rα	Anti-interleukin 5 receptor alpha (monoclonal antibody)
Anti-TSLP	Anti-thymic stromal lymphopoietin (monoclonal antibody)
APGAR	Activities, Persistent, triGgers, Asthma medications, Response to therapy
ATS/ERS	American Thoracic Society and European Respiratory Society
BDP	Beclometasone dipropionate
BEC	Blood eosinophil count
BD	Bronchodilator
BMI	Body mass index
BNP	B-type natriuretic peptide
bpm	Beats per minute
BTS	British Thoracic Society
cACT	Childhood Asthma Control Test
CBC	Complete blood count (also known as full blood count [FBC])
CDC	Centers for Disease Control and Prevention [USA]
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CRSwNP	Chronic rhinosinusitis with nasal polyps
CRSsNP	Chronic rhinosinusitis without nasal polyps
CT	Computerized tomography
CXR	Chest X-ray
DLCO	Diffusing capacity in the lung for carbon monoxide
DEXA	Dual-energy X-ray absorptiometry
DPI	Dry-powder inhaler
ED	Emergency department

EGPA	Eosinophilic granulomatosis with polyangiitis
FeNO	Fractional concentration of exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second (measured by spirometry)
FVC	Forced vital capacity (measured by spirometry)
FEV_1/FVC	Ratio of forced expiratory volume in 1 second to forced vital capacity
GERD	Gastro-esophageal reflux disease (GORD in some countries)
GOLD	Global Initiative for Chronic Obstructive Pulmonary Disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation (an approach to clinical practice guideline development)
HDM	House dust mite
HEPA	High-efficiency particulate air
HFA	Hydrofluoroalkane propellant
HIV/AIDS	Human immunodeficiency virus/acquired immunodeficiency syndrome
ICS	Inhaled corticosteroid
Ig	Immunoglobulin
IL	Interleukin
IM	Intramuscular
ICU	Intensive care unit
IV	Intravenous
LABA	Long-acting $beta_2$-agonist
LAMA	Long-acting muscarinic antagonist (also called long-acting anticholinergic)
LM	Leukotriene modifier
LMIC	Low- and middle-income countries
LTRA	Leukotriene receptor antagonist
MART	Maintenance-and-reliever therapy (with ICS-formoterol); in some countries called SMART (single-inhaler maintenance-and-reliever therapy)
n.a	Not applicable
NSAID	Nonsteroidal anti-inflammatory drug
NO2	Nitrogen dioxide (air pollutant)
O_2	Oxygen
OCS	Oral corticosteroid
OSA	Obstructive sleep apnea
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
PEF	Peak expiratory flow
PM_{10}	Particulate matter with a particle diameter of 10 micrometers or less (air pollution)
pMDI	Pressurized metered-dose inhaler
QTc	Corrected QT interval on electrocardiogram

RCT	Randomized controlled trial
SABA	Short-acting $beta_2$-agonist
SC	Subcutaneous
SCIT	Subcutaneous allergen immunotherapy
sIgE	Specific immunoglobulin E
SLIT	Sublingual immunotherapy
$S0_2$	Sulfur dioxide (air pollutant)
TSLP	Thymic stromal lymphopoietin
URTI	Upper respiratory tract infection
VCD	Vocal cord dysfunction (included in inducible laryngeal obstruction)
WHO	World Health Organization
WHO-PEN	The World Health Organization Package of essential noncommunicable disease interventions for primary care

Introduction

Asthma is a serious global health problem, affecting approximately 300 million people around the world, and causing around 1,000 deaths per day. Most of these deaths occur in low- and middle-income countries, and most of them are preventable. Asthma interferes with people's work, education and family life, especially when children have asthma. Asthma is becoming more prevalent in many economically developing countries, and the cost of asthma treatment for healthcare systems, communities and individuals is increasing.

The Global Initiative for Asthma (GINA) was established to increase awareness about asthma among healthcare providers, public health authorities and communities, to improve management of asthma, and to help prevent asthma.

Every year GINA publishes a strategy report, containing information and recommendations on asthma, based on the latest medical evidence. GINA's aim is for these to be available and used throughout the world. GINA also promotes international collaboration on asthma research. GINA Committee members are listed on page 9.

Goals of asthma management

For populations, the goal of asthma management is to prevent asthma deaths and minimize the burden of asthma on individuals, families, communities, health systems and the environment.

For individuals with asthma of all ages, the goal of asthma management is to achieve the patient's **best possible** long-term outcomes:

- Long-term asthma symptom control, which may include:
  - Few/no asthma symptoms
  - No sleep disturbance due to asthma
  - Unimpaired physical activity
- Long-term asthma risk minimization, which may include:
  - No exacerbations
  - Improved or stable personal best lung function
  - No requirement for maintenance oral corticosteroids (OCS)
  - No medication side-effects.

The patient's goals for their asthma may be different from these medical goals; and patients with few or no asthma symptoms can still have severe or fatal exacerbations, including those due to external triggers such as viral infections, allergen exposure (if sensitized) or pollution.

Challenges in global asthma management

For healthcare providers, the challenges of managing asthma differ between regions and health systems. Despite laudable efforts to improve asthma care over the past 30 years, and the availability of effective medications, 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. GINA recognizes that the recommendations in this report must be adapted to fit local practices and the availability of healthcare resources. To improve asthma care and patient outcomes, evidence-based recommendations must also be disseminated and implemented nationally and locally, and integrated into health systems and clinical practice. Implementation requires an evidence-based strategy that involves professional groups and stakeholders, and that considering local cultural and socioeconomic conditions. GINA is a partner organization in the Global Alliance against Chronic Respiratory Diseases (GARD). Through the work of GINA, and in cooperation with GARD and the International Union Against Tuberculosis and Lung Diseases (IUATLD), substantial progress toward better care for all patients with asthma should be achieved in the next decade.

Patients in many regions lack access to inhaled corticosteroid-containing medications, which are the cornerstone of care for all patients with asthma, regardless of its severity. Medications remain the major contributor to the overall costs of asthma management, so access to and pricing of high-quality asthma medications continues to be an issue of urgent need and a growing area of research interest.[1-3] The safest and most effective approach to asthma treatment in adolescents and adults uses the combination of inhaled corticosteroid (ICS) and formoterol across all asthma severity

levels. This approach, which avoids the consequences of starting treatment with short-acting beta$_2$-agonist (SABA) alone and requires only a single medication, depends on universal access to combination ICS–formoterol inhalers.[4,5] Budesonide-formoterol is included in the World Health Organization (WHO) essential medicines list. Its use as an anti-inflammatory reliever, recommended by GINA since 2019[6] may provide a feasible strategy to reduce the risk of severe exacerbations in low- and middle-income countries.[5]

The urgent need to ensure access to affordable, quality-assured inhaled asthma medications as part of universal health coverage must now be prioritized by all relevant stakeholders, particularly manufacturers of asthma inhalers. GINA is collaborating with IUATLD and other organizations to work towards a World Health Assembly Resolution to improve equitable access to affordable care, including inhaled medicines, for children, adolescents and adults with asthma.[3]

There is increasing global concern about climate change and its impact on the health and security of populations, particularly in low- and middle-income countries. The propellants in pressurized metered-dose inhalers contribute significantly to the carbon footprint of health care, particularly from use of SABAs (i.e., in GINA Track 2). Compared with SABA-only treatment, the GINA Track 1 approach in Track 1 Steps 1–2 not only provides a large reduction in exacerbations, in risk of adverse effects of OCS, and in urgent health care, but also, if implemented with a dry powder inhaler (as in most of the clinical trials), it provides a very large reduction in carbon footprint.[7,87] For both Track 1 and Track 2, GINA fully supports initiatives to encourage use of dry-powder inhalers, where they are available and clinically appropriate, and to replace environmentally harmful propellants with low-carbon alternatives. At the same time, it is essential to ensure continuity of supply of essential inhaled medicines to people in low-resource areas, to avoid exacerbating the existing serious global inequities in health care for asthma.[9]

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, and members are drawn from diverse geographic regions. The Science Committee normally meets in person three times yearly, in conjunction with the American Thoracic Society (ATS) and European Respiratory Society (ERS) international conferences and at a stand-alone meeting, to review asthma-related scientific literature, together with virtual meetings every 1–2 months. Committee members' disclosures of competing interest are published on the GINA website www.ginasthma.org.

PROCESSES FOR UPDATES AND REVISIONS OF THE GINA STRATEGY REPORT

Literature search

Details are provided on the GINA website (www.ginasthma.org/about-us/methodology). In summary, two PubMed searches are performed each year, each covering the previous 18 months, using filters established by the Science Committee. The search terms include asthma, all ages, only items with abstracts, clinical trial or meta-analysis or systematic review, and human. The search is not limited to specific PICOT (Population, Intervention, Comparison, Outcomes, Time) questions. The search strategy identifies, not only conventional randomized controlled trials, but also pragmatic, real-life and observational studies. The search for systematic reviews includes, but is not limited to, those conducted using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[10] An additional search is conducted for guidelines documents published by other international organizations. Members of the respiratory community are also invited to submit any other fully published peer-reviewed publications that they believe have been missed, providing that the full paper is 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.

Systematic reviews

Unique among evidence-based recommendations in asthma, and rare among clinical practice guidelines in most other therapeutic areas, the GINA report is based on an ongoing twice-yearly cumulative update of the evidence base for its recommendations. GINA does not normally carry out or commission its own GRADE-based reviews, because of the current cost of such reviews and the large number of PICOT questions that would be necessary for a comprehensive practical report of this scope, and because it would limit the responsiveness of the GINA Strategy Report to emerging evidence and new developments in asthma management. However, the Science Committee reviews relevant published systematic reviews conducted with GRADE methodology as part of its normal process. GINA recommendations are constantly being reviewed and considered for update as new evidence (including GRADE-based systematic reviews on specific topics) is identified.[11,12]

Literature screening and review

After removal of duplicates and articles already reviewed, each article identified by the literature search is pre-screened in Covidence for relevance and major quality issues by the Editorial Assistant and by at least two non-conflicted members of the Science Committee. Each publication selected from screening is reviewed for quality and relevance by at least two members of the Science Committee, neither of whom may be an author (or co-author) or declare a conflict of interest in relation to the publication. Articles that have been accepted for publication and are online in advance of print are eligible for full text review if the approved/corrected copy-edited proof is available. All members receive a copy of all abstracts and full text publications, and non-conflicted members can provide comments before the meeting at which the article is scheduled for review. Members evaluate the abstract and the full text publication, and complete a review template of written questions about whether the scientific data affect GINA recommendations and, if so, what specific changes should be made. Since 2020, the Critical Appraisal Skills Programme (CASP) checklist[13] has been included in the review template, to assist in evaluation of systematic reviews. A list of all publications reviewed by the Committee is posted on the GINA website (www.ginasthma.org).

Discussion and decisions during Science Committee meetings

Each publication that, in the assessment of at least one reviewer, potentially impacts on the GINA Strategy Report is discussed in a Science Committee meeting (virtual or face-to-face). This process comprises three parts, as follows:

1. Quality and relevance of original research and systematic review publications. First, the Committee considers the relevance of the publication to the GINA Strategy Report, the quality of the study, the reliability of the findings, and the interpretation of the results, based on the responses from reviewers and discussion by members of the Committee. For systematic reviews, GRADE assessments, if available, are considered. However, for any systematic review, GINA members also independently consider the clinical relevance of the question addressed by the review, and the scientific and clinical validity of the included populations and study design. For network meta-analyses, reviewers also consider the appropriateness of the comparisons (e.g., whether differences in background exacerbation risk and ICS dose were taken into account) and the generalizability of the findings. During this discussion, a member who is an author (or was involved in the study) may be requested to provide clarification or respond to questions about the study, but they may not otherwise take part in this discussion about the quality and relevance of the publication.

2. Decision about inclusion of the evidence. During this phase, the Committee decides whether the publication or its findings affect GINA recommendations or statements and should be included in the GINA Strategy Report. These decisions to modify the report or its references are made by consensus by Committee members present and, again, any member with a conflict of interest is excluded from these decisions. 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.

3. Discussion about related changes to the GINA Strategy Report. If the committee resolves to include the publication or its findings in the report, an author or conflicted member, if present, is permitted to take part in the subsequent 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 the year as new evidence emerges or as other changes to the report are agreed and implemented. The approach to managing conflicts of interest, as described above, also applies to members of the GINA Board who, ex-officio, attend GINA Science Committee meetings.

As with all previous GINA Strategy Reports, levels of evidence are assigned to management recommendations where appropriate. Current criteria (Table A) are based on those originally developed by the National Heart Lung and Blood Institute. From 2019, GINA has included in Level A strong observational evidence that provides a consistent pattern of findings in the population for which the recommendation is made, and has also described the values and preferences that were considered in making major new recommendations. The table was updated in 2021 to avoid ambiguity about the positioning of observational data and systematic reviews.

Table. Description of levels of evidence used in this report

Evidence level	Sources of evidence	Definition
A	Randomized controlled trials (RCTs), systematic reviews, observational evidence. Rich body of data	Evidence is from endpoints of well-designed RCTs, systematic reviews of relevant studies or observational studies 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 and systematic reviews. 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 systematic reviews of such RCTs. In general, Category B applies when few randomized trials exist, they have a small sample size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomized trials or observational studies	Evidence is from non-randomized trials or observational studies without consistent findings.
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.

New therapies and indications

The GINA Strategy Report is a global strategy document. Since regulatory approvals differ from country to country, and manufacturers do not necessarily make regulatory submissions in all countries, some GINA recommendations are likely to be off-label in some countries. This is a particular issue for pediatrics, where across different diseases, many treatment recommendations for preschool children and for children aged 6–11 years are off-label.

For new therapies, GINA's aim is to provide clinicians with evidence-based guidance about new therapies and their positioning in the overall asthma treatment strategy as soon as possible; otherwise, the gap between regulatory approval and the periodic update of many national guidelines is filled only by advertising or educational material produced by the manufacturer or distributor. For new therapies for which the GINA Science Committee considers there is sufficient good-quality evidence for safety and efficacy or effectiveness in relevant asthma populations, recommendations may be held until after approval for asthma by at least one major regulatory agency (e.g., European Medicines Agency or US Food and Drug Administration), since regulators often receive substantially more safety and/or efficacy data on new medications than are available to GINA through peer-reviewed literature. However, decisions by GINA to make or not make a recommendation about any therapy, or about its use in any specific population, are based on the best available peer-reviewed evidence and not on labeling directives from regulators.

For existing therapies with evidence for new regimens or in different populations, the Science Committee may, where relevant, make recommendations that are not necessarily covered by regulatory indications in any country at the time, provided the Committee is satisfied with the available evidence around safety and efficacy/effectiveness. Since the GINA Strategy Report is a global strategy, the report does not refer to recommendations as being "off-label". However, readers are advised that, when assessing and treating patients, they should use their own professional

judgment and should also consider local and national guidelines and eligibility criteria, as well as locally licensed drug doses.

External review

Prior to publication each year, the GINA Strategy Report undergoes extensive external review by patient advocates and by asthma care experts from primary and specialist care in multiple countries. There is also continuous external review throughout the year in the form of feedback from end-users and stakeholders through the contact form on the GINA website.

Literature reviewed for GINA 2025 update

The GINA Strategy Report has been updated in 2025 following the routine twice-yearly review of the literature by the GINA Science Committee. The literature searches for clinical trials (see above), systematic reviews and guidelines identified a total of 4373 publications, of which 3231 duplicates/animal studies/non-asthma/pilot studies and protocols were removed. A total of 317 publications underwent screening of title and abstract by at least two reviewers, and 239 were screened out for relevance and/or quality. A total of 78 publications underwent full-text review by at least two members of the Science Committee, and 59 full-text publications were subsequently discussed at meetings of the Science Committee.

A list of key changes in GINA 2025 is shown on page19, and a copy showing tracked changes is archived on the GINA website at www.ginasthma.org/archived-reports.

What's new in GINA 2025?

The GINA Strategy Report has been updated in 2025 following the routine twice-yearly cumulative review of the literature by the GINA Science Committee, and extensive discussion about issues relevant to clinical practice and research. A copy showing tracked changes from the 2024 GINA Strategy Report is archived on the GINA website.

KEY CHANGES

- **Biomarkers of Type 2 inflammation:** Information about the role of Type 2 biomarkers (particularly blood eosinophils and fractional exhaled nitric oxide [FeNO]) in the diagnosis, assessment and management of asthma has been collated from multiple sections in the GINA report and expanded, and is presented as a new resource at the end of the Report (Appendix A, p.217). Links to this resource have been added throughout the Report. Information has also been added about factors contributing to variability in blood eosinophil count and FeNO, including the marked circadian (but opposite) variability of both blood eosinophils and FeNO. This information may be highly relevant when clinicians are assessing a patient's eligibility for Type 2-targeted biologic therapy in clinical practice; it also indicates that caution is needed when comparing a patient's biomarker results with absolute thresholds in clinical practice.
- **Risk factors for severe exacerbations in adults and adolescents**: GINA welcomes publication of the ORACLE2 study,[14] which supports the longstanding recommendation by GINA that multiple factors, including Type 2 biomarkers, should be considered in the assessment of patients' risk of future exacerbations (Box 2-2B, p.37). The authors reported a data-driven patient-level meta-analysis of risk factors for the rate of severe exacerbations based on data from the placebo arms of multiple randomized controlled clinical trials (RCTs), including as many of the GINA list of risk factors as were available from these studies. The risks associated with over-use of short-acting beta$_2$-agonist (SABA) could not be examined in ORACLE2 because surprisingly few of the studies had recorded data on SABA use. Given this, and the highly selective nature of RCT populations, similar analyses to ORACLE2 in real-world populations are needed, together with investigation of the outcome of targeted risk reduction strategies based on the identified risk factors. The large reduction in asthma exacerbations and hospitalizations seen during COVID-19 lockdowns (p.121), and when air quality was improved for some summer Olympic Games (p.64) is a reminder that external and environmental factors also have a significant impact on asthma exacerbation risk.
- **Impact of extreme weather**: A new section has been added about the impact of climate change and extreme weather on people with asthma (p.130), both by impacting health infrastructure, and also by direct effects on asthma. Extreme heat and extreme cold are both associated with an increased risk of asthma exacerbations and need for urgent health care.
- **Diagnosis of asthma in children aged 5 years and younger:** Section 10 (p.181) has undergone extensive review and revision by pediatric members of the GINA Science Committee. The most important change is confirmation that the diagnosis of asthma can be made in this age-group, and clear advice about how this can be undertaken. A pragmatic approach to diagnosis is presented (Box 10-1, p.181; Box 10-2, p.182), with three clinical criteria that can be summarized as: (1) recurrent acute episodes of wheezing, with or without interval asthma-like symptoms, (2) assessment that an alternative diagnosis is unlikely to be causing the symptoms or signs, and (3) a timely response to asthma treatment, including symptomatic improvement within minutes after administration of SABA (in a healthcare setting or at home) or during a diagnostic trial with daily ICS plus as-needed SABA for 2–3 months.
- **Treatment of asthma in children aged 5 years and younger:** Section 11 (p.189) has been revised to reflect the focus on children with a diagnosis of asthma. The treatment figure (p.194) has been updated based on evidence for efficacy, effectiveness and safety. Currently, there are few options for children who have asthma symptoms ≤2 days/week and who do not have a history of severe wheezing episodes. However, several studies of anti-inflammatory reliever therapy with low-dose ICS-formoterol in children are underway, including in children aged 5 years and younger.
- **Asthma exacerbations in children aged 5 years and younger:** Section 12 (p.201) has also been revised, including updates on use of magnesium sulfate (further evidence-based support for intravenous magnesium in moderate or severe exacerbations, but nebulized magnesium no longer recommended) and on dosage of inhaled medications during an acute care presentation (p.204). The oxygen saturation target for children has been changed

from 94–98% to ≥94%, with reminders (for other age-groups as well) to take into account the effect of skin color and adjustment for altitude if relevant.

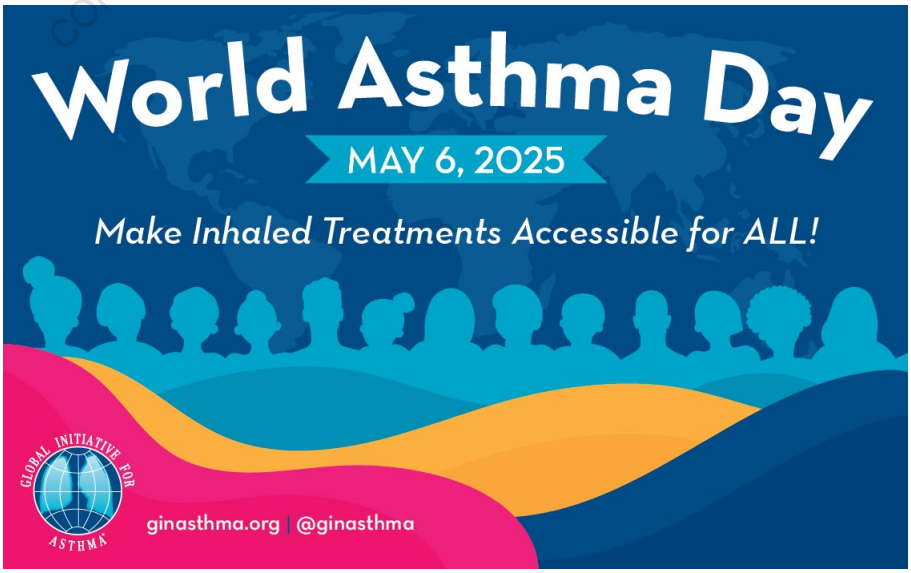
- **Diagnosis of asthma in adults and adolescents:** The diagnostic flowchart (Box 1-1, p.24) has been updated for clarity. Variability in symptoms and variability in expiratory airflow are the two distinctive characteristics of asthma, so assessment of lung function remains the first option for confirming the diagnosis. The (limited) role of biomarkers in diagnosis of asthma, previously described in the footnote and text, has been added to the diagnostic flowchart for greater visibility. Further details about the role of biomarkers in diagnosis of asthma are included in the new Appendix (p.217).
- **Diagnostic criteria for asthma:** We became aware that the term "variable expiratory airflow limitation" in the previous criteria for diagnosis (Box 1-2, p.25) had caused some confusion, so it has been replaced by "variable expiratory airflow". In a patient with (untreated) asthma, lung function is characteristically variable, so airflow limitation may be present at some times and not others. GINA has never intended to mean that airflow limitation must be present at the time of diagnostic assessment. The role of biomarkers in diagnosis, previously in footnotes and text, has been added to Box 1-2 and Box 1-4 (p.30) and a reference to a calculator of peak expiratory flow (PEF) variability has been added.
- **Personalized asthma care: Assess–Adjust–Review**: The asthma cycle of care graphic (Box 3-4, p.52), which has illustrated the GINA's recommendations for personalized asthma management since 2014, has been redesigned for emphasis. "Consider biomarkers" has been added to the guidance on reviewing response to treatment. Biomarkers are positioned within the "Review response" section because FeNO suppression tests have shown that, in many patients, an elevated FeNO is due to poor adherence with inhaled corticosteroid (ICS)-containing therapy (see p.111). Accordingly, it is more efficient to consider these biomarkers after ICS has been added, and after basic (and very common) problems with adherence and inhaler technique have been addressed.
- **Population-level and personalized patient-level treatment decisions**: This concept has been fundamental to GINA recommendations for personalized asthma management since 2014. Population-level recommendations, as in guidelines and formulary decisions, are based on high quality group level evidence. For patient-level decisions, clinicians should consider several factors, including the patient's phenotypic characteristics (including biomarkers), comorbidities, patient views, and practical issues. The previous table has been converted to a figure (Box 3-4, p.54) for greater visibility.
- **Treatment recommendations for adults and adolescents**:
  - The two-track treatment figure has been retained (Box 4-6, p.77), given the poor access to combination ICS-formoterol in most low- and middle-income countries. Track 1 with ICS-formoterol anti-inflammatory reliever remains the preferred treatment approach (if available), because it substantially reduces the risk of severe exacerbations, systemic corticosteroid exposure, and need for urgent health care, compared with SABA-based regimens. In addition, it is a simpler regimen, with a single combination medication (ICS plus formoterol, a rapid-onset, long-acting beta$_2$-agonist [LABA]) used across steps 1 to 4, to both relieve symptoms and reduce risk. Use of a single inhaler reduces inhaler technique errors and avoids selective or inadvertent non-adherence, compared with the separate reliever and maintenance inhalers that are required in Track 2.
  - In Track 2, Step 4 has been changed from medium-to-high dose of ICS-LABA to medium-dose ICS-LABA (p.77, p.89), reflecting the Report's longstanding emphasis on minimizing exposure to the adverse effects of high-dose ICS. If high-dose ICS-LABA is needed, its use should be limited to 3–6 months if possible.
  - In Box 4-2 (p.71), daily doses of fluticasone furoate have been reclassified as low-medium (100 mcg) and medium-high (200 mcg). This change is because of the difficulty in aligning doses of this ICS with older molecules, and to avoid ambiguity about ICS-LABAs that can be used in Track 2 Step 4 of the treatment figure for adults and adolescents (p.77).
  - "Other controller options" with less evidence for efficacy and/or safety than the standard treatments shown in Tracks 1 and 2 were previously shown in gray boxes underneath individual treatment steps (p.77), representing *alternatives* to the standard treatment at that step (e.g., add-on LAMA at Step 4 meant addition of LAMA to low-dose ICS-LABA). However, this was not widely understood, and it is important that referral of patients with difficult-to-treat asthma for expert advice should not be delayed by trials of multiple different add-on treatments.

Accordingly, the individual boxes have been replaced by text that briefly summarizes non-pharmacologic strategies, allergen immunotherapy, and other controller options that are described in the text.

- Fenoterol has been added to the list of non-recommended bronchodilators (p.93) because of its higher risk of cardiovascular adverse effects and asthma mortality.

- **Shared decision-making for inhaler choice**: Box 5-1 (p.109, the "flower" figure) has been updated to clarify the order of consideration of factors, and the stage at which a healthcare provider and individual patient might consider the relative environmental impact of different inhaler devices. The first step is to choose the preferred medication that is best for the patient; the environmental impact becomes relevant at the individual patient level only if this medication is available in more than one type of inhaler device that the patient can use correctly.
- **Action plans**: The previous table about options for treatment changes within action plans (Box 9-2, p.163) has been reorganized by treatment Track, due to the marked difference in approach for action plans depending on the type of reliever. For patients using conventional SABA-based treatment (Track 2), SABA is increased for symptom relief and there is only modest evidence that doubling or quadrupling the maintenance ICS dose reduces progression to a severe exacerbation, as indicated by need for oral corticosteroid (OCS). For patients using the anti-inflammatory reliever ICS-formoterol (Track 1), the patient continues taking their usual maintenance dose, but increases their as-needed doses incrementally to achieve control of increasing inflammation and bronchoconstriction; here, there is strong evidence for significant reduction in the risk of severe exacerbations needing OCS, and needing urgent health care.
- **Treatment of severe exacerbations in adults, adolescents and children 6–11 years:** Doses of SABA for initial treatment in primary care and emergency departments have been clarified, to avoid excessive use. Nebulized magnesium is no longer recommended.
- **Severe asthma decision tree**: This has been reviewed and updated (Boxes 8-2 to 8-5, starting p.142), including reorganization and simplification of investigations performed by specialists. In recognition that specialist investigations sometimes identify that a patient does not have asthma, or that their symptoms and exacerbations are due to a treatable comorbidity, confirmation of the diagnosis of severe asthma has been moved to stage 5, after the initial specialist assessment (Box 8-3, p.143). The section of the decision tree relating to assessment of Type 2 biomarkers has been reviewed and clarified, with a prompt to re-evaluate previously low blood eosinophils and/or FeNO if the clinical context changes (Box 8-3, p.143). Long-term efficacy and safety of biologic therapies will be reported up to 5 years, but not beyond that. The updated decision tree and content of Section 8 will again be published as a standalone Short Guide.

WORLD ASTHMA DAY 2025



1. Definition, description, and diagnosis of asthma in adults, adolescents and children 6–11 years

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. Airflow limitation may later become persistent.

Asthma is usually associated with airway hyperresponsiveness and airway inflammation, but these are not necessary or sufficient to make the diagnosis.

Recognizable clusters of demographic and clinical characteristics are called “clinical asthma phenotypes”. In general, clinical phenotypes do not correlate strongly with specific pathological processes or treatment responses. Biomarkers reflecting Type 2 airway inflammation are useful, particularly in the assessment and treatment of difficult-to-treat asthma and severe asthma.

How is asthma diagnosed?

The diagnosis of asthma is based on the history of characteristic symptom patterns and evidence of variable expiratory airflow. This should be documented from bronchodilator responsiveness (“reversibility”) testing or other lung function tests. More than one test may be needed to confirm asthma or exclude alternative causes of respiratory symptoms.

Many health providers do not have access to spirometry. If so, measurement of peak expiratory flow (PEF) should be used, rather than relying on symptoms alone.

Test before treating, wherever possible: confirm the diagnosis of asthma before starting inhaled corticosteroid (ICS)-containing treatment, as it is often more difficult to confirm the diagnosis after asthma control has improved.

Additional or alternative strategies may be needed to confirm the diagnosis of asthma in particular populations, including patients already on ICS-containing treatment, the elderly, patients presenting with cough as the only symptom (including cough variant asthma), and patients in low-resource settings. In patients with typical asthma symptoms, if lung function testing is not available or results are normal, elevated fractional exhaled nitric oxide (FeNO) or elevated blood eosinophils can support the diagnosis of Type 2 asthma. However, these biomarkers may be elevated in non-asthma conditions, and lower levels do not rule out asthma.

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.

This definition was reached by consensus, based on consideration of the characteristics that are typical of asthma before ICS-containing 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 1–29% of the population in different countries.[15,16] Asthma is characterized by variable symptoms of wheeze, shortness of breath, chest tightness and/or cough, and by variable expiratory airflow. Both symptoms and airflow 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. Conversely, patients can experience episodic flare-ups (exacerbations, attacks) of asthma that may be life-threatening and place a significant burden on patients and the community. The majority of asthma deaths occur in low- and middle-income countries.[2] 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.

Clinical asthma phenotypes

Asthma is a heterogeneous disease, with various underlying disease processes. Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called "asthma phenotypes".[17-20] Except in patients with severe asthma, phenotypes have not been shown to correlate strongly with clinical patterns or treatment responses. In patients with more severe asthma, some phenotype-guided treatments are available. More research is needed to understand the clinical utility of phenotypic classification in asthma.

Many clinical phenotypes of asthma have been identified.[17-19] Some of the most common are:

- *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. Allergic asthma usually responds well to 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 experience a lesser short-term response to ICS.
- *Cough variant asthma and cough predominant asthma*:[21] In some children and adults, cough may be the only symptom of asthma, and evidence of airflow limitation may be absent except during bronchial provocation testing. Some patients later develop wheezing and bronchodilator responsiveness. ICS-containing treatment is effective. For more details, see p.33.
- *Adult-onset (late-onset) asthma*: Some adults, particularly women, present with asthma for the first time in adulthood. Adult-onset asthma tends to be non-allergic, and often requires higher doses of ICS or is 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 longstanding asthma develop airflow limitation that is persistent or incompletely responsive ("reversible") to treatment (see p.28). This is thought to be due to airway wall remodeling. See Section 5 (p.108) for more details about patients with features of both asthma and chronic obstructive pulmonary disease (COPD).
- *Asthma with obesity*: Some obese patients with asthma have prominent respiratory symptoms and a different pattern of airway inflammation, with little eosinophilic inflammation.[22]

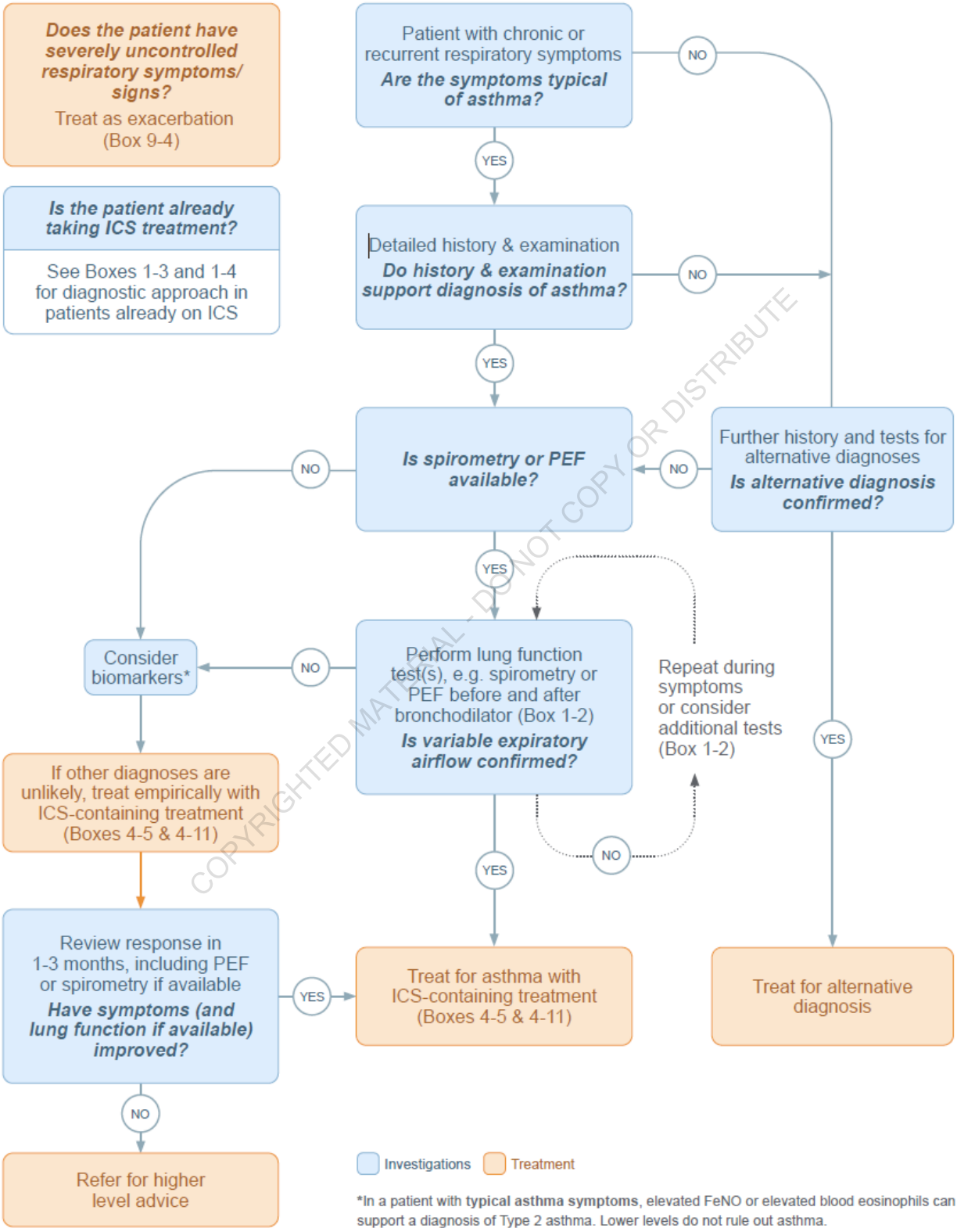
There is little evidence about the natural history of asthma after diagnosis, but one longitudinal study showed that, among adults with recently diagnosed asthma, approximately 16% may experience clinical remission (no symptoms or asthma medication for at least 1 year) within 5 years.[23] See p.50 for more information about remission.

MAKING THE INITIAL DIAGNOSIS

Making the diagnosis of asthma before treatment is started (Box 1-1, p.24 and Box 1-2, p.25) 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.[24] The pattern of symptoms is important, as respiratory symptoms may be due to acute or chronic conditions other than asthma (see Box 1-3, p.27). If possible, the evidence supporting a diagnosis of asthma (Box 1-2, p.25) should be documented when the patient first presents, as the features that are characteristic of asthma may improve spontaneously or with treatment. It is often more difficult to confirm a diagnosis of asthma after the patient has started ICS-containing treatment, because this reduces variability of both symptoms and lung function (see p.28). In recognition that many health providers lack access (or ready access) to spirometry,[25] GINA also provides advice on the use of PEF measurement in asthma diagnosis.

Box 1-1. Diagnostic flowchart for adults, adolescents and children 6–11 years in clinical practice

This flowchart is for patients presenting with chronic or recurrent respiratory symptoms in clinical practice. See Box 9-4 (p.168) and Box 9-6 (p.172) for information on patients presenting with an acute exacerbation.



ICS: inhaled corticosteroid; PEF: peak expiratory flow. PEF is less reliable than spirometry, but it is better than no objective measurement of lung function. When measuring PEF, use the same meter each time as the value may vary by up to 20% between different meters, and use only the highest of three readings. For more information about diagnosis, see text and Box 1-2, p.25.

Box 1-2. Criteria for initial diagnosis of asthma in adults (≥18 years) and children (6–17 years)

1. HISTORY OF TYPICAL VARIABLE RESPIRATORY SYMPTOMS	
Feature	*Symptoms or features that support the diagnosis of asthma*
Wheeze, shortness of breath, chest tightness and/or cough (Descriptors may vary by region and by age)	• 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 worsen after end-exercise (very distinctive) • Symptoms often appear or worsen with viral infections
2. CONFIRMED VARIABLE EXPIRATORY AIRFLOW	
Feature	*Considerations, definitions, criteria*
Excessive variability in expiratory lung function (one or more of the following):	The greater the variations, or the more occasions excess variation is seen, the more confidently the diagnosis of asthma can be made. If spirometry is not possible, PEF† may be used, but it is less reliable.
Positive bronchodilator (BD) responsiveness (reversibility) test with spirometry (or PEF†) When possible, test during symptoms or in the morning	Measure change 10–15 minutes after 200–400 mcg salbutamol (albuterol) or equivalent, compared with pre-BD readings. Positive test more likely if BD withheld before test: SABA ≥4 hours, long-acting bronchodilators 24–48 hours (see below). *Adults*: increase from baseline in FEV_1 or FVC of ≥12% and ≥200 mL, with greater confidence if the increase is ≥15% and ≥400 mL; or increase in PEF† ≥20% if spirometry is not available *Children*: increase from baseline in FEV_1 of ≥12% predicted (or in PEF† of ≥15%)
Excessive variability in twice-daily PEF over 2 weeks*	*Adults*: average daily diurnal PEF variability >10%* *Children*: average daily diurnal PEF variability >13%*
Increase in lung function after 4 weeks of ICS-containing treatment	*Adults*: increase from baseline in FEV_1 by ≥12% and ≥200 mL (or PEF† by ≥20%) after 4 weeks of daily ICS-containing treatment *Children*: increase from baseline in FEV_1 of ≥12% predicted (or in PEF† of ≥15%).
Positive bronchial provocation test	*Adults*: Fall from baseline in FEV_1 of ≥20% with standard doses of methacholine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge, or >10% and >200 mL with standardized exercise challenge. *Children*: fall from baseline in FEV_1 of >12% predicted (or fall in PEF† >15%) with standardized exercise challenge. If FEV_1 decreases during a challenge test, check that FEV_1/FVC ratio has also decreased, since incomplete inhalation, e.g., due to inducible laryngeal obstruction or poor effort, can result in a false reduction in FEV_1.
Excessive variation in lung function between visits (good specificity but poor sensitivity)	*Adults*: variation in FEV_1 of ≥12% and ≥200 mL (or in PEF† of ≥20%) between visits. *Children*: variation of ≥12% in FEV_1 (or ≥15% in PEF†) between visits
ROLE OF TYPE 2 BIOMARKERS IN DIAGNOSIS OF ASTHMA	
In patients with typical asthma symptoms, if spirometry or PEF is not available or testing is negative, elevated FeNO (adults/adolescents: >50 ppb; children: >35 ppb) or blood eosinophils above national/regional reference range can support the diagnosis of Type 2 asthma, but can also be due to non-asthma conditions. Lower levels of FeNO or blood eosinophils do **not** rule out asthma. FeNO and blood eosinophils vary substantially by sex, age and (for FeNO) device and site). Blood eosinophils are higher in the morning, and FeNO is lower in the morning. See Appendix A for more details (p.216).	

Abbreviations and footnotes for Box 1-2

BD: bronchodilator; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; ICS: inhaled corticosteroids; LABA: long-acting $beta_2$-agonist; PEF: peak expiratory flow; SABA: short-acting $beta_2$-agonist.

For how to confirm the diagnosis in patients already taking ICS-containing treatment, see Box 1-3 (p.27).

Bronchodilator responsiveness testing, use either a SABA or a rapid-acting ICS-LABA; see p.28. Withholding periods: short-acting $beta_2$-agonists: ≥4 hours; formoterol, salmeterol: 24 hours; indacaterol, vilanterol: 36 hours; tiotropium, umeclidinium, aclidinium, glycopyrronium: 36–48 hours.

†For each PEF measurement, use the highest of 3 readings. Use the same PEF meter each time, as PEF may vary by up to 20% between different meters. *Daily diurnal PEF variability is calculated from twice daily PEF as (day's highest minus day's lowest) divided by (mean of day's highest and lowest), averaged over two weeks. A PEF variability calculator is available.[26]

BD responsiveness may be lost temporarily during severe exacerbations or respiratory viral infections,[27] and airflow limitation may become persistent over time. If responsiveness is not detectable 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.30), but other conditions that can mimic asthma (Box 1-3, p.27) should be considered, and the diagnosis confirmed as soon as possible.

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.[24]

Respiratory symptoms of wheeze, shortness of breath, cough and/or chest tightness:

- Symptoms are 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:

- Chronic production of sputum
- Shortness of breath associated with dizziness, light-headedness or peripheral tingling (paresthesia)
- Chest pain
- Exercise-induced dyspnea with noisy inspiration.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in a patient with suspected asthma varies with age (Box 1-3, p.27). Any of these alternative diagnoses may also occur with asthma. See Section 6 (p.117) for management of multimorbidity.

Box 1-3. Differential diagnosis of asthma in adults, adolescents and children 6–11 years

Age	If the symptoms or signs below are present, consider…	Condition
6–11 years	Sneezing, itching, blocked nose, throat-clearing	Chronic upper airway cough syndrome
	Sudden onset of symptoms, unilateral wheeze	Inhaled foreign body
	Recurrent infections, productive cough	Bronchiectasis Congenital immunodeficiency
	Recurrent infections, productive cough, sinusitis	Primary ciliary dyskinesia Congenital immunodeficiency
	Cardiac murmurs	Congenital heart disease
	Pre-term delivery, symptoms since birth	Bronchopulmonary dysplasia
	Excessive cough and mucus production, gastrointestinal symptoms	Cystic fibrosis
12–39 years	Sneezing, itching, blocked nose, throat-clearing	Chronic upper airway cough syndrome
	Dyspnea, inspiratory wheezing (stridor)	Inducible laryngeal obstruction
	Dizziness, paresthesia, sighing	Hyperventilation, dysfunctional breathing
	Productive cough, recurrent infections	Bronchiectasis
	Excessive cough and mucus production	Cystic fibrosis
	Cardiac murmurs	Heart disease
	Shortness of breath, family history of early emphysema	Alpha$_1$-antitrypsin deficiency
	Sudden onset of symptoms	Inhaled foreign body
40+ years	Dyspnea, inspiratory wheezing (stridor)	Inducible laryngeal obstruction
	Dizziness, paresthesia, sighing	Hyperventilation, dysfunctional breathing
	Cough, sputum, dyspnea on exertion, smoking or noxious exposure	Chronic obstructive pulmonary disease*
	Productive cough, recurrent infections	Bronchiectasis
	Dyspnea with exertion, nocturnal symptoms, ankle edema	Cardiac failure
	Treatment with angiotensin-converting enzyme (ACE) inhibitor	Medication-related cough
	Dyspnea with exertion, non-productive cough, finger clubbing	Parenchymal lung disease
	Sudden onset of dyspnea, chest pain	Pulmonary embolism
	Dyspnea, unresponsive to bronchodilators	Central airway obstruction
All ages	Chronic cough, hemoptysis, dyspnea; and/or fatigue, fever, (night) sweats, anorexia, weight loss; sometimes unilateral wheeze	Tuberculosis
	Prolonged paroxysms of coughing, sometimes stridor	Pertussis

*See Section 7 (p.131). Any of the above conditions may also contribute to respiratory symptoms in patients with confirmed asthma.

CONFIRMING THE DIAGNOSIS OF ASTHMA

Why is it important to confirm the diagnosis of asthma?

This is important to avoid unnecessary treatment or over-treatment, and to avoid missing other important diagnoses. In a sample of 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 with staged withdrawal of ICS-containing treatment. The diagnosis of asthma was less likely to be confirmed in patients who did not undergo lung function testing at the time of initial diagnosis. Some patients (2%) had serious cardiorespiratory conditions that had been misdiagnosed as asthma.[28] It is important to confirm the diagnosis of asthma in people with suggestive respiratory symptoms; a study in Canada found that patients with undiagnosed asthma had worse health-related quality of life and more unscheduled healthcare visits than those without asthma, and similar to those with diagnosed asthma.[29]

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, COPD, respiratory infections, tracheomalacia, or inhaled foreign body (when wheezing may be unilateral). Crackles (crepitations) and inspiratory wheezing are not features of asthma. Examination of the nose may reveal signs of allergic rhinitis or nasal polyps.

Lung function testing to document variable expiratory airflow

Asthma is characterized by variable expiratory airflow, 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 over time 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.[27]

Lung function is most reliably assessed by spirometry testing, with assessment of forced expiratory volume in 1 second (FEV_1) and the ratio of FEV_1 to forced vital capacity (FEV_1/FVC). Spirometry testing should be carried out by well-trained operators with well-maintained and regularly calibrated equipment,[30] with an inline filter to protect against transmission of infection.[31] However, globally, many clinicians do not have ready (or any) access to spirometry. In this context, assessment of PEF, although less reliable, is better than no objective measurement of lung function. If PEF is used, the best of 3 measurements should be used each time, and the same meter should be used for follow-up testing, as measurements may differ from meter to meter by up to 20%.[32]

A reduced FEV_1 or PEF may be found with many other lung diseases, or due to poor technique with inadequate inhalation. This may be due to lack of effort or to inducible laryngeal obstruction. Reduced FEV_1/FVC (compared with baseline or compared with the lower limit of normal) indicates expiratory airflow limitation. Many spirometers now include age-specific predicted values for lower limit of normal in their software.[33]

In clinical practice, variation in expiratory airflow is generally assessed from variation in FEV_1 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 responsiveness test.

Responsiveness (previously called “reversibility”)[30] generally refers to rapid improvements in FEV_1 (or PEF), measured within minutes after inhalation of a rapid-acting bronchodilator such as 200–400 mcg salbutamol, or more sustained improvement over days or weeks after the introduction of ICS treatment.[34]

In a patient with typical or suggestive respiratory symptoms, obtaining evidence of excessive variability in expiratory lung function is an essential component of the diagnosis of asthma.

Specific examples of excessive variability in expiratory airflow include:

- An increase in lung function 10–15 minutes after administration of a bronchodilator, or after a trial of ICS-containing treatment; lung function may improve gradually, so it should be assessed after at least 4 weeks
- A decrease in lung function after exercise (spontaneous or standardized) 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 twice-daily 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.25). A decrease in FEV_1 or PEF 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.

If there is a significant decrease in FEV_1 during a challenge test, check that FEV_1/FVC ratio has also decreased, since incomplete inhalation (e.g., due to inducible laryngeal obstruction or poor effort) can result in a false reduction in FEV_1.

How much variation in expiratory airflow is consistent with asthma?

Bronchodilator responsiveness: There is overlap in bronchodilator responsiveness and other measures of variation between health and disease.[35] 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.25). Generally, in adults with respiratory symptoms typical of asthma, an increase or decrease in FEV_1 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. A Technical Standards Committee recommended changing the criterion for a positive bronchodilator responsiveness test from an increase from baseline in FEV_1 or FVC of ≥12% and ≥200 mL (as at present) to an increase from baseline of >10% of the patient's predicted value.[36] This recommendation was based on data for survival, and the Technical Standards Committee avoided making any recommendation about the use of this criterion for diagnostic decisions in clinical practice. This topic will be considered again by GINA when more data are available, including comparison with other diagnostic tests for asthma.

If FEV_1 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 FEV_1 is >80% predicted can have a clinically important increase in lung function with bronchodilator or ICS-containing treatment. Predicted normal ranges (especially for PEF) have limitations, so the patient's own best reading ("personal best") is recommended as their "normal" value.

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. An online calculator is available.[26] The upper 95% confidence limit of diurnal variability (amplitude percent mean) from twice daily readings is 9% in healthy adults,[37] and 12.3% in healthy children[38] so, in general, diurnal variability >10% for adults and >13% for children is regarded as excessive.

Box 1-4. Steps for confirming the diagnosis of asthma in a patient already taking ICS-containing treatment

Current status	Steps to confirm the diagnosis of asthma
Typical and variable respiratory symptoms and variable expiratory airflow	**Diagnosis of asthma is confirmed.** Assess the level of asthma control (Box 2-2A and Box 2-2B, p.37) and review ICS-containing treatment (Box 4-6, p.77; Box 4-12, p.96.)
Typical and variable respiratory symptoms but no variable expiratory airflow	**Consider repeating spirometry** (or PEF*) after withholding bronchodilator (4 hrs for SABA, 24–48 hrs for long-acting bronchodilators (see below) or during symptoms. Check between-visit variability of FEV_1, and bronchodilator responsiveness. If still normal, consider other diagnoses (Box 1-3, p.27). *If FEV_1 (or PEF*) is >70% predicted*: consider stepping down ICS-containing treatment (see Box 1-5, p.32) and reassess in 2–4 weeks, then consider bronchial provocation test or repeating bronchodilator responsiveness test. *If FEV_1 (or PEF*) is <70% predicted*: consider starting or stepping up maintenance ICS-containing treatment for 3 months (Box 4-6, p.77), then reassess symptoms and lung function. If no response, resume previous ICS dose and refer patient for diagnosis and investigation. Consider biomarkers: in patients with typical asthma symptoms, elevated FeNO (adults/adolescents: >50 ppb; children: >35 ppb) or blood eosinophils above the national/regional reference range can support the diagnosis of Type 2 asthma, but can also be due to non-asthma conditions. Lower levels of FeNO or blood eosinophils do not rule out asthma. FeNO and blood eosinophils vary by sex, age, time of day and (for FeNO) device and site (p.31). For details, see Appendix A, p.216.
Symptoms not typical of asthma, and no variable expiratory airflow	**Investigate** for alternative diagnoses or comorbidities that may be contributing to symptoms and/or exacerbations (see Box 1-3, p.27).
Few (but typical) respiratory symptoms, normal lung function, and no variable expiratory airflow	**Consider repeating BD responsiveness test** again after withholding bronchodilator as above or during symptoms. If normal, consider investigation for alternative diagnoses (Box 1-3, p.27). **Consider stepping down ICS-containing treatment** (see Box 1-5, p.32): • *If symptoms emerge and lung function falls*: asthma is confirmed. Step up ICS-containing treatment to previous lowest effective dose. • *If no change in symptoms or lung function at lowest controller step*: consider ceasing maintenance ICS-containing treatment, or switching to as-needed-only ICS-formoterol, and monitor patient closely for at least 12 months (Box 4-13, p.102). Consider biomarkers, as above.
Persistent shortness of breath and persistent airflow limitation	**Consider stepping up ICS-containing treatment for 3 months** (Box 4-6, p.77), then reassess symptoms and lung function. If no response, resume previous ICS dose and refer patient for further investigation and management, or manage as for patients with features of both asthma and COPD (Section 7, p.131). Consider biomarkers, as above.

BD: bronchodilator; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; LABA: long-acting $beta_2$-agonist; PEF: peak expiratory flow; SABA: short-acting $beta_2$-agonist.

Withholding period for long-acting bronchodilators: 24 hours for formoterol, salmeterol; 36 hours for indacaterol, vilanterol; 36-48 hours for tiotropium, umeclidinium, aclidinium, glycopyrronium. *If spirometry is not possible, PEF may be used, but it is less reliable. Use the same PEF meter each time, as PEF may vary by up to 20% between different meters. For each PEF measurement, use the highest of 3 readings.

When can variable expiratory airflow be documented?

If possible, evidence of variable expiratory airflow should be documented before treatment is started. This is because variability usually decreases with ICS treatment as lung function improves. In addition, any increase in lung function after initiating ICS-containing treatment can help to confirm the diagnosis of asthma. Bronchodilator response may not be present between symptoms, during viral infections or if the patient has used a beta$_2$-agonist within the previous few hours; and in some patients with asthma, airflow limitation may become persistent or nonresponsive over time.

If neither spirometry nor PEF is available, or variable expiratory airflow is not documented, the decision about whether to investigate further or start ICS-containing treatment immediately depends on clinical urgency and access to other tests.[25] Elevated FeNO or blood eosinophils may support the diagnosis of Type 2 asthma (asthma characterized by eosinophilic and/or allergic inflammation) but lower levels do not rule out asthma (p.217). Box 1-4 (p.30) describes how to confirm the diagnosis of asthma in a patient already taking ICS-containing treatment.

Other tests that may be used in diagnosis of asthma

Bronchial provocation tests

One option for documenting variable expiratory airflow is to refer the patient for bronchial provocation testing to assess airway hyperresponsiveness. Challenge agents include inhaled methacholine,[39] histamine, exercise,[40] eucapnic voluntary hyperventilation or inhaled mannitol. These tests are moderately sensitive for a diagnosis of asthma but have limited specificity[39,40]. For example, airway hyperresponsiveness to inhaled methacholine has been described in patients with allergic rhinitis,[41] cystic fibrosis[42], bronchopulmonary dysplasia[43] and COPD.[44] 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.25) and other clinical features (Box 1-3, p.27) must also be considered.

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 prick 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.[45] 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.

Imaging

Imaging studies are not routinely used in the diagnosis of asthma, but may be useful to investigate the possibility of comorbid conditions or alternative diagnoses in adults with difficult-to-treat asthma. Imaging may also be used to identify congenital abnormalities in infants with asthma-like symptoms, and alternative diagnoses in children with difficult-to-treat asthma. High-resolution computed tomography (CT) of the lungs can identify conditions such as bronchiectasis, emphysema, lung nodules, airway wall thickening and lung distension, and may assess airway distensibility. The presence of radiographically detected emphysema is considered when differentiating asthma from COPD (Box 7-4, p.137), but there is no accepted threshold, and these conditions can coexist. Moreover, air trapping (which may be present in asthma, and is also a feature of ageing) can be difficult to distinguish from emphysema. Chest imaging is not currently recommended to predict treatment outcomes or lung function decline, or to assess treatment response.

CT of the sinuses can identify changes suggestive of chronic rhinosinusitis with or without nasal polyps (p.120), which in patients with severe asthma may help with choice of biologic therapy (see Box 8-4, p.144).

Exhaled nitric oxide

The fractional concentration of exhaled nitric oxide (FeNO) is modestly associated with levels of sputum and blood eosinophils.[46] FeNO is higher in asthma that is characterized by Type 2 airway inflammation with elevated interleukin (IL)-4 and IL-13,[47] but it is also elevated in non-asthma conditions (e.g., eosinophilic bronchitis, atopy, allergic rhinitis,

atopic dermatitis), and it is not elevated in some asthma phenotypes (e.g., neutrophilic asthma, asthma with obesity).[22,4820] In patients with typical asthma symptoms, FeNO >50 ppb in adults/adolescents or >35 ppb in children can support a diagnosis of Type 2 asthma, but lower levels do not rule out asthma.[49] In addition, FeNO levels vary by multiple factors including sex, age, time of day (higher in afternoon than morning), FeNO device, and site, precluding the establishment of reference values.[50] FeNO is also lower in smokers and during bronchoconstriction[51] and the early phases of allergic response;[52] it may be increased or decreased during viral respiratory infections.[51] For information on the role of FeNO in asthma treatment, see Section 4 (p.72) and the biomarker summary in Appendix A (p.216).

Blood eosinophil count

In a patient with typical asthma symptoms, a blood eosinophil count above the national/regional reference range can support a diagnosis of Type 2 asthma, but lower levels do not rule out asthma. Blood eosinophils are also elevated in non-asthma conditions including parasitic infection, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis with nasal polyps (CRSwNP), hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis (EGPA). Blood eosinophil counts vary significantly by age, sex, time of day (lower in afternoon than in morning), geographic location, obesity, and by allergen exposure in sensitized individuals,[53,54] so it is important to use national/regional reference ranges. Blood eosinophils may be decreased by nasal, inhaled or oral corticosteroids (see Appendix A, p.216).

CONFIRMING THE DIAGNOSIS IN PATIENTS ALREADY TAKING ICS-CONTAINING TREATMENT

If the basis of a patient's diagnosis of asthma has not previously been documented, confirmation with objective testing should be sought. In primary care, the presence of asthma cannot be confirmed in many patients (25–35%) who have previously received this diagnosis.[28,55-58]

The process for confirming the diagnosis in patients already on ICS-containing treatment depends on the patient's symptoms and lung function (Box 1-4, p.30). It may include a trial of a lower or higher ICS dose (Box 1-5, p.32). If the diagnosis of asthma cannot be confirmed, refer the patient for expert investigation and diagnosis.

Box 1-5. How to step down ICS-containing treatment to help confirm the diagnosis of asthma

1. ASSESS

- Document the patient's current status including asthma symptom control and risk factors (Box 2-2, p.37) and lung function. If the patient has risk factors for asthma exacerbations (Box 2-2B), step down treatment only with 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 9-2, p.163) so the patient/caregiver knows how to recognize and respond if symptoms worsen. Ensure they will have enough medication to be able to resume their previous dose if their asthma worsens after stepping down.

2. ADJUST

- Show the patient/caregiver how to reduce their ICS dose by 25–50%, or stop other maintenance medication (e.g., LABA) if being used. See step-down options in Box 4-13, p.102. Schedule a review visit for 2–4 weeks.

3. REVIEW RESPONSE

- Repeat assessment of asthma control and lung function tests in 2–4 weeks (Box 1-2, p.25).
- If symptoms increase and excessive variation in expiratory airflow is confirmed after stepping down treatment, the diagnosis of asthma is confirmed. The patient should be returned to their lowest previous effective treatment.
- If, after stepping down to a low-dose ICS-containing treatment, symptoms do not worsen and there is still no evidence of variable expiratory airflow limitation to confirm the diagnosis of asthma, consider ceasing ICS-containing treatment and repeating asthma control assessment and lung function tests in 2–3 weeks, but follow the patient for at least 12 months.[28]

ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist.

HOW TO MAKE THE DIAGNOSIS OF ASTHMA IN OTHER CONTEXTS

Patients presenting with persistent cough as the only respiratory symptom

Common causes of an isolated non-productive cough include cough-variant asthma, chronic upper airway cough syndrome (often called "postnasal drip"), cough induced by angiotensin-converting enzyme (ACE) inhibitors, gastroesophageal reflux, chronic sinusitis, post-infectious cough,[59] inducible laryngeal obstruction,[60,61] and eosinophilic bronchitis.

In cough variant asthma, a persistent cough is the only symptom, or, in cough predominant asthma, the most prominent symptom.[20,21,62] The cough may be worse at night or with exercise, and in some patients it is productive. Spirometry is usually normal, and the only abnormality in lung function may be airway hyperresponsiveness on bronchial provocation testing (Box 1-2, p.25,). Some patients with cough variant asthma may later develop wheeze and significant bronchodilator responsiveness on spirometry.[63] Most patients with cough variant asthma have sputum eosinophilia, and they may also have elevated FeNO.[20] Cough-variant asthma must also be distinguished from eosinophilic bronchitis in which patients have cough and sputum eosinophilia but normal spirometry and normal airway responsiveness.[64] Treatment of cough variant asthma follows usual recommendations for asthma.

Occupational asthma and work-exacerbated 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.[65,66]

An estimated 5–20% of new cases of adult-onset asthma can be attributed to occupational exposure.[65] Adult-onset asthma requires a systematic inquiry about work history and exposures, including hobbies. Asking patients whether their symptoms improve when they are away from work (weekends or vacation) is an essential screening question.[67] 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. There is more information about occupational asthma in Section 6 (p.117) and in specific guidelines.[65,6858]

Athletes

The diagnosis of asthma in athletes should be confirmed by lung function tests, usually with bronchial provocation testing.[69] Conditions that may either mimic or be associated with asthma, such as rhinitis, laryngeal disorders (e.g., inducible laryngeal obstruction),[61] dysfunctional breathing, cardiac conditions and over-training, must be excluded.[70]

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 (p.126).[71] If the clinical history is consistent with asthma, and other diagnoses appear unlikely (Box 1-3, p.27) but the diagnosis of asthma is not confirmed on initial bronchodilator responsiveness testing (Box 1-2, p.25), manage as asthma with ICS-containing treatment (p.126) and postpone other diagnostic investigations until after delivery. During pregnancy, bronchial provocation testing is contraindicated, and it is not advisable to step down ICS-containing treatment.

The elderly

Asthma is frequently undiagnosed in the elderly,[72] due to poor perception of airflow limitation; acceptance of dyspnea as normal in old age, lack of fitness, and reduced physical activity. The presence of multimorbidity 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.[73] 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.[74] Measurement of plasma brain natriuretic polypeptide and assessment of cardiac function with echocardiography may also be helpful.[75] In older people with a history of smoking or biomass fuel exposure, COPD and overlapping asthma and COPD should be considered (Section 7, p.131).

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', formerly called asthma-COPD overlap). The Global Strategy for Diagnosis, Management and Prevention of COPD (GOLD) 2025[76] defines COPD on the basis of chronic respiratory symptoms, environmental exposures such as smoking or inhalation of toxic particles or gases, with confirmation by post-bronchodilator FEV_1/FVC <0.7. Clinically important bronchodilator responsiveness (≥12% and ≥200 mL) is often found in patients with a diagnosis of COPD.[77] Low diffusion capacity is more common in COPD than asthma. In current smokers, FeNO is lower and blood eosinophil count is higher (see Appendix A).

The history and pattern of symptoms and past records can help to distinguish patients with COPD from those with longstanding asthma who have developed persistent airflow limitation. Uncertainty in the diagnosis should prompt early referral for specialized investigation and treatment recommendations, as patients with asthma+COPD have worse outcomes than those with asthma or COPD alone (see Section 7, p.131).[78]

Obese patients

While asthma is more common in obese than non-obese people,[79] 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 expiratory airflow. 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).[55] Another study found both over- and under-diagnosis of asthma in obese patients.[80]

Low- and middle-income countries

Diagnosis of asthma in low-resource settings, including low- and middle-income countries (LMICs), presents substantial challenges for clinical practice.[25] Access to lung function testing, particularly spirometry, is often very limited. Even when available, lung function testing may be substantially underused (e.g., unaffordable for the patient or health system,[81] or too time-consuming in a busy clinic). A single lung function test may not be sufficient to confirm the diagnosis of asthma or indicate an alternative cause, so more than one visit by the patient (with resulting costs of time and travel) may be needed.[25] The differential diagnosis of asthma in these countries may often include other endemic respiratory diseases (e.g., tuberculosis, HIV/AIDS-associated lung diseases, and parasitic or fungal lung diseases).

As a result of these issues, clinicians often use a syndromic approach to diagnosis and initial management, based on history and clinical findings.[82] Practical evidence-based resources have been developed and implemented in several countries.[83,84] This approach reduces diagnostic precision but is based on the assumption (valid in most LMICs) that under-diagnosis and under-treatment of asthma is more likely[85] than the overdiagnosis and overtreatment often seen in high income countries.[28,86]

GINA does not recommend that diagnosis of asthma should be solely based on syndromic clinical patterns, and suggests lung function testing with a PEF meter if spirometry is not available.[25] The World Health Organization (WHO) Package of essential noncommunicable (PEN) disease interventions for primary care[87] lists the PEF meter as an essential tool in the management of chronic respiratory diseases.

When spirometry is not available, the presence of variable expiratory airflow (including responsiveness) can be confirmed by PEF, as outlined in Box 1-2, p.25.

For example, before starting long-term ICS-containing treatment, the following findings can help to confirm the diagnosis of asthma (or prompt investigation for alternative diagnoses):

- ≥20% improvement in PEF 15 minutes after giving 2 puffs of salbutamol (albuterol)[87]
- Improvement in symptoms and PEF after a 4-week therapeutic trial with ICS-containing treatment.[25]

Either of these findings would increase the likelihood of a diagnosis of asthma versus other diagnoses.

A structured algorithmic approach to patients presenting with respiratory symptoms forms part of several strategies developed for improving respiratory disease management in LMICs.[5] These strategies particularly useful in countries where, owing to the high prevalence of tuberculosis, large numbers of patients with respiratory symptoms present for assessment at tuberculosis clinics.

There is a pressing need for access to affordable diagnostic tools (peak flow meters and spirometry), and training in their use, to be substantially scaled up in LMICs.[25]

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

KEY POINTS

Asthma control

- Asthma control is the extent to which the features of asthma have been reduced or resolved by treatment.
- It is assessed in two domains: ***symptom control*** and ***risk* of adverse outcomes**. Poor symptom control is burdensome to patients and increases the risk of exacerbations, but patients with good symptom control can still have severe exacerbations.

Asthma severity

- The current definition of asthma severity is based on retrospective assessment, after at least 2–3 months of asthma treatment, from the intensity of treatment required to control symptoms and exacerbations.
- This definition is clinically useful for severe asthma, as it identifies patients whose asthma is relatively refractory to high intensity treatment with high-dose inhaled corticosteroids (ICS) and a long-acting beta$_2$-agonist (LABA) and who may benefit from additional treatment such as biologic therapy. It is important to distinguish between severe asthma and asthma that is uncontrolled due to modifiable factors such as incorrect inhaler technique and/or poor adherence.
- However, the retrospective definition of mild asthma as "easy to treat" is less useful, as patients with few interval symptoms can have exacerbations triggered by external factors such as viral infections or allergen exposure, and the treatment regimen that was historically regarded as the lowest intensity – short-acting beta$_2$-agonist (SABA) alone – actually *increases* the risk of exacerbations, compared with any ICS-containing treatment.
- "Mild asthma" is a retrospective label, so it cannot be used to decide which patients are suitable to receive Step 1 or Step 2 treatment.
- In clinical practice and in the general community, the term "mild asthma" is often used to mean infrequent or mild symptoms, and it is often assumed that these patients are not at risk and do not need ICS-containing treatment.
- For these reasons, GINA suggests that the term "mild asthma" should generally be avoided in clinical practice if possible or, if used, qualified with a reminder that patients with infrequent symptoms can still have severe or fatal exacerbations, and that this risk is substantially reduced with ICS-containing treatment.

How to assess a patient's asthma

- Assess symptom control from the frequency of daytime and night-time asthma symptoms, night waking and activity limitation and, for patients using SABA reliever, their frequency of SABA use. Other tools for assessing recent symptom control include Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ). There are no validated tools for assessing symptom control over a longer period.
- Also, separately, assess the patient's risk factors for exacerbations, even if their symptom control is good. Risk factors for exacerbations that are independent of symptom control include a history of ≥1 exacerbation in the previous year, SABA-only treatment (without any ICS), over-use of SABA, socioeconomic problems, poor adherence, incorrect inhaler technique, low forced expiratory volume in 1 second (FEV_1), exposures such as smoking, and elevated blood eosinophils or FeNO.
- Also assess risk factors for persistent airflow limitation and medication side-effects (including from oral corticosteroids), treatment issues such as inhaler technique and adherence, and comorbidities, and ask the patient/caregiver about their asthma goals and treatment preferences.
- Once the diagnosis of asthma has been made, the main role of lung function testing is in the assessment of future risk. It should be recorded at diagnosis, 3–6 months after starting treatment, and periodically thereafter.
- Investigate for impaired perception of bronchoconstriction if there are few symptoms but low lung function, and investigate for alternative diagnoses if there are frequent symptoms despite good lung function.

OVERVIEW

The long-term goal of asthma treatment is to achieve the best possible long-term outcomes for the patient (Box 3-2, p.50). 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, p.36). Lung function, particularly FEV_1 as a percentage of predicted value, is an important part of the assessment of future risk.

The use of digital technology, telemedicine and telehealthcare in the monitoring of patients with asthma is rapidly increasing, particularly during the COVID-19 pandemic. However, the types of interactions are diverse, and high-quality studies are needed to evaluate their utility and effectiveness.

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

1. Assess asthma control, i.e., symptom control AND future risk of adverse outcomes

- Assess symptom control over the last 4 weeks (Box 2-2A, p.37) or longer.
- 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 ICS-containing treatment, then periodically, e.g., at least once every 1–2 years, but more often in at-risk patients and those with severe asthma.

2. Assess treatment issues

- Document the patient's current treatment step (Box 4-6, p.77).
- Watch inhaler technique (Box 5-2, p.110), assess adherence (Box 5-3, p.112) 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 multimorbidity

- 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 (see Section 6, p.117).

ICS: inhaled corticosteroid

What is meant by "asthma control"?

The level of asthma control is the extent to which the manifestations of asthma have been reduced or removed by treatment.[37,88] 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.[88]

Asthma control has two domains: symptom control and future risk of adverse outcomes (Box 2-2, p.37). 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.

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

A. Recent asthma symptom control (but also ask the patient/caregiver about the whole period since last review*)

In the past 4 weeks, has the patient had:		Well controlled	Partly controlled	Uncontrolled
• Daytime asthma symptoms more than twice/week?	Yes☐ No☐	None of these	1–2 of these	3–4 of these
• Any night waking due to asthma?	Yes☐ No☐			
• SABA† reliever for symptoms more than twice/week?	Yes☐ No☐			
• Any activity limitation due to asthma?	Yes☐ No☐			

B. Risk factors for poor asthma outcomes

Assess risk factors at diagnosis and periodically, including after an exacerbation.

Measure FEV_1 at start of treatment, after 3–6 months of ICS-containing treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment.

i. Risk factors for exacerbations

Uncontrolled asthma symptoms: Having uncontrolled symptoms is an important risk factor for exacerbations.[89]

Factors that increase the risk of exacerbations even if the patient has few asthma symptoms‡:[14,90,91]

- *SABA over-use:* High SABA use (≥3 x 200-dose canisters/year associated with increased risk of exacerbations, increased mortality particularly if ≥1 canister per month)[92-95]
- *Inadequate ICS*: not prescribed ICS, poor adherence,[96] or incorrect inhaler technique[97]
- *Other medical conditions:* Obesity,[14,91,98,99] chronic rhinosinusitis,[14,99] GERD,[99] confirmed food allergy,[100] pregnancy[101]
- *Exposures:* Smoking,[91,102] e-cigarettes,[103] allergen exposure if sensitized,[102,104] air pollution[105-108]
- *Psychosocial*: Major psychological or socioeconomic problems[109,110]
- *Lung function:* Low FEV_1 (especially <60% predicted),[102,111] high bronchodilator responsiveness[99,112,113]
- *Type 2 inflammatory markers:* Raised blood eosinophils,[14,99,114,115] high FeNO[14,116] (see biomarker overview, p.216)
- *Exacerbation history:* Ever intubated or in intensive care unit for asthma,[117] ≥1 severe exacerbation in last year[118,119]

ii. Risk factors for developing persistent airflow limitation

- *History:* Preterm birth, low birth weight and greater infant weight gain,[120] frequent productive cough[121,122]
- *Medications:* Lack of ICS treatment in patient with history of severe exacerbation[123]
- *Exposures:* Tobacco smoke,[121] noxious chemicals; occupational or domestic exposures[65]
- *Investigation findings:* Low initial FEV_1,[122] sputum or blood eosinophilia[122]

iii. Risk factors for medication side-effects

- *Systemic* Frequent OCS, long-term, high-dose and/or potent ICS, cytochrome P450 inhibitors§[124]
- *Local:* High-dose or potent ICS,[124,125] poor inhaler technique[126]

FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; GERD: gastro-esophageal reflux disease; ICS: inhaled corticosteroid; SABA: short-acting $beta_2$-agonist; OCS: oral corticosteroid. *In addition to assessing recent asthma symptom control, also ask the patient about symptom control over the whole period since their last clinical review. There are no validated tools for assessing long-term symptom control (>4 weeks); † Based on SABA (as-needed ICS-formoterol reliever not included); excludes reliever taken before exercise (see Assessing asthma symptom control, p.38); ‡ Independent risk factors after adjustment for the level of symptom control. Some studies have evaluated several of the above risk factors for exacerbations;[14,90,91] § Cytochrome P450 inhibitors such as ritonavir, ketoconazole, itraconazole may increase systemic exposure to some types of ICS and some long-acting $beta_2$-agonists; see drug interaction websites and p.122 for details. For children 6–11 years, also refer to Box 2-3, p.40. See Box 3-5, p.56 for specific risk reduction strategies.

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 overestimate their level of control or underestimate its severity, but that patients understand and use the word "control" differently from healthcare providers, e.g., based on how quickly their symptoms resolve when they take reliever medication.[88,127] If the term "asthma control" is used with patients, the meaning should always be explained.

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.[128-130]

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 may differ 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 recent symptom control (Box 2-2A, p.37) 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, for patients using a SABA reliever, frequency of its use for relief of symptoms. In general, do not include reliever taken before exercise, because some people take this routinely without knowing whether they need it.

Frequency of reliever use

Historically, frequency of SABA reliever use (<2 or ≥2 days/week) has been included in composite assessments of symptom control. This distinction was arbitrary, based on the assumption that if SABA was used on >2 days in a week, the patient needed to start maintenance ICS-containing therapy or increase the dose. In addition, higher average use of SABA over a year is associated with a higher risk of severe exacerbations,[92,93] and in the shorter term, increasing use of as-needed SABA is associated with an increased likelihood of a severe exacerbation in subsequent days or weeks.[131]

However, for patients prescribed an anti-inflammatory reliever (AIR) such as as-needed low-dose ICS-formoterol (GINA Track 1, Box 4-6, p.77), use of this reliever more than 2 days/week is already providing additional ICS therapy, so further dose escalation may not be needed. In addition, increasing use of as-needed ICS-formoterol is associated with a significantly lower risk of severe exacerbation in subsequent days or weeks, compared with SABA reliever used with maintenance ICS-containing treatment ,[132,133] or compared with SABA alone.[134]

For these reasons, while the assessment of symptom control in Box 2-2A (p.37) includes a criterion for SABA reliever use on ≤2 versus >2 days/week, it does not include a similar criterion for an anti-inflammatory reliever such as as-needed ICS-formoterol. However, the patient's average frequency of as-needed ICS-formoterol use over the past 4 weeks should be assessed, and considered when the patient's maintenance ICS dose (or need for maintenance ICS-formoterol) is reviewed. This issue will be reviewed again when more data become available.

Tools for assessing recent asthma symptom control in 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, p.37). This classification correlates with assessments made using numerical asthma control scores.[135,136] It can be used, together with a risk assessment (Box 2-2B), to guide treatment decisions (Box 4-6, p.77). Other examples are the Primary Care

Asthma Control Screening Tool (PACS),[137] and the 30-second Asthma Test, which also includes work/school absence.[138]

Categorical symptom control tools: Examples include the consensus-based "Royal College of Physicians (RCP) Three Questions" tool,[139] which asks about difficulty sleeping, daytime symptoms and activity limitation due to asthma in the previous month. The Asthma Activities, Persistent, triGgers, Asthma medications, Response to therapy (APGAR) tool 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 years in primary care was associated with improved rates of asthma control; reduced asthma-related urgent care, and hospital visits; and increased practices' adherence to asthma management guidelines.[140]

Numerical "asthma control" tools: These tools provide scores and cut points to distinguish different levels of **symptom** control, validated against healthcare 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.[135]

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

- **Asthma Control Questionnaire (ACQ):**[141,142] Scores range from 0–6 (higher is worse), with scores calculated as the average from all questions. The authors stated that ACQ ≤0.75 indicated a high probability that asthma was well controlled; 0.75–1.5 was a "grey zone"; and ≥1.5 indicated a high probability that asthma was poorly controlled, based on concepts of asthma control at the time. They later identified 1.0 as the approximate crossover point between "well-controlled" and "not well-controlled" asthma.[143] The 5-item ACQ (ACQ-5), comprises five symptom questions. Two additional versions were published: ACQ-6 includes SABA frequency, and ACQ-7 also includes pre-bronchodilator FEV_1% predicted. The minimum clinically important difference for all three versions of ACQ is 0.5.[143] GINA recommends ACQ 5 over ACQ-6 or 7 because the reliever question for ACQ-6 and 7 assumes regular, rather than as-needed use of SABA, there is no option between zero SABA use in a week and SABA use every day, and ACQ has not been validated with ICS-formoterol or ICS-SABA as the reliever. In addition, if ACQ-7 were to be used in adjustment of treatment, the inclusion of FEV_1 in the composite score could lead to repeated step-up in ICS dose for patients with persistent airflow limitation. For these reasons, data for ACQ-5, ACQ-6 and ACQ-7 cannot be combined for meta-analysis.
- **Asthma Control Test (ACT):**[136,144,145] Scores range from 5–25 (higher is better). Scores of 20–25 are classified as "well-controlled", 16–19 as "not well-controlled", and 5–15 as "very poorly controlled" asthma. The ACT has four symptom/ reliever questions plus patient self-assessed control. The minimum clinically important difference is 3 points.[145] It has not been validated with ICS-formoterol or ICS-SABA reliever.

Patients with good symptom control can still be at risk of future severe exacerbations or asthma-related death, and there are many modifiable risk factors for exacerbations that are independent of symptom control (Box 2-2B, p.37), so GINA does not recommend assessment tools that combine symptom control with exacerbation history.

When different tools 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 whether symptoms are due to asthma.

Recent symptom control can be assessed over the previous 1–4 weeks using tools such as in GINA Box 2-2A (p.37), or ACQ-5 or ACT. There are no validated tools for assessing asthma symptom control over a longer period (e.g., 12 months). In clinical practice, clinicians can use a simple question to ask patients about asthma control over previous months, but substantial recall error is likely, particularly for mild symptoms.

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

Asthma symptom control	
Day symptoms	Ask: 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 symptoms managed?
Night symptoms	Cough, awakenings, tiredness during the day? (If the only symptom is nocturnal cough, consider other diagnoses such as 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/caregiver.
Risk factors for adverse outcomes	
Exacerbations	Ask: 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? Risk factors for exacerbations include a history of exacerbations, poor symptom control, poor adherence and poverty,[119] and persistent bronchodilator response even if the child has few symptoms.[113]
Lung function	Check spirogram 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,[146] and growth velocity may be lower in the first 1–2 years of ICS treatment.[147,148] 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	Is there any of the child's prescribed maintenance medication (inhalers and/or tablets) in the home at present? On how many days in a week does the child use it (e.g., 0, 2, 4, 7 days)? Is it easier to remember to use it in the morning or evening? Where is the medication kept: is it in plain view to reduce forgetting? Check date on inhaler.
Goals/concerns	Does the child or their parent or caregiver have any concerns about their asthma (e.g., fear of medication, side-effects, interference with activity)? What are their 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.)[100]
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/caregiver to keep a daily diary of asthma symptoms, reliever use and peak expiratory flow (best of three) for 2 weeks.
Formal exercise challenge	Provides information about airway hyperresponsiveness and fitness (Box 1-2, p.25). Only perform challenge testing if it is otherwise difficult to assess asthma control.

BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; ICS: inhaled corticosteroid: OCS: oral corticosteroid.

Tools for assessing recent asthma symptom control for children aged 6–11 years

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 parent or caregiver. They may report irritability, tiredness, and changes in mood in their child as the main problems when the child's asthma is not controlled. Parents/caregivers have a longer recall period than children, who may recall only the last few days. Therefore, it is important to include information from both the parent/caregiver and the child when assessing the level of symptom control.

Several numeric tools have been developed for assessing recent asthma symptom control for children. These include:

- **Childhood Asthma Control Test (c-ACT)**[149] with separate sections for parent/caregiver and child to complete
- **Asthma Control Questionnaire (ACQ)**.[150,151]

Some asthma control scores for children include history of exacerbations with symptoms, but these may have the same limitations as described above for adults. They include the Test for Respiratory and Asthma Control in Kids (TRACK)[152-154] and the Composite Asthma Severity Index (CASI).[155]

The results of these various tests correlate, to some extent, with each other and with the GINA classification of symptom control. Box 2-3 (p.40) provides more details about assessing asthma control in children.

ASSESSING FUTURE RISK OF EXACERBATIONS, LUNG FUNCTION DECLINE AND ADVERSE EFFECTS

The second component of asthma control to assess (Box 2-2B, p.37) is 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 strongly predict an individual's of risk of future exacerbations, but assessing only symptoms is not sufficient for several reasons:

- Asthma symptoms can be controlled by placebo or sham treatments[156,157] or by inappropriate use of SABA or LABA alone,[158] all of which leave airway inflammation untreated.
- Respiratory symptoms may be due to other conditions such as lack of fitness, or comorbidities such as inducible laryngeal obstruction.[61]
- Anxiety or depression may contribute to higher symptom reporting.
- Some patients have impaired perception of bronchoconstriction, with few symptoms despite low lung function.[159]
- In patients with good symptom control, exacerbations can be triggered by environmental exposures such as viral infections, allergen exposure and poor air quality.

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.[128-130] 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, p.37) include a history of ≥1 exacerbation in the previous year, poor adherence, incorrect inhaler technique, low lung function, chronic sinusitis, smoking, fractional exhaled nitric oxide (FeNO) and blood eosinophils, all of which can be assessed in primary care.[14,90,91] Analysis of the placebo groups of randomized controlled trials, mainly in patients with moderate-severe asthma, confirmed that many of the factors in Box 2-2B (p.37) were independently associated with an increased rate of severe exacerbations.[14]

The risk of severe exacerbations and mortality increases incrementally with higher SABA use, independent of treatment step.[93] Prescribing of three or more 200-dose SABA inhalers in a year, corresponding to more than daily

use, is associated with an increased risk of severe exacerbations[92,93] and increased mortality.[93,95] Risk factors and comorbidities that are modifiable (or potentially modifiable) are often called “treatable traits”.[160]

Environmental exposures to respiratory viruses, aeroallergens, air pollution and weather changes (p.130)can also contribute substantially to exacerbation risk, and are often not recorded in clinical trials. The large reduction in asthma hospitalizations during the COVID-19 pandemic that was seen in many countries demonstrated that reducing exposure to respiratory viruses can significantly reduce the risk of exacerbations in patients with asthma.[161,162]

In children, the risk of exacerbations is greatly increased if there is a history of previous exacerbations; it is also increased with poor symptom control, suboptimal drug regimen, comorbid allergic disease and poverty.[119]

Risk factors for development of persistent airflow limitation

The average rate of decline in FEV_1 in non-smoking healthy adults is 15–20 mL/year.[163] People with asthma may have an accelerated decline in lung function and develop airflow limitation that is not fully responsive to bronchodilators. 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, frequent productive cough, and asthma exacerbations in patients not taking ICS[123] (see Box 2-2B, p.37). 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.[164] There is no clear evidence that treatment with ICS prevents accelerated decline in post-bronchodilator lung function, i.e., that it prevents development of persistent airflow limitation.

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 and fragility fractures, cataracts, glaucoma, and adrenal suppression. Local side-effects of ICS include oral candidiasis (thrush) and dysphonia. Patients are at greater risk of ICS side-effects with higher doses or more potent formulations[124,125] and, for local side-effects, with incorrect inhaler technique.[126] A summary of asthma medications has been added as an appendix at the end of this report (p.222).

Drug interactions with asthma medications: concomitant treatment with cytochrome P450 inhibitors such as ketoconazole, ritonavir, itraconazole, erythromycin and clarithromycin may increase the risk of ICS adverse effects such as adrenal suppression, and with short-term use, may increase the risk of cardiovascular adverse effects of the LABAs salmeterol and vilanterol (alone or in combination with ICS). Concomitant use of these medications is not recommended (see also p.122).[165]

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 adults[166] or children.[167] In some asthma control tools, lung function is numerically averaged or combined with symptoms[141,168] but this is not recommended because, if the tool includes several symptom items, these can outweigh clinically important differences in lung function.[169] In addition, low FEV_1 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 ICS-containing treatment to assess the patient’s personal best FEV_1, and periodically thereafter. For example, lung function should be recorded at least every 1–2 years for most adult patients, but more frequently for higher-risk patients, including those with exacerbations and those at risk of decline in lung function (see Box 2-2B, p.37). 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,[37] but preferably the same conditions should apply at each visit.

How to interpret lung function test results in asthma

A low FEV_1 percent predicted:

- Identifies patients at risk of asthma exacerbations, independent of symptom levels, especially if FEV_1 is <60% predicted[102,111,170,171]
- Is a risk factor for lung function decline, independent of symptom levels[122]
- If symptoms are few, suggests limitation of lifestyle, or poor perception of airflow limitation,[172] which may be due to untreated airway inflammation.[159]

Normal FEV_1: A "normal" or near-normal FEV_1 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.27).

Persistent bronchodilator responsiveness: Significant bronchodilator responsiveness (increase in FEV_1 ≥12% and ≥200 mL from baseline)[34] in a patient taking ICS-containing treatment, or who has taken a SABA within 4 hours, or a LABA within 12 hours (or 24 hours for a once-daily LABA), suggests uncontrolled asthma, particularly poor adherence and/or incorrect technique.

In children, spirometry cannot be reliably obtained until age 5 years or later, 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, FEV_1 starts to improve within days, and reaches a plateau after around 2 months.[173] The patient's highest FEV_1 reading (personal best) should be documented, as this provides a more useful comparison for clinical practice than FEV_1 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 persistent (incompletely responsive) airflow limitation. While a short-term (e.g., 3 months) trial of higher dose ICS or ICS-LABA may be appropriate to see if FEV_1 can be improved, high doses should not be continued longer than this if there is no response.

The between-visit variability of FEV_1 (up to 12% week-to-week or 15% year-to-year in healthy individuals)[34] limits its use in adjusting asthma treatment or identifying accelerated decline in clinical practice. The minimal important difference for improvement and worsening in FEV_1, based on patient perception of change, has been reported to be about 10%.[174,175]

The role of short-term and long-term lung function monitoring

Once the diagnosis of asthma is made, short-term peak expiratory flow (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.[176] Average PEF continues to increase, and diurnal PEF variability to decrease, for about 3 months.[166,176] Excessive variation in PEF suggests suboptimal asthma control, and increases the risk of exacerbations.[177]

Long-term PEF monitoring is now generally only recommended for patients with severe asthma, or those with impaired perception of airflow limitation (e.g., few symptoms despite low initial lung function).[159,178-181] In clinical practice, displaying PEF results on a standardized chart may improve accuracy of interpretation.[182]

Home spirometric monitoring has been used in some clinical trials; careful training of patients in spirometric technique is essential. Results from clinic-based and home-recorded spirometry are not interchangeable.

ASSESSING ASTHMA SEVERITY

The current concept of asthma severity is based on "difficulty to treat"

The current concept of asthma severity, recommended by an ATS/ERS Task Force[37,88] and included in most asthma guidelines, is that asthma severity should be assessed retrospectively from how difficult the patient's asthma is to treat. This is reflected by the level of treatment required to control the patient's symptoms and exacerbations, i.e., after at least several months of treatment.[37,88,183] This definition is mainly relevant to, and useful for, severe asthma.

By this definition:

- Severe asthma is defined as asthma that remains uncontrolled despite optimized treatment with high-dose ICS-LABA, or that requires high-dose ICS-LABA to prevent it from becoming uncontrolled. Severe asthma, i.e., asthma that is relatively refractory to corticosteroid treatment must be distinguished from asthma that is difficult to treat due to inadequate or inappropriate treatment, or problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, since correction of these comorbidities or risk factors ("treatable traits") can significantly improve asthma control.[183] See Box 2-4 (p.47) for how to distinguish difficult-to-treat asthma from severe asthma, and Section 8 (p.139) for more detail about assessment, referral and treatment in this population.
- Moderate asthma is asthma that is well controlled with Step 3 or Step 4 treatment e.g., with low- or medium-dose ICS LABA in either treatment track
- Mild asthma is asthma that is well controlled with low-intensity treatment, i.e., as needed low-dose ICS-formoterol, or low-dose ICS plus as-needed SABA.

However, the utility of this retrospective definition of asthma severity is limited by the fact that it cannot be assessed unless good asthma control has been achieved and treatment stepped down to find the patient's minimum effective dose at which their asthma remains well controlled (Box 4-13, p.102), or unless asthma remains uncontrolled despite at least several months of optimized maximal therapy.

The terms "severe asthma" and "mild asthma" are often used with different meanings than this

In the community and in primary care, the terms "severe" or "mild" asthma are more commonly based on the frequency or severity of symptoms or exacerbations, irrespective of treatment. For example, asthma is commonly called "severe" if patients have frequent or troublesome asthma symptoms, regardless of their treatment, and 'mild asthma' is commonly used if patients do not have daily symptoms or if symptoms are quickly relieved.

In epidemiological studies and clinical trials, asthma is often classified as "mild", "moderate" or "severe" based only on the prescribed treatment by GINA or BTS Step, regardless of patients' level of asthma control. This assumes that the prescribed treatment was appropriate for the patient's needs, but asthma is often under-treated or over-treated.

Most *clinical trials of biologic therapy* enroll patients with asthma that is uncontrolled despite taking medium- or high-dose ICS-LABA, but contributory factors such as incorrect inhaler technique, poor adherence, or comorbidities are rarely assessed and treated before the patient's eligibility for enrolment is considered.[184,185] Some clinical trial participants may therefore have "difficult-to-treat", rather than severe asthma.

Some *guidelines* [186,187] also retain another, older, classification of asthma severity based on symptom and SABA frequency, night waking, lung function and exacerbations before ICS-containing treatment is started.[37,88] This classification also distinguishes between "intermittent" and "mild persistent" asthma, but this historical distinction was arbitrary: it was not based on evidence, but on an untested assumption that patients with symptoms ≤2 days/week were not at risk and would not benefit from ICS, so should be treated with SABA alone. However, it is now known that patients with so-called "intermittent" asthma can have severe or fatal exacerbations,[188,189] and that their risk is substantially reduced by ICS-containing treatment, compared with SABA alone.[190-192] Although this symptom-based classification is stated to apply to patients not on ICS-containing treatment,[186,187] it is often used for patients taking these medications. This can cause confusion, as a patient's asthma may be classified differently, and they may be prescribed different treatment, depending on which definition the clinician or healthcare system uses.

For *low-resource countries* without access to effective medications such as ICS, the World Health Organization definition of severe asthma[193] includes a category of "untreated severe asthma". This category corresponds to uncontrolled asthma in patients not taking any ICS-containing treatment.

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 and lung function can rapidly become well controlled with commencement of ICS-containing treatment, or improved inhaler technique or adherence.[37,88] Likewise, patients often perceive their asthma as mild if they have symptoms that are easily relieved by SABA, or that are infrequent.[37,88] Of concern, patients often interpret the term "mild asthma" to mean that they are not at risk of severe exacerbations and do not need to take ICS-containing treatment. This is often described as patients "underestimating" their asthma severity, but instead it reflects their different interpretation of the words "severity" and "mild", compared with the academic usage of these terms.[37,88]

How useful is the current retrospective definition of asthma severity?

The retrospective definition of **severe asthma** based on difficulty to treat has been widely accepted in guidelines and in specialist clinical practice. It has obvious clinical utility as it identifies patients who, because of their burden of disease and incomplete response to optimized conventional ICS-based treatment, may benefit from referral to a respiratory physician (if available) for further investigation, phenotyping, and consideration of additional treatment such as biologic therapy (See Section 8, p.139). It is appropriate to classify asthma as "difficult-to-treat" rather than severe if there are modifiable factors such as incorrect inhaler technique, poor adherence or untreated comorbidities, because asthma may become well controlled when such issues are addressed.[37,88,183]

By contrast, the clinical utility of the retrospective definition of **mild asthma** is much less clear. There is substantial variation in opinions about the specific criteria that should be used, for example whether FEV_1 should be ≥80% predicted in order for asthma to be considered "mild", and whether the occurrence of any exacerbation precludes a patient's asthma being classified as "mild" for the next 12 months.[194] There are too few studies of the underlying pathology to discern whether isolated exacerbations necessarily imply greater inherent severity, especially given the contribution of external triggers such as viral infections or allergen exposure to sporadic exacerbations.

Further, by this definition, asthma can be classified as mild only after several months of ICS-containing treatment, and only if asthma is well controlled on low-dose ICS or as-needed low-dose ICS-formoterol, so this definition clearly cannot be applied to patients with uncontrolled or partly controlled symptoms who are taking SABA.

Finally, retrospective classification of asthma as mild appears of little value in deciding on future treatment. In addition, in the studies of as-needed ICS-formoterol, baseline patient characteristics such as daily reliever use, lower lung function or history of exacerbations (or even baseline blood eosinophils or FeNO) did not identify patients who should instead be treated with daily ICS.[195,196] Instead, decisions about ongoing treatment should be based upon the large evidence base about the efficacy and effectiveness of as-needed ICS-formoterol or daily ICS, together with an individualized assessment of the patient's symptom control, exacerbation risk, predictors of response, and patient preferences (see Box 3-3, p.52 and Box 3-4, p.52).

However, the most urgent problem with the term "mild asthma", regardless of how it is defined, is that it encourages complacency, since patients, clinicians and health policy makers often interpret "mild asthma" to mean that the patient is at low risk and does not need ICS-containing treatment. However, up to 30% of asthma exacerbations and deaths occur in people with infrequent symptoms, for example, less than weekly or only on strenuous exercise.[188,189]

Interim advice about asthma severity descriptors

For clinical practice

GINA continues to support the current definition of severe asthma as asthma that remains uncontrolled despite optimized treatment with high-dose ICS-LABA, or that requires high-dose ICS-LABA or biologic therapy to prevent it from becoming uncontrolled. GINA also maintains the clinically important distinction between difficult-to-treat and severe asthma (Box 2-4, p.47 and Section 8, p.139). For patients who have had a good asthma response to biologic therapy, a precise description in the medical record would be, e.g., "severe eosinophilic asthma, well controlled on [therapy]", to indicate that the biologic therapy is needed to maintain their improved status. For discussion about the related concept of asthma remission on treatment, see p.50.

We suggest that in clinical practice, the term "mild asthma" should generally be avoided if possible, because of the common but mistaken assumption by patients and clinicians that it equates to low risk, and that ICS treatment is not needed. Instead, assess each patient's symptom control and risk factors on their current treatment (Box 2-1, p.36), as

well as multimorbidity and patient goals and preferences. Explain that patients with infrequent or mild asthma symptoms can still have severe or fatal exacerbations if treated with SABA alone,[188,189] and that this risk is reduced by half to two-thirds with low-dose ICS or with as-needed low-dose ICS formoterol.[190,191] Routinely prescribe ICS-containing therapy to reduce the patient's risk of severe exacerbations (Box 4-3, p.74), and treat any modifiable risk factors or comorbidities using pharmacologic or non-pharmacologic strategies (see Box 3-5, p.56 and Box 3-6, p.57).

"Mild asthma" is a retrospective label, so it cannot be used to decide which treatment patients should receive. Advice has been provided in Section 4 about which patients are suitable for low intensity treatment (Step 1 and 2).

For healthcare provider education

The term "apparently mild asthma" may be useful to highlight the discordance between symptoms and risk, i.e., that patients with infrequent or mild symptoms, who might therefore appear to have mild asthma, can still have severe or fatal exacerbations. However, "apparently mild asthma" in English can easily be mistranslated into some languages as "obviously mild asthma", which is the opposite of the intended meaning. Alternative phrases include "asthma that seems to be mild".

Regardless of the term used, explain that "asthma control" tools such as ACQ and ACT assess only one domain of asthma control, and only over a short period of time (see Assessing asthma symptom control, p.38), and that patients with infrequent interval symptoms are over-represented in studies of severe, near-fatal and fatal asthma exacerbations.[188,189] Always emphasize the need for and benefit from ICS-containing treatment in patients with asthma, regardless of their symptom frequency or severity, and even if they have no obvious additional risk factors.

For epidemiologic studies

If clinical details are not available, describe the prescribed (or dispensed) treatment, without imputing severity, e.g., "patients prescribed SABA with no ICS" rather than "mild asthma". Since treatment options change over time, and may differ between guidelines, state the actual treatment class, rather than a treatment Step (e.g., "low-dose maintenance-and-reliever therapy with ICS-formoterol" rather than "Step 3 treatment").

For clinical trials

Describe the patient population by their level of asthma control and treatment, e.g., "patients with uncontrolled asthma despite medium-dose ICS-LABA plus as-needed SABA" rather than "moderate asthma".

Further discussion is clearly needed

Given the importance of mild asthma and the discordance between its current academic definition and the various ways that the term is used in clinical practice, GINA is continuing to discuss these issues with a wide range of stakeholders. The aim is to obtain agreement among patients, healthcare providers, researchers, industry and regulators about the implications for clinical practice and clinical research of current knowledge about asthma pathophysiology and treatment,[37,88] and whether/how the term "mild asthma" should be used in the future. Pending the outcomes of this discussion, no change has been made to use of the term "mild asthma" elsewhere in this GINA Strategy Report.

HOW TO DISTINGUISH BETWEEN UNCONTROLLED ASTHMA AND SEVERE ASTHMA

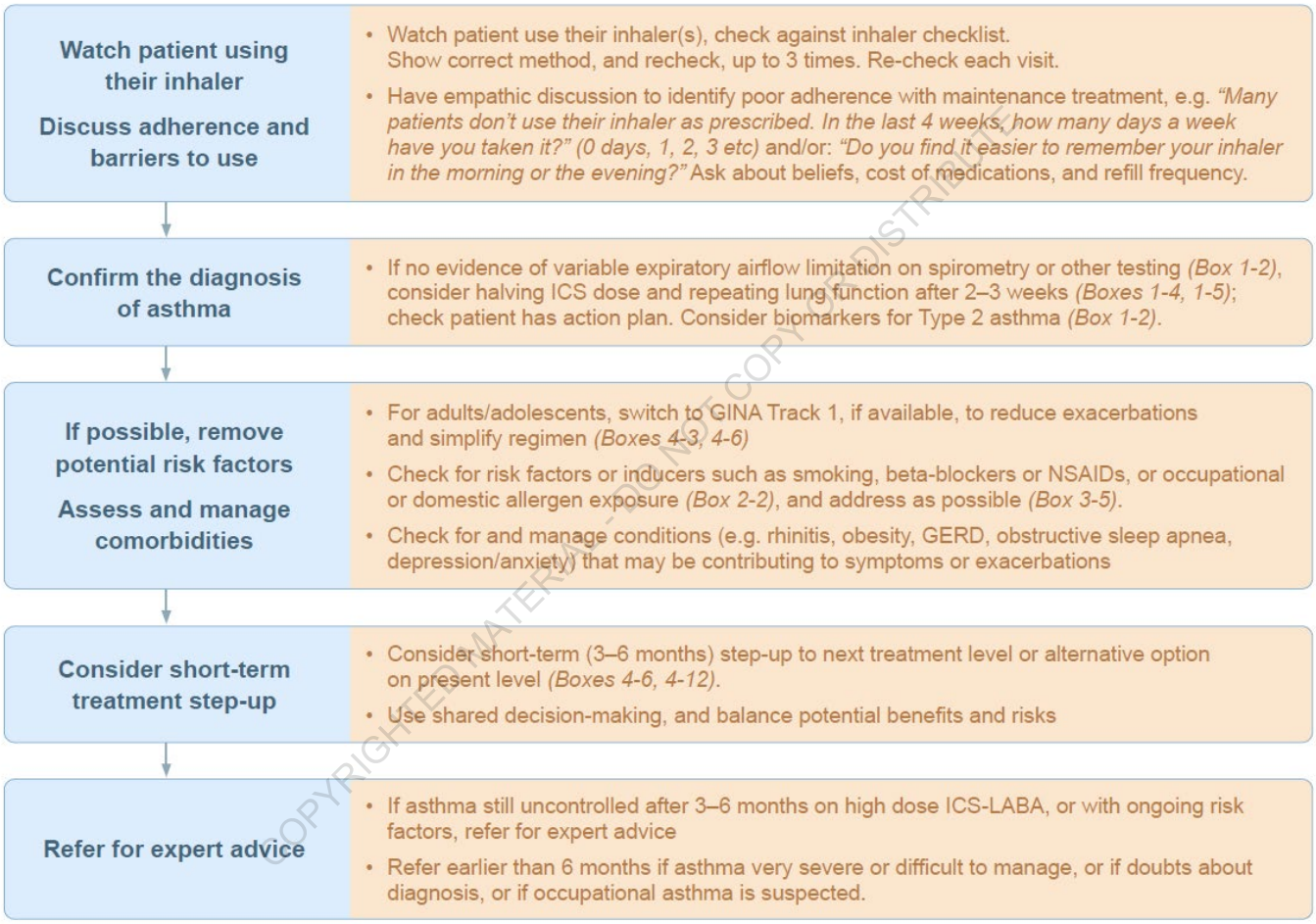
Although good symptom control and minimal exacerbations can usually be achieved with ICS-containing treatment, some patients will not achieve one or both of these goals even with a long period of high-dose therapy.[168,183] In some patients this is due to truly refractory severe asthma, but in many others, it is due to incorrect inhaler technique, poor adherence, over-use of SABA, comorbidities, persistent environmental exposures, or psychosocial factors.

It is important to distinguish between severe asthma and uncontrolled asthma, because lack of asthma control is a much more common reason for persistent symptoms and exacerbations, and may be more easily improved. Box 2-4 (p.47) shows the initial steps that can be carried out in primary care to identify common causes of uncontrolled asthma. More details are given in Section 8 (p.139) about investigation and management of difficult-to-treat and severe asthma, including referral to a respiratory physician or severe asthma clinic where possible, and use of add-on treatment including biologic therapy.

The most common problems that need to be excluded before making a diagnosis of severe asthma are:

- Poor inhaler technique (up to 80% of community patients)[97] (Box 5-2, p.110)
- Poor medication adherence[197,198] (Box 5-3, p.112)
- 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.27)
- Multimorbidity such as rhinosinusitis, GERD, obesity and obstructive sleep apnea[99,199] (Section 6, p.117)
- Ongoing exposure to sensitizing or irritant agents in the home or work environment, including tobacco smoke.

Box 2-4. Investigating poor symptom control and/or exacerbations despite ICS-containing treatment



GERD: gastro-esophageal reflux disease; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; NSAID: nonsteroidal anti-inflammatory drug. See Section 8 (p.139) for more details about assessment and management of difficult-to-treat and severe asthma.

3. Principles of asthma management in adults, adolescents and children 6–11 years

KEY POINTS

The partnership between patient and healthcare provider

Effective asthma management requires a partnership between the person with asthma (or the parent/caregiver) and their healthcare providers.

Teaching communication skills to healthcare providers may lead to increased patient satisfaction, better health outcomes, and reduced use of healthcare resources.

Healthcare providers should consider the patient's ability to obtain, process and understand basic health information to make appropriate health decisions ('health literacy').

Goals of asthma management

The GINA long-term goal of asthma management is to achieve the best possible long-term outcomes for the individual patient. This may include good long-term symptom control (few/no asthma symptoms, no sleep disturbance due to asthma, and unimpaired physical activity), and minimized long-term risk of asthma-related mortality, exacerbations, persistent airflow limitation and side-effects of treatment. The patient's own goals should also be identified.

Remission of asthma

Remission of asthma can be seen in children and in adults, either clinical remission or complete remission, and either off treatment or on treatment. Definitions and criteria vary.

The concept of clinical remission on treatment is consistent with the long-term goal of asthma management promoted by GINA: to achieve the best possible long-term asthma outcomes for each patient.

Research among patients who have (or have not) experienced clinical or complete remission of asthma, either off treatment or on treatment, provides important opportunities to understand the underlying mechanisms of asthma and to develop new approaches to asthma prevention and management. The use of standardized criteria and assessment tools will facilitate this research.

Take care if using the term "remission" in conversations with patients or parents/caregivers, as they may assume it means a cure, or may associate it with cancer or leukemia. Explain what you mean, and that if asthma symptoms have "gone quiet" for a while, they may recur.

Making decisions about asthma treatment

Asthma treatment is adjusted in a continual cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk (of exacerbations and side-effects), and of patient preferences.

For population-level decisions about asthma medications, e.g., national guidelines, insurers, health maintenance organizations or national formularies, the "preferred" regimens in Steps 1–4 represent the best treatments for most patients, based on evidence from randomized controlled trials, meta-analyses and observational studies of safety, efficacy and effectiveness, with a particular emphasis on symptom burden and exacerbation risk. For Steps 1–5, there are different preferred population-level recommendations for different age-groups (adults/adolescents, children 6–11 years, children 5 years and younger). In Step 5, there are also different preferred population-level recommendations depending on the inflammatory phenotype.

For individual patients, shared decision-making about treatment should also consider any patient characteristics, (such as asthma phenotype) or environmental exposures that predict the patient's risk of exacerbations or other adverse outcomes, or their likely response to treatment, together with the patient's goals or concerns and practical issues (inhaler technique, adherence, medication access and cost to the patient).

Optimize asthma management, including inhaled therapy and non-pharmacologic strategies, to reduce the need for oral corticosteroids (OCS) and their multiple adverse effects.

THE PATIENT–HEALTHCARE PROVIDER PARTNERSHIP

Effective asthma management requires the development of a partnership between the person with asthma (or the parent/caregiver) and healthcare providers.[200] 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 adults[201] (Evidence A) and children[202] (Evidence A).

Shared decision-making is associated with improved outcomes.[203,204] Patients and caregivers should be encouraged to participate in decisions about treatment, and given the opportunity to express their expectations and concerns. This partnership must be individualized for 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 healthcare system. Shared decision-making may also vary based on health system culture and physician attitudes.

Good communication

Good communication by healthcare providers is essential as the basis for good outcomes (Evidence B).[205-207] Teaching healthcare providers to improve their communication skills (Box 3-1) can result in increased patient satisfaction, better health outcomes, and reduced use of healthcare resources[205-207] without lengthening consultation times.[208] It can also enhance patient adherence.[208] Training patients to give information clearly, seek information, and check their understanding of information provided is also associated with improved adherence to treatment recommendations.[208]

Box 3-1. Communication strategies for healthcare providers

Key strategies to facilitate good communication:[206,207]

- 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 support and encouragement
- Giving appropriate (personalized) information
- Providing feedback and review

How to reduce the impact of low health literacy:[209]

- 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.
- Make patients feel comfortable about asking questions.

Health literacy and asthma

There is increasing recognition of the impact of low health literacy on health outcomes, including in asthma.[209,210] 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".[209] Low health literacy is associated with reduced knowledge and worse asthma control.[211] In one study, low numeracy among parents of children with asthma was associated with higher risk of exacerbations.[210] Interventions adapted for cultural and ethnicity perspectives have been associated with improved knowledge and significant improvements in inhaler technique.[212] Suggested strategies for communicating with patients who have low health literacy are shown in Box 3-1 (p.49).

LONG-TERM GOAL OF ASTHMA MANAGEMENT

The long-term goal of asthma management from a clinical perspective is to achieve the best possible outcomes for the patient, including long-term symptom control and long-term asthma risk minimization (Box 3-3, p.52). This includes preventing exacerbations, accelerated decline in lung function, and medication adverse effects. At a population level, the goals of asthma management also include minimizing asthma deaths, urgent health care utilization, and the socioeconomic impacts of uncontrolled asthma.

It is also important to elicit the patient's (or parent/caregiver's) goals regarding their asthma, as these may differ from medical goals. Shared goals for asthma management can be achieved in various ways, with consideration of differing healthcare systems, medication availability, and cultural and personal preferences.

Box 3-2. Long-term goal of asthma management

The goal of asthma management is to achieve the best possible long-term asthma outcomes for the patient:

- Long-term asthma symptom control, which may include:
  - Few/no asthma symptoms
  - No sleep disturbance due to asthma
  - Unimpaired physical activity
- Long-term asthma risk minimization, which may include:
  - No exacerbations
  - Improved or stable personal best lung function
  - No requirement for maintenance systemic corticosteroids
  - No medication side-effects.

The patient's goals for their asthma may be different from these medical goals; ask the patient what they want from their asthma treatment.

When discussing the best possible asthma outcomes with a patient, consider their goals, their asthma phenotype, clinical features, multimorbidity, risk factors (including severity of airflow limitation), practical issues including the availability and cost of medications, and the potential adverse effects of treatment (Box 3-4, p.54).

Assessing symptom control is NOT enough: the patient's risk factors (Box 2-2B, p.37), including history of exacerbations, should always also be assessed.

Symptom control and risk may be discordant: patients with few or no symptoms can still have severe or fatal exacerbations, including from external triggers such as viral infections, allergen exposure (if sensitized) or pollution.

REMISSION OF ASTHMA

Remission of asthma has been investigated extensively in the past, most commonly remission of childhood asthma off treatment. Definitions and criteria vary, but they commonly refer to either *clinical remission* (e.g., no asthma symptoms or exacerbations for a specific period) or *complete (or pathophysiological) remission* (e.g., also including normal lung function, airway responsiveness and/or inflammatory markers).

There has been interest in *remission off treatment*, and *remission on treatment*, for example with biologic therapy for severe asthma.[213-215] The concept of clinical remission on treatment is consistent with the *long-term goal of asthma management* promoted by GINA, which is to achieve the best possible long-term asthma outcomes for the patient (see Box 3-2, p.50). When discussing the best possible outcomes with a patient, consider their own asthma goals, their asthma phenotype, clinical features, multimorbidity, risk factors (including severity of airflow limitation), practical issues including the availability and cost of medications, and the potential adverse effects of treatment (Box 3-4, p.54).

Research in patients who have (or have not) experienced clinical or complete remission of asthma, either off treatment or on treatment, provides important opportunities for understanding the heterogeneous and interconnected underlying mechanisms of asthma, and for developing new approaches to asthma prevention and management. The use of standardized criteria and tools will facilitate this research.

Remission of childhood asthma

Reported rates of *remission off treatment* from studies in children with wheezing or asthma vary depending on the populations, definitions, and length of follow-up. For example, in one study, 59% of wheezing preschool children had no wheezing at 6 years,[216] whereas in another study, only 15% of children with persistent wheezing at/after 9 years had no wheezing at 26 years.[217] Clinical remission is more frequent than pathophysiological remission at all ages.[218,219]

The most important predictors of asthma remission in school-aged children are fewer, milder or decreasing frequency of symptomatic episodes,[220-223] good or improving lung function, and less airway hyperresponsiveness.[219] Risk factors for persistence of childhood asthma include atopy, parental asthma/allergy, later onset of symptoms, wheezing without colds, and maternal smoking or tobacco smoke exposure.

Remission is not cure: after remission in childhood or adolescence, asthma often recurs later in life. Children whose asthma has remitted have an increased risk of accelerated lung decline in adulthood, independent from, but synergistic with, tobacco smoking; and they may develop persistent airflow limitation, although this is less likely than for those whose asthma has persisted.[224] This suggests the importance of monitoring lung function in people with remission of asthma symptoms.

To date, there is no evidence that interventions in childhood increase the likelihood of remission of asthma or reduce the risk of recurrence. However, treatment of asthma in childhood with inhaled corticosteroid (ICS) substantially reduces the burden of asthma on the child and family, reduces absence from school and social events, reduces the risk of exacerbations and hospitalizations, and allows the child to participate in normal physical activity.

Parents/caregivers often ask if their child will grow out of their asthma, and will not need treatment in the future. Current consensus supports the following advice for discussions like these:

- If the child has no reported symptoms, check for evidence of ongoing disease activity (e.g., wheezing; child avoiding physical activity), and check lung function if testing is available.
- Use a description like “asthma has gone quiet for now” to help avoid misunderstandings. If you use the term “remission” with parents/caregivers, explain the medical meaning, because it is often interpreted as meaning a permanent cure.
- Advise parents/caregivers that, even if the child’s symptoms resolve completely, their asthma may recur later.
- Emphasize the benefits of taking controller treatment for the child’s current health, their risk of asthma attacks, and their ability to participate in school and sporting activities, while avoiding claims about effect of therapy on future asthma outcomes.

Research needs: clinical questions about remission off treatment in children focus on the risk factors for asthma persistence and recurrence (including clinical, pathological, and genetic factors), the effect of risk reduction strategies on the likelihood of remission, whether monitoring after remission to allow early identification of asthma recurrence improves outcomes, and whether progression to persistent airflow limitation can be prevented. Clinical questions about remission on treatment (e.g., in children with severe asthma treated with biologic therapy) include investigating whether inhaled anti-inflammatory therapy can be down-titrated.

Remission of adult asthma

Clinical or complete *remission off treatment* has been observed in some adults, either spontaneously or after cessation of controller treatment. For example, 15.9% of patients with adult-onset asthma experienced clinical remission (no asthma symptoms and no asthma medications) within 5 years.[23] Remission is sometimes seen in people with occupational asthma after cessation of exposure.[225] Clinical remission of asthma in adult life is more common with childhood-onset asthma than adult-onset asthma. However, persistence of airway hyperresponsiveness and/or airway inflammation is found in most adults with clinical remission of asthma.[218]

In recent years, there has been increasing interest in asthma *remission on treatment,* particularly with biologic therapy for severe asthma. Various definitions have been proposed. For clinical remission, these often include criteria such as no asthma symptoms, no exacerbations, no use of oral corticosteroids (OCS), and stable or improving lung function, over a defined prolonged period. For complete remission, normalization of airway responsiveness and/or inflammatory markers has been proposed.

For patients with severe asthma treated with biological therapy and medium- or high-dose ICS in combination with a long-acting beta$_2$-agonist (LABA), remission rates will vary depending on the baseline characteristics of the populations studied and the criteria for and duration of, remission (including how "no symptoms" is assessed).[213-215,226,218]

Baseline predictors of *remission on treatment* with various biologic therapies for severe asthma include better short-term asthma symptom control scores (Asthma Control Test [ACT] or Asthma Control Questionnaire [ACQ]), better lung function, fewer comorbidities, earlier asthma onset, and no or lower maintenance OCS use at baseline.[215,227] In a study of clinical *remission off treatment* of adult-onset asthma, the only baseline predictors of clinical persistence were moderate-to-severe airway hyperresponsiveness and nasal polyps.[23]

Although clinical asthma remission on treatment has been most extensively investigated in adults with severe asthma treated with biologics, the concept is relevant to patients with asthma of any severity and any treatment, including ICS-containing therapy, oral pharmacotherapies, allergen immunotherapy and non-pharmacological interventions (e.g., lifestyle interventions).

In the mainstream media, the word "remission" is most often heard in association with cancer or leukemia, so if it is used in discussion with patients, the medical meaning for asthma should be explained. If the patient experiences clinical remission, explain that this does not mean permanent cure, and that they should not stop taking any of their asthma medications except on medical advice.

Research needs: for asthma remission on treatment in adults include examination of the association between clinical criteria with biomarkers, imaging, or pathology samples (including for "omics" analysis) that may reflect the underlying disease processes, and investigation of predictors of long-term remission or recurrence. The framework for validating proposed criteria for remission on treatment will depend on their intended purpose, for example as an assessment tool in clinical practice, for prognosis of continued long-term stability, or for identifying new targets for therapy. There is a need for clinical and qualitative research with a range of treatments, to learn whether aiming for remission will improve long-term outcomes for patients with asthma.

PERSONALIZED CONTROL-BASED ASTHMA MANAGEMENT

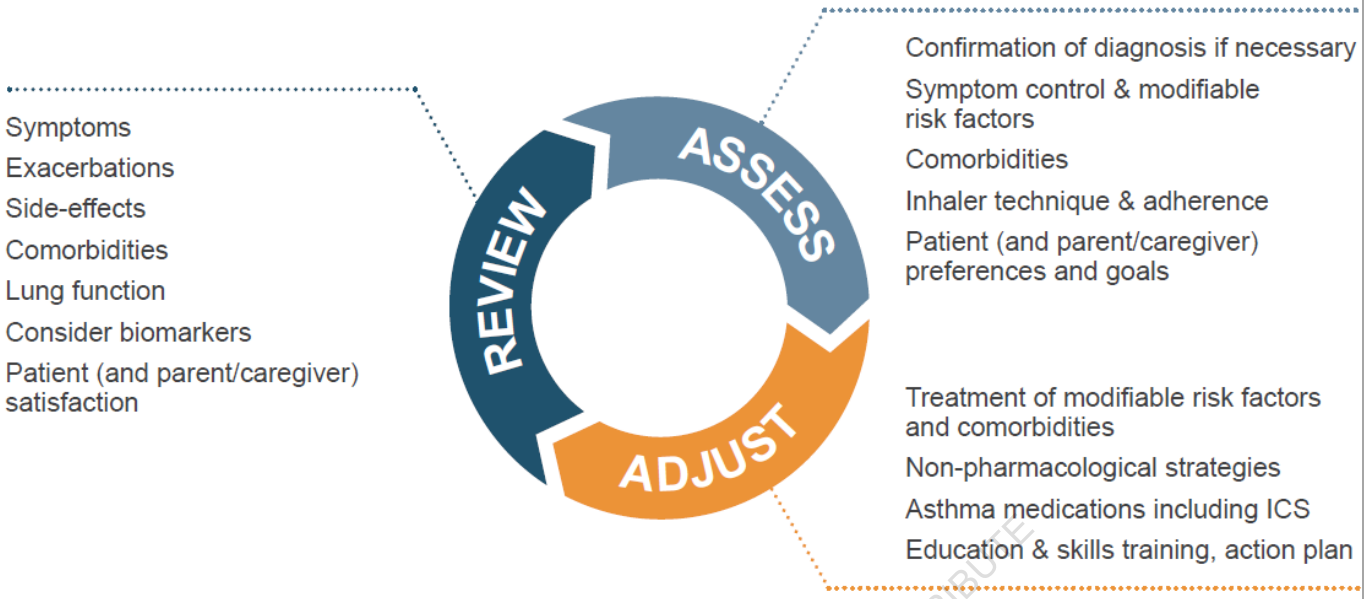
Asthma control has two domains: symptom control and risk reduction (see Box 2-2, p.37). In control-based asthma management, pharmacological and non-pharmacological treatment is adjusted in a continual cycle that involves assessment of symptom control and risk factors, treatment and review by appropriately trained personnel (Box 3-3, p.52) to achieve the goals of asthma treatment (Section 3, p.48). Asthma outcomes have been shown to improve after the introduction of control-based guidelines[228,229] or practical tools for implementation of control-based management strategies.[203,230]

The concept of control-based management is also supported by the design of most randomized controlled medication trials, in which patients are identified for a change in asthma treatment based on features of poor symptom control with or without other risk factors such as low lung function or a history of exacerbations. Since 2014, GINA asthma management has focused not only on asthma symptom control, but also on personalized management of the patient's modifiable risk factors for exacerbations, other adverse outcomes and multimorbidity, while also considering the patient's preferences and goals. Non-modifiable risk factors, such as a history of admission to an intensive care unit for asthma, should also be documented.

For many patients in primary care, achieving good symptom control is a good guide to a reduced risk of exacerbations.[231] When ICSs were introduced into asthma management, large improvements were observed in symptom control and lung function, and exacerbations and asthma-related mortality also decreased.

However, **patients with few or intermittent symptoms may be still at risk of severe exacerbations**[190] (Box 2-2B, p.37). 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; Box 2-2, p.37) should be considered when choosing asthma treatment and reviewing the response.[37,88]

Box 3-3. The asthma management cycle for personalized asthma care



Personalized asthma management involves a continual cycle of assessment, adjustment of treatment and review:

- **ASSESS** the patient's symptom control and their risk factors for exacerbations, for decline in lung function and for medication adverse effects (Box 2-2, p.37), with particular attention to inhaler technique and adherence. Assess comorbidities and the patient's goals and preferences, and confirm the diagnosis of asthma if not yet done.
- **ADJUST** the patient's management, based on these assessments. This includes treatment of modifiable risk factors (Box 3-5, p.56) and comorbidities (Section 6, p.117), relevant non-pharmacologic strategies (Box 3-6, p.57), education and skills training (Section 5, p.108), and adjustment of medication as required (Section 4, p.67). For adults and adolescents, the preferred controller and reliever treatment across all steps is with combination ICS-formoterol, as shown in GINA Track 1 (Box 4-6, p.77).
- **REVIEW** the patient's asthma in line with the goals of treatment (Box 3-2, p.50), reassess factors affecting symptoms, risk of adverse outcomes and patient satisfaction, consider Type 2 biomarkers if asthma remains uncontrolled (see p.216), arrange further investigations if needed, and readjust treatment if needed.

Choosing between asthma treatment options

At each treatment step in asthma management, different medication options are available that may be alternatives for controlling asthma, although their efficacy is not identical.

Different considerations apply to recommendations or choices made for broad populations than recommendations for individual patients (Box 3-4, p.54):

- **Population-level medication choices:** Population-level medication choices are often made by bodies such as national formularies or managed care organizations. Population-level recommendations aim to represent the best option for most patients in the particular population. At each treatment step, recommended "preferred" controller and reliever regimens provide the best benefit-to-risk ratio for both symptom control and risk reduction. Choice of the preferred controller and/or preferred reliever is based on evidence 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),[232] with a particular focus on symptoms and exacerbation risk. Safety and relative cost are also considered. In **Step 5**, there are different population-level recommendations depending on the inflammatory phenotype.

Box 3-4. 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**

Mainly based on evidence about symptoms and exacerbations (from randomized controlled trials, pragmatic studies and strong observational data)

- **Access**

Population-level availability and cost

There are different population-level recommendations by age-group (adults/adolescents, children 6–11 years, children 5 years and younger). For patients with severe asthma, there are also different population-level recommendations depending on the inflammatory phenotype.

Choosing between controller options for individual patients

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

1. Preferred medication

- What is the best medication for symptom control and risk reduction (as above)?

2. Patient characteristics or phenotype

- Does the patient have any factors that predict differences in risk or treatment response, compared with other patients, e.g., smoking; SABA over-use; exacerbation history; high FeNO or eosinophils; environmental exposures; comorbidities?

3. Patient views

- What are the patient's goals, beliefs and concerns about asthma and its treatment?

4. Practical issues

- For the preferred medication(s), which inhalers are available to this patient?
- Can they use the inhaler correctly after training?
- Can they afford the medication?
- Adherence – how often are they likely to take the medication?
- If more than one inhaler is suitable for the patient, which has the lowest environmental impact?

- In the treatment figure for adults and adolescents (Box 4-6, p.77), the options are shown in two "tracks". **Track 1**, with as-needed low-dose ICS-formoterol as the reliever, is the preferred approach for most patients, based on evidence of overall lower exacerbation risk and similar symptom control, and a simpler regimen for stepping treatment up and down as needed, compared with treatments in **Track 2** in which the reliever is short-acting beta$_2$-agonist (SABA) or, in some cases, combination ICS-SABA (for more details, see Section 4, p.67).
- **Patient-level medication choices:** Treatment choices for individual patients also take into account any patient characteristics or phenotype, or any environmental exposures, that may predict their **risk of exacerbations or other adverse outcomes**, or a clinically important difference in their response, compared with other patients, together with assessment of multimorbidity, the patient's goals and preferences, and practical issues such as cost, ability to use the medication and adherence (see Box 3-3, p.52). For factors guiding the choice of inhaler, see Section 5 (p.108).

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.

Minimizing adverse effects of medication

Reduce the potential for local and/or systemic side-effects of inhaled medications by:

- Choosing GINA Track 1, where available and suitable, because it requires lower doses of ICS
- Ensuring correct inhaler technique (Box 5-2, p.110), including use of a spacer with ICS-containing medication delivered by pMDI
- Reminding patients to rinse and spit out after using ICS
- After good asthma control has been maintained for 3 months, finding each patient's minimum effective dose of ICS-containing therapy (the lowest dose that will, in conjunction with an action plan, maintain good symptom control and minimize exacerbations, Box 4-13, p.102)
- Checking for drug interactions particularly with cytochrome P450 inhibitors (see Risk factors for medication side-effects, p.42).

To reduce the need for OCS, with its multiple cumulative adverse effects,[233,234] optimize inhaled therapy, including by switching treatment to GINA Track 1 with anti-inflammatory reliever therapy (if available). Anti-inflammatory reliever (AIR) treatment alone ('AIR-only') markedly reduces the risk of severe exacerbations requiring OCS, compared with SABA alone, while maintenance-and-reliever therapy (MART) with ICS-formoterol reduces the risk of severe exacerbations requiring OCS, compared with the same or higher dose of ICS or ICS-LABA, or compared with usual care.[235] Treating modifiable risk factors (Box 3-5, p.56) and comorbidities (Section 6, p.117) may also reduce the risk of exacerbations and use of OCS (Box 9-3, p.166).

Managing 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.[118] There is increasing research interest in identifying at-risk patients (Box 2-2B, p.37), 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 3-5, p.56). Not all risk factors require, or respond to, a step-up in controller treatment.

Box 3-5. Treating potentially modifiable risk factors to reduce exacerbations and minimize OCS use

Risk factor	Treatment strategy	Evidence
Any patient with one or more risk factors for exacerbations (including poor symptom control)	Ensure patient is prescribed an ICS-containing treatment.	A
	Switch to a regimen with an anti-inflammatory reliever (ICS-formoterol or ICS-SABA) if available, as this reduces the risk of severe exacerbations, compared with SABA reliever.	A
	Ensure patient has a written action plan appropriate for their health literacy.	A
	Review patient more frequently than low-risk patients.	A
	Check inhaler technique and adherence frequently; correct as needed.	A
	Identify and manage any modifiable risk factors (Box 2-2, p.37).	D
≥1 severe exacerbation in last year	Switch to a regimen with an anti-inflammatory reliever (as-needed ICS-formoterol or ICS-SABA) if available, as this reduces the risk of severe exacerbations, compared with SABA reliever.	A
	If no modifiable risk factors, consider stepping up treatment, e.g., addition of LAMA (as combination inhaler or separate inhaler) to medium-dose ICS-LABA; increasing ICS dose (particularly if Type 2 biomarkers are elevated); referring for specialist opinion and consideration of biologic therapy.	A
	Identify and manage any avoidable triggers for exacerbations.	C
Exposure to tobacco smoke or e-cigarettes	Encourage smoking cessation by patient/family; provide advice and resources (see Box 3-6, p.57).	A
	Consider higher dose of ICS if asthma poorly controlled.	B
Low FEV_1, especially if <60% predicted	Address problems with adherence and inhaler technique	A
	Consider trial of 3 months' treatment with high-dose ICS.	B
	Exclude other lung disease, e.g., COPD.	D
	Refer for expert advice if no improvement.	D
Obesity	Provide strategies for weight reduction	B
	Distinguish asthma symptoms from symptoms due to deconditioning, mechanical restriction, and/or sleep apnea.	D
Major psychological problems	Refer for mental health assessment/treatment.	D
	Help patient to distinguish between symptoms of anxiety and asthma; provide advice about management of panic attacks.	D
Major socioeconomic problem	Identify most cost-effective ICS-based regimen based on local costs.	D
	Optimize inhaler technique to maximize benefit from available medications.	D
Confirmed food allergy	Appropriate food avoidance; anaphylaxis action plan; injectable epinephrine; refer for expert advice.	A
Occupational or domestic exposure to irritants	Remove from exposure as soon as possible.	A
	Refer for expert advice as soon as possible.	D
Allergen exposure if sensitized	Consider trial of simple avoidance strategies if there is evidence for their effectiveness (see p.61); consider cost.	C
	Consider step up of asthma treatment if exposure is unavoidable.	D

	Consider adding SLIT in symptomatic HDM-sensitive adults or adolescents with partly-controlled asthma despite ICS, provided FEV_1 is >70% predicted.	A
High FeNO in patients taking medium/high dose ICS	Check and improve adherence; in a study of patients with uncontrolled asthma despite prescription of high dose ICS-LABA, FeNO was suppressed by directly observed corticosteroid therapy in about two-thirds of these patients, and this was associated with previous poor adherence and improved outcomes when adherence subsequently improved.[236]	A
Sputum eosinophilia despite medium/high ICS (few centers)	Consider increasing ICS dose, independent of level of symptom control.	A*

COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting $beta_2$-agonist; LAMA: long-acting muscarinic antagonist; SABA: short-acting $beta_2$-agonist; SLIT: sublingual allergen immunotherapy * Based on evidence from relatively small studies in selected populations. Also see Box 3–6 (p.57) and Non-pharmacological strategies (p.59).

NON-PHARMACOLOGICAL STRATEGIES

In addition to pharmacological treatments, other strategies should be considered where relevant, to assist in improving symptom control and/or reducing future risk. The advice and evidence level are summarized in Box 3-6, with more detail on the following pages.

Box 3-6. Non-pharmacological interventions – summary (see following text for details)

Intervention	Advice/recommendation	Evidence
Cessation of smoking, environmental tobacco exposure (ETS) and vaping	• At every visit, strongly encourage people with asthma who smoke or vape to quit. Provide access to counseling and smoking cessation programs (if available).	A
	• Advise parents/caregivers of children with asthma not to smoke or vape, and not to allow smoking or vaping in rooms or cars that their children use.	A
	• Strongly encourage people with asthma to avoid environmental smoke exposure.	B
	• Assess smokers/ex-smokers for COPD or overlapping features of asthma and COPD (asthma+COPD, Section 7, p.131), as additional treatment strategies may be required.	D
Physical activity	• Encourage people with asthma to engage in regular physical activity for its general health benefits.	A
	• Provide advice about prevention of exercise-induced bronchoconstriction with low-dose ICS-formoterol used as needed and before exercise, or with regular daily ICS.	A/B

	• Provide advice about prevention of breakthrough exercise-induced bronchoconstriction with:
	  • warm-up before exercise
	  • SABA (or ICS-SABA) before exercise
	  • low-dose ICS-formoterol before exercise (see Box 4-8, p.84).
		
		A
		A
		B

	• Regular physical activity improves cardiopulmonary fitness, and can have a small benefit for asthma control and lung function, including swimming in young people with asthma.	B

	• Physical activity interventions in adults with moderate/severe asthma is associated with improved symptoms and quality of life.	A
	• There is little evidence to recommend one form of physical activity over another for people with asthma.	D
Pulmonary rehabilitation programs	• Structured outpatient pulmonary rehabilitation programs can improve functional exercise capacity (6-minute walk) and quality of life.	A
Avoidance of occupational or domestic exposures to allergens or irritants	• Ask all patients with adult-onset asthma about their work history and other exposures to irritant gases or particles, including at home.	D
	• 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.	A
	• Patients with suspected or confirmed occupational asthma should be referred promptly for expert assessment and advice, if available.	A
Avoidance of medications that may make asthma worse	• Always ask about asthma before prescribing NSAIDs, and advise patients to stop using them if asthma worsens.	D
	• Always ask people with asthma about concomitant medications.	D
	• 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.128).	A
	• Decide about prescription of oral or ophthalmic beta-blockers on a case-by-case basis. Initiate treatment under close medical supervision by a specialist.	D
	• 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.	D
Healthy diet	• Encourage patients with asthma to consume a diet high in fruit and vegetables for its general health benefits.	A
Avoidance of indoor allergens	• Allergen avoidance is not recommended as a general strategy in asthma.	A
	• For sensitized patients, there is limited evidence of clinical benefit for asthma in most circumstances with single-strategy indoor allergen avoidance.	A
	• Remediation of dampness or mold in homes reduces asthma symptoms and medication use in adults.	A
	• 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).	B
	• Allergen avoidance strategies are often complicated and expensive, and there are no validated methods for identifying those who are likely to benefit.	D
Weight reduction	• Include weight reduction in the treatment plan for obese patients with asthma.	B
	• 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
	• The greatest improvement in asthma outcomes with weight reduction is seen with bariatric surgery.	A

Breathing exercises	• Breathing exercises may be a useful supplement to asthma pharmacotherapy for symptoms and quality of life, but they do not reduce exacerbation risk or have consistent effects on lung function.	A
Avoidance of indoor air pollution	• 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	• For sensitized patients, when pollen and mold counts are highest (e.g., using regional/national apps/alerts), closing windows and doors, remaining indoors, and using air conditioning may reduce exposure to outdoor allergens.	D
Dealing with emotional stress	• Encourage patients to identify goals and strategies to deal with emotional stress if it makes their asthma worse.	D
	• There is insufficient evidence to support one stress-reduction strategy over another, but relaxation strategies and breathing exercises may be helpful.	B
	• Arrange a mental health assessment for patients with symptoms of anxiety or depression.	D
Addressing social risk	• In US studies, comprehensive social risk interventions were associated with reduced emergency department visits and hospitalizations for children. Studies from other countries and settings are needed.	A
Avoidance of outdoor air pollutants/weather conditions	• During unfavorable environmental conditions (very cold weather or high air pollution) it may be helpful, if feasible, 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	• Food avoidance should not be recommended unless an allergy or food chemical sensitivity has been clearly demonstrated, usually by carefully supervised oral challenges.	D
	• For patients with confirmed food allergy, refer for specialist advice if available.	D
	• For patients with confirmed food allergy, food allergen avoidance may reduce asthma exacerbations.	D
	• If food chemical sensitivity is confirmed, complete avoidance is not usually necessary, and sensitivity often decreases when asthma control improves.	D

COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; NSAID: nonsteroidal anti-inflammatory drug; SABA: short-acting beta$_2$-agonist. Interventions with highest level evidence are shown first.

Cessation of smoking and vaping, 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, chronic obstructive pulmonary disease (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 environmental tobacco 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; increased rate of decline of lung function and may lead to COPD; and reduced the effectiveness of inhaled and oral corticosteroids.[237] After smoking cessation, lung function improves and airway inflammation decreases.[238] Reduction of environmental tobacco smoke exposure improves asthma control and reduces hospital admissions in adults and children.[239] Use of e-cigarettes (vaping) is associated with an increased risk of asthma symptoms or diagnosis and with an increased risk of asthma exacerbations.[103,240]

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 who vape to quit.
- Strongly encourage people with asthma to avoid environmental smoke exposure (Evidence B).
- Advise parents/caregivers of children with asthma not to smoke or vape and not to allow smoking or vaping in rooms or cars that their children use (Evidence A).
- Assess patients with a >10 pack–year smoking history for COPD or for asthma+COPD, as additional treatment strategies may be required (see Section 7, p.131).

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.[241] There is some evidence that aerobic exercise training can have a small beneficial effect on asthma symptom control and lung function, although not airway inflammation.[242] In physically inactive adults with moderate/severe asthma, physical activity interventions were associated with reduced symptoms and improved quality of life.[243] Further studies are needed to identify the optimal regimen. 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.[244] In young people with asthma, swimming training is well tolerated and leads to increased lung function and cardio-pulmonary fitness;[245] however, there are some concerns about exposure to chlorine and trichloramine with indoor pools.[69]

Exercise is an important cause of asthma symptoms for many asthma patients, but EIB can usually be reduced with maintenance ICS.[69] Breakthrough exercise-related symptoms can be managed with warm-up before exercise,[69] and/or by taking SABA[69] or low-dose ICS-formoterol[246] 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 treatment with low-dose ICS-formoterol as-needed and before exercise (Evidence B), with warm-up before exercise if needed (Evidence A). For doses of ICS-formoterol, see Box 4-8, p.84. For patients prescribed as-needed ICS-SABA, this can also be used before exercise.

Pulmonary rehabilitation

A systematic review and meta-analysis found that pulmonary rehabilitation programs of 4–12 weeks' duration that included aerobic training, nutritional advice, psychological counselling, and education in adults with asthma had little or no effect on asthma symptom control, but they achieved clinically meaningful short-term improvements in functional exercise capacity and quality of life (moderate certainty of evidence). It is not known whether these benefits continue long-term after the completion of the program.[247]

Advice

- For asthma patients who have limited exercise tolerance, or have dyspnea due to persistent airflow limitation, refer for pulmonary rehabilitation, if available.

Avoidance of occupational or domestic exposures

Occupational exposures to allergens or sensitizers account for a substantial proportion of the incidence of adult-onset asthma.[248] 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.[65] Cost-effective minimization of latex sensitization can be achieved by using non-powdered low-allergen gloves instead of powdered latex gloves.[65]

Advice

- Ask all patients with adult-onset asthma about their work history and other exposures to inhaled allergens or irritants, including at home (Evidence D).
- 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 nonsteroidal anti-inflammatory drugs (NSAIDs) can cause severe exacerbations.[249] Beta-blocker drugs, including topical ophthalmic preparations, may cause bronchospasm[250] 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 beta-blockers within 24 hours of hospital admission have been found to have lower in-hospital mortality rates than those who did not receive beta-blockers.[251]

Advice

- Always ask people with asthma about concomitant medications, including eyedrops (Evidence D).
- 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.128).
- For people with asthma who may benefit from oral or ophthalmic 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.[252]

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. Inhaled corticosteroid-containing 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.[253,254] The majority of single interventions have failed to achieve a sufficient reduction in allergen load to lead to clinical improvement.[253,255,256] It is likely that no single intervention will achieve sufficient benefits to be cost effective (Box 3-7, p.62). 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.[257]

House dust mites

House dust mites (HDM) 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 HDM, showed no benefit for asthma in adults and a small benefit for children.[258] One study that used a rigorously applied integrated approach to HDM control led to a significant decrease in symptoms, medication use and improvement in pulmonary function for children with HDM sensitization and asthma.[259] However, this approach is complicated and expensive and is not generally recommended. A study in HDM-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.[260]

Furred pets

Complete avoidance of pet allergens is impossible for sensitized patients as these allergens are ubiquitous outside the home[261] in schools,[262] public transport, and even cat-free buildings, probably transferred on clothes.[262] Although removal of such animals from the home of a sensitized patient is encouraged,[263] it can be many months before allergen levels decrease,[264] and the clinical effectiveness of this and other interventions remains unproven.[265]

Pest rodents

Symptomatic patients suspected of domestic exposure to pest rodents should be evaluated with skin prick tests or specific immunoglobin E, as exposure may not be apparent unless there is an obvious infestation.[266] High-level evidence for the effectiveness of removing rodents is lacking, as most integrated pest management interventions also remove other allergen sources;[266] one non-sham-controlled study showed comparable clinical improvement with pest reduction education and integrated pest management.[267]

Box 3-7. Effectiveness of avoidance measures for indoor allergens

Allergen and avoidance measure	Degree of effectiveness (evidence level)	
	Reduction in allergen levels	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	Little (C)	None (D)
• Minimize objects that accumulate dust	None (D)	None (D)
• Vacuum cleaners with integral HEPA filter and double-thickness bags	Little (C)	None (D)
• Remove, hot wash, or freeze soft toys	None (D)	None
Pets		
• Remove cat/dog from the home	Little (C)	None (D)
• Keep pet from the main living areas/bedrooms	Little (C)	None (D)
• HEPA-filter air cleaners	Some (B)	None (A)
• Wash pet	Little (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 homes	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)

HEPA: high-efficiency particle air. This table is adapted from Custovic et al.[271]

Cockroaches

Avoidance measures for cockroaches are only partially effective in removing residual allergens[268] 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.[269] 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 HDM allergens.[270]

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 little 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.[272]

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 can be more difficult to control in obese patients,[273-275] the risk of exacerbations is greater,[98,99] and response to ICS may be reduced.[276] There is limited evidence about the effect of weight loss on asthma control. Studies have ranged from dietary restriction to multifactorial interventions with exercise training and cognitive behavioral therapy, but populations have generally been small, and interventions and results have been heterogeneous.[277] In some studies, weight loss has improved asthma control, lung function and health status, and reduced medication needs in obese patients with asthma.[278,279] The most striking results have been observed after bariatric surgery,[280-282] but even 5–10% weight loss with diet, with or without exercise, can lead to improved asthma control and quality of life.[283]

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 in adults with 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 with no consistent effect on lung function and no reduction in risk of exacerbations.[284]

Studies of non-pharmacological strategies, such as breathing exercises, can only be considered high quality when control groups are appropriately matched for level of contact with healthcare providers and for asthma education. A study of two physiologically contrasting breathing exercises, which were matched for contact with healthcare providers and instructions about rescue inhaler use, showed similar improvements in reliever use and ICS dose after down-titration in both groups.[285] 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 commercial programs may be a potential limitation. Breathing exercises used in some of these studies are available at www.breathestudy.co.uk [286] and www.woolcock.org.au/resources/breathing-techniques-asthma.[285]

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).[287,288] Sources include cooking and heating devices using gas and solid biomass fuels, 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.[289] Air filters can reduce fine particle exposure, but there is no consistent effect on asthma outcomes.[290,291]

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 children[292] and adults. Hyperventilation associated with laughing, crying, anger, or fear can cause airway narrowing.[293,294] Panic attacks have a similar effect.[295,296] 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).

Interventions addressing social risks

A systematic review of social risk intervention studies based in the USA found that interventions that addressed these challenges, including health and health care, neighborhood and built environment, and social and community context, were associated with a marked reduction in pediatric emergency department visits and hospitalizations for asthma.[297] Data are needed from studies in other countries and other socioeconomic settings.

Avoidance of outdoor allergens

For patients sensitized to outdoor allergens such as pollens and molds, these may be impossible to avoid completely. Thunderstorms and other weather events may increase the level of respirable grass pollen allergens, fungal spores or other allergens and can trigger epidemics of asthma exacerbations in the community.[298-302]

Advice

- For sensitized patients, exposure may be reduced when pollen and mold counts are highest by closing windows and doors, remaining indoors, and using air conditioning (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 department visits and hospitalizations.[106] Use of digital monitoring identified a lag of 0–3 days between higher levels of multiple pollutants and increased asthma medication use.[108] Proximity to main roads at home and school is associated with greater asthma morbidity.[303] Certain weather and atmospheric conditions, like thunderstorms,[298,299] 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 2008 Olympics reduced pollution and was associated with a significant fall in asthma outpatient visits.[304]

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).
- During unfavorable environmental conditions (very cold weather, low humidity or high air pollution), it may be helpful to avoid strenuous outdoor physical activity and stay indoors in a climate-controlled environment, if possible, 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.[100]

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.[305] 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.[305] 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.[100]
- Patients with suspected or confirmed food allergy should be referred for expert advice about management of asthma and anaphylaxis (Evidence D).
- 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).[247]

REFERRAL FOR EXPERT ADVICE

For most patients asthma can usually be managed in primary care, but some clinical situations warrant referral for expert advice regarding diagnosis and/or management (Box 3-8). This list is based on consensus. Indications for referral may vary, because the level at which asthma care is mainly delivered (primary care or specialist care) varies substantially between countries.

Box 3-8. 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.27) (immediate referral recommended).
- Diagnosis is unclear, even after a trial of therapy with ICS or systemic corticosteroids.
- Patient has features of both asthma and COPD, and there is doubt about priorities for treatment.

Suspected occupational asthma

- Refer for confirmatory testing and identification of sensitizing or irritant agent, and specific advice about eliminating exposure and pharmacological treatment. See specific guidelines[65] for details.

Persistent or severely uncontrolled asthma or frequent exacerbations

- Symptoms remain uncontrolled, or patient has ongoing exacerbations or low lung function despite correct inhaler technique and good adherence on Step 4 treatment (medium-dose ICS-LABA, Box 4-6, p.77). Before referral, depending on the clinical context, identify and treat modifiable risk factors (Box 2-2, p.37; Box 3-5, p.56) and comorbidities (Section 6, p.117).
- Patient frequently uses asthma-related health care, e.g., multiple ED visits or urgent primary care visits.
- For more information, see Section 8 (p.139) on difficult-to-treat and severe asthma, including a decision tree

Any risk factors for asthma-related death (see Box 9-1, p.161)

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

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

- 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.128); allergic bronchopulmonary aspergillosis (ABPA) (p.129)

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 that remain uncontrolled despite medium-dose ICS (Box 4-2B, p.71) with correct inhaler technique and good adherence
- Suspected side-effects of treatment (e.g., growth delay)
- Concerns about the child's welfare or well-being

COPD: chronic obstructive pulmonary disease; ED: emergency department; ICU: intensive care unit; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist. For indications for referral in children 0–5 years, see p.189.

4. Medications and treatment regimens for adults, adolescents and children 6–11 years

KEY POINTS

For safety, GINA does not recommend treatment of asthma in adults, adolescents or children 6–11 years with short-acting beta$_2$-agonist (SABA) alone. Instead, they should receive inhaled corticosteroid (ICS)-containing treatment to reduce their risk of severe exacerbations and to control symptoms.

ICS-containing treatment can be delivered either with regular daily treatment or, in adults and adolescents who have asthma symptoms less than daily and normal or mildly reduced lung function, with as-needed low-dose ICS-formoterol taken whenever needed for symptom relief. For children unlikely to adhere to maintenance ICS, the ICS can be taken whenever the child uses their SABA reliever.

Prevention of severe exacerbations is a high priority across all treatment steps, to reduce the risk and burden to patients and the burden to the health system, and to reduce the need for oral corticosteroids (OCS), which have cumulative long-term adverse effects.

Tables of low, medium or high dose ICS do not represent equivalent potency. If a patient is switched from one medication to another, monitor asthma stability.

Treatment tracks for adults and adolescents

For clarity, the treatment figure for adults and adolescents shows two "tracks", largely based on the choice of reliever. Treatment may be stepped up or down within a track using the same reliever at each step, or treatment may be switched between tracks, according to the individual patient's needs.

Track 1, in which the reliever is low-dose ICS-formoterol, is the preferred approach recommended by GINA. When a patient at any step has asthma symptoms, they use low-dose ICS-formoterol as needed for symptom relief. In Steps 3–5, they also take ICS-formoterol as regular daily treatment. This approach is preferred because it reduces the risk of severe exacerbations, compared with using a SABA reliever, with similar symptom control, and because of the simplicity for patients and clinicians of needing only a single medication across treatment Steps 1–4.

Medications and doses for Track 1 are explained in Box 4-8, p.84, including the maximum recommended total formoterol (with ICS) dose in any day for each formulation. Based on extensive evidence with budesonide-formoterol, GINA suggests that the same maximum total daily dose should apply for beclometasone-formoterol.

Track 2, in which the reliever is an ICS-SABA or SABA, is an alternative if Track 1 is not possible, or if a patient is stable, with good adherence and no exacerbations in the past year on their current therapy. In Step 1, the patient takes a SABA and a low-dose ICS together for symptom relief (in combination if available, or with the ICS taken immediately after the SABA). In Steps 2–5, the reliever is a SABA or combination ICS-SABA. Before considering a SABA reliever, consider whether the patient is likely to adhere to their ICS-containing treatment, as poor adherence (with resulting SABA-only treatment) will increase the risk of exacerbations.

Steps 1 and 2 for adults and adolescents

Track 1: (Steps 1–2 combined) In adults and adolescents who were considered by their clinician to have mild asthma, and were taking SABA alone or had controlled asthma on daily low-dose ICS or leukotriene receptor antagonist (LTRA), treatment with as-needed-only low-dose ICS-formoterol reduced the risk of severe exacerbations and emergency department visits or hospitalizations by about two-thirds, compared with SABA-only treatment. As-needed-only low-dose ICS-formoterol reduced the risk of emergency department visits and hospitalizations, compared with daily ICS, with no clinically important difference in symptom control. In patients previously using SABA alone, as-needed low-dose ICS-formoterol also significantly reduced the risk of severe exacerbations needing OCS, compared with daily ICS.

Track 2: Treatment with regular daily low-dose ICS plus as-needed SABA (Step 2), if taken, is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization and death, compared with SABA alone. However, adherence to maintenance ICS treatment in the community is poor, leaving patients taking SABA alone and at increased risk of exacerbations. For patients with infrequent symptoms, who are likely to have very poor adherence, as-needed-only ICS-SABA, with separate or combination inhalers, is the best option for Step 1 in Track 2. However, evidence supporting this treatment option is limited to small studies that were not powered to detect differences in exacerbation rates.

Consider step-up if asthma remains uncontrolled despite good adherence and inhaler technique

Before considering any step up, **first confirm that the symptoms are due to asthma and identify and address common problems** such as inhaler technique, adherence, allergen exposure and multimorbidity; provide patient education.

For adults and adolescents, the preferred Step 3 treatment is the Track 1 regimen with low-dose ICS-formoterol as maintenance-and-reliever therapy (MART). This reduces the risk of severe exacerbations, with similar or better symptom control, compared with maintenance treatment using a combination of an ICS and a long-acting beta$_2$-agonist (LABA) as controller, plus as-needed SABA. If needed, the maintenance dose of ICS-formoterol can be increased to medium (i.e., Step 4) by increasing the number of maintenance inhalations. MART is also a preferred treatment option at Steps 3 and 4 for children 6–11 years, with a lower dose ICS-formoterol inhaler.

ICS-formoterol should not be used as the reliever for patients taking a different ICS-LABA maintenance treatment, because clinical evidence for safety and efficacy is lacking.

Other Step 3 options for adults and adolescents in Track 2, and in children, include maintenance ICS-LABA plus as-needed SABA or plus as-needed ICS-SABA (if available) or, for children 6–11 years, medium-dose ICS plus as-needed SABA. For children, try other controller options at the same step before stepping up.

Step down to find the minimum effective treatment

Once good asthma control has been achieved and maintained for 2–3 months, consider stepping down gradually 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 asthma education and training in essential skills

After choosing the right class of medication for the patient, the choice of inhaler device depends on which inhalers are available for the patient for that medication, which of these inhalers the patient can use correctly after training, and their relative environmental impact. Check inhaler technique frequently.

Provide inhaler skills training: this is essential for medications to be effective, but technique is often incorrect.

Encourage adherence to ICS-containing medication, even when symptoms are infrequent.

Provide training in asthma self-management (self-monitoring of symptoms and/or peak expiratory flow (PEF), written asthma action plan and regular medical review) to control symptoms and minimize the risk of exacerbations.

For patients with one or more risk factors for exacerbations

Prescribe ICS-containing medication, preferably from Track 1 options, i.e., with as-needed low-dose ICS-formoterol as reliever; provide a written asthma action plan; and arrange review more frequently than for lower-risk patients.

Identify and address modifiable risk factors (e.g., smoking, low lung function, over-use of SABA).

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 8, p.139)

Patients who have poor symptom control and/or exacerbations, despite medium- or high-dose ICS-LABA treatment, should be assessed for contributing factors, and asthma treatment should be optimized.

If the problems continue or diagnosis is uncertain, refer to a specialist center for phenotypic assessment and consideration of add-on therapy including biologics.

Allergen immunotherapy

Allergen-specific immunotherapy may be considered as add-on therapy for patients with asthma who have clinically significant sensitization to aeroallergens, and stable but not well-controlled asthma.

For all patients, use your own professional judgment, and always check local eligibility and payer criteria.

CATEGORIES OF ASTHMA MEDICATIONS

The pharmacological options for long-term treatment of asthma fall into the following main categories (Box 4-1, p.70):

- **Controller medications:** In the past, this term mostly referred to medications containing ICS that were used to reduce airway inflammation, control symptoms, and reduce risks such as exacerbations and the associated decline in lung function.[123] In GINA Track 1, controller treatment is delivered through an anti-inflammatory reliever (AIR), low-dose ICS-formoterol, taken when symptoms occur and before exercise or allergen exposure; in Steps 3–5, the patient also takes maintenance controller treatment as daily or twice-daily ICS-formoterol. This is called "maintenance-and-reliever therapy" (MART). The dose and regimen of controller medications should be optimized to minimize the risk of medication side-effects, including risks of needing OCS.
- **Reliever medications:** All patients should be provided with a reliever inhaler 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.

  Relievers include the anti-inflammatory relievers ICS-formoterol and ICS-SABA, and SABA. Combination ICS-LABA with non-formoterol LABAs cannot be used as a reliever, due to a slower onset of action (e.g., ICS-salmeterol), or due to lack of safety and/or efficacy with more than once-daily use (e.g., ICS-vilanterol, ICS-indacaterol). ICS-formoterol should not be used as the reliever for patients taking maintenance ICS-LABA with a non-formoterol LABA.[306]

  Over-use of SABA (e.g., dispensing of three or more 200-dose canisters in a year, corresponding to average use more than daily), is associated with increased risk of asthma exacerbations, compared with 0–2 canisters/year.[92,93] Regular SABA also increases the risk of poor symptom control.[307]
- **Add-on therapies including for patients with severe asthma** (Section 8, p.139).

When compared with medications used for other chronic diseases, most of the medications used for treatment of asthma have very favorable therapeutic ratios. See Box 4-2 (p.71) for low, medium and high ICS doses.

Box 4-1. Terminology for asthma medications

Term	Definition	Notes
Maintenance treatment	Asthma treatment that is prescribed for use every day (or on a regularly scheduled basis)	Medications intended to be used continuously, even when the person does not have asthma symptoms. Examples include ICS-containing medications (ICS, ICS-LABA, ICS-LABA-LAMA), LTRA,* and biologic therapy. The term "maintenance" describes the prescribed frequency of administration, not a particular class of asthma medicine.
Controller	Medication targeting both domains of asthma control (symptom control and future risk)	In the past, "controller" was largely used for ICS-containing medications prescribed for regular daily treatment, so "controller" and "maintenance" became almost synonymous. However, this became confusing after the introduction of combination ICS-containing relievers for as-needed use. To avoid confusion, "ICS-containing treatment" and "maintenance treatment" have been substituted as appropriate where the intended meaning was unclear.
Reliever	Asthma inhaler taken as needed, for quick relief of asthma symptoms	Sometimes called rescue inhalers. As well as being used for symptom relief, reliever inhalers can also be used before exercise, to prevent exercise-induced asthma symptoms. Includes SABAs (e.g., salbutamol [albuterol], terbutaline, ICS-salbutamol), as-needed ICS-formoterol, and as-needed ICS-SABA. SABA-containing relievers should not be used for regular maintenance use, or to be taken when the person does not have asthma symptoms (except before exercise).
Anti-inflammatory reliever (AIR)	Reliever inhaler that contains both a low-dose ICS and a rapid-acting bronchodilator	Includes budesonide-formoterol, beclometasone-formoterol and ICS-salbutamol combinations. Patients can also use AIRs as needed before exercise or allergen exposure to prevent asthma symptoms and bronchoconstriction. Non-formoterol LABAs in combination with ICS cannot be used as relievers. ICS-formoterol should not be used as the reliever with maintenance ICS-non-formoterol LABAs (p.69).[306] The anti-inflammatory effect of as-needed ICS-formoterol was demonstrated by reduction in FeNO in several studies.[195,196,308] Some anti-inflammatory relievers can be used as-needed at Steps 1–2 as the person's sole asthma treatment, without a maintenance treatment ("**AIR-only**" treatment). Almost all evidence for this is with ICS-formoterol. Some ICS-formoterol combinations can be used as both maintenance treatment and reliever treatment at Steps 3–5 (see **MART**, below). For medications and doses, see Box 4-8 (p.84).
Maintenance-and-reliever therapy (MART)	Treatment regimen in which the patient uses an ICS-formoterol inhaler every day (maintenance dose), and also uses the same medication as needed for relief of asthma symptoms (reliever doses)	**MART** (**M**aintenance-**A**nd-**R**eliever **T**herapy) can be used **only** with combination ICS-formoterol inhalers such as budesonide-formoterol and beclometasone-formoterol. Other ICS-formoterol inhalers can also potentially be used, but combinations of ICS with non-formoterol LABAs, or ICS-SABA, cannot be used for MART. MART is also sometimes called SMART (single-inhaler maintenance-and-reliever therapy); the meaning is the same. For medications and doses, see Box 4-8 (p.84).

*If prescribing LTRA, advise patient/caregiver about risk of neuropsychiatric adverse effects.[309]

AIR: anti-inflammatory reliever; FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; MART: maintenance-and-reliever therapy with ICS-formoterol; SABA: short-acting beta$_2$-agonist.

Box 4-2. Low, medium and high daily metered doses of inhaled corticosteroids (alone or with LABA)

This is not a table of equivalence, but suggested total daily doses for "low", "medium" and "high" dose ICS options for adults/adolescents (Box 4-6, p.77) and children 6–11 years (Box 4-12, p.96), based on product information.

The table does NOT imply potency equivalence. For example, if you switch treatment from a "medium" dose of one ICS to a "medium" dose of another ICS, this may represent a decrease (or an increase) in potency, and the patient's asthma may become unstable (or they may be at increased risk of adverse effects).

A patient's asthma should be monitored for stability after any change of treatment or inhaler device. Doses and potency may also differ by country, depending on local products, inhaler devices, regulatory labelling and clinical guidelines or, for one product, with addition of a LAMA to an ICS-LABA.[310]

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, or they have ongoing exacerbations, 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. The timing of medication use also affects outcomes, particularly for exacerbations, as seen with an anti-inflammatory reliever in GINA Track 1. **For Track 1 medications and doses, see Box 4-8, p.84.**

Daily doses in this table are shown as metered doses. See product information for delivered doses.

Inhaled corticosteroid (alone or in combination with LABA)	Total daily ICS dose (mcg) – see notes above		
	Low	Medium	High
Adults and adolescents (12 years and older)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	200–500	>500–1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200–400		>400
Children 6–11 years – see notes above (for children 5 years and younger, see Box 11-3, p.195			
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle, HFA)	50–100	>100–200	>200
Budesonide (DPI, or pMDI, standard particle, HFA)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80–160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50–100	>100–200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50–100	>100–200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

DPI: dry-powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; pMDI: pressurized metered-dose inhaler. ICS by pMDI should preferably be used with a spacer.

For new preparations, including generic ICS, the manufacturer's information should be reviewed carefully, as products containing the same molecule may not be clinically equivalent. Combination inhalers that include a long-acting muscarinic antagonist (LAMA) may have different ICS dosing – see product information.

ICS-CONTAINING MEDICATION

Why should ICS-containing medication be commenced from time of asthma diagnosis?

For the best outcomes, ICS-containing treatment should be initiated when (or as soon as possible after) the diagnosis of asthma is made. All patients should also be provided with a reliever inhaler for quick symptom relief, preferably an anti-inflammatory reliever (AIR).

GINA recommends ICS-containing medication from diagnosis for several reasons:

- As-needed low-dose ICS-formoterol reduces the risk of severe exacerbations and emergency department visits or hospitalizations by 65%, compared with SABA-only treatment.[191] This anti-inflammatory reliever regimen (AIR-only) significantly reduces severe exacerbations regardless of the patient's baseline symptom frequency, lung function, exacerbation history or inflammatory profile (high or low blood eosinophils or FeNO).[195,196]
- Starting treatment with SABA alone trains patients to regard it as their main asthma treatment, and increases the risk of poor adherence when daily ICS is subsequently prescribed.
- 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.[311,312] One study showed that after this time, higher ICS doses were required, and lower lung function was achieved.[312]
- Patients not taking ICS who experience a severe exacerbation have a greater long-term decline in lung function than those who are taking ICS.[123]
- For patients with occupational asthma, early removal from exposure to the sensitizing agent and early ICS-containing treatment increase the probability of resolution of symptoms, and improvement of lung function and airway hyperresponsiveness.[65,66]

For adults and adolescents, recommended options for initial asthma treatment, based on evidence (where available) and consensus, are listed in Box 4-4 (p.75) and shown in Box 4-5 (p.76). Treatment for adults and adolescents is shown in two tracks, depending on the reliever inhaler (Box 4-6, p.77).

For children 6–11 years, recommendations about initial treatment are shown in Box 4-10 (p.94) and Box 4-11 (p.95).

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 4-12 (p.96).

Does FeNO help in deciding whether to commence ICS?

In studies mainly limited to non-smoking adult patients, fractional concentration of exhaled nitric oxide (FeNO) >50 parts per billion (ppb) was associated with a good short-term (weeks) symptomatic response to ICS.[313,314] However, these studies did not examine the longer-term risk of exacerbations, and the relationship between FeNO and other Type 2 biomarkers is lost in obese patients.[22,48] In two 12-month studies in patients with mild asthma or taking SABA alone, severe exacerbations were reduced with as-needed low-dose ICS-formoterol versus as-needed SABA and versus maintenance ICS, independent of baseline inflammatory characteristics including FeNO.[195,196]

Several factors are associated with variation in FeNO levels between and within patients.[50] See biomarker overview for details (p.216).

Consequently, in patients with a diagnosis or suspected diagnosis of asthma, high FeNO can support the decision to start ICS, but low FeNO cannot be used to decide against treatment with ICS. Based on past and current evidence, GINA recommends treatment with as-needed low-dose ICS-formoterol (preferred) or with daily low-dose ICS plus as-needed SABA (alternative) for all adults and adolescents with mild asthma, to reduce the risk of severe exacerbations.[6,195,196,315,316]

Choice of medication, device and dose

In clinical practice, the choice of medication, device and dose for maintenance and for reliever for each individual patient should be based on assessment of symptom control, risk factors, which inhalers are available for the relevant medication class, which of these the patient can use correctly after training, their cost, their environmental impact and the patient's likely adherence. For more detail about choice of inhaler, see Section 5 (p.108) and Box 5-1 (p.109).

Monitor the response to treatment and any side-effects, and adjust the dose accordingly (Box 4-6, p.77). There is currently insufficient good-quality evidence to support use of extrafine-particle ICS aerosols over others.[317]

Once good symptom control has been maintained for 2–3 months, and if the patient has not had any exacerbations, asthma treatment can be carefully down-titrated to the minimum medications and dose that will maintain good symptom control and minimize exacerbation risk, while reducing the potential for side-effects (Box 4-6, p.77). For patients with severe asthma who have had a good asthma response to biologic therapy, a longer period of stability is recommended before the ICS dose is reduced, and reduction and cessation of OCS should be undertaken first. More details are given in Section 8, p.139. If a high daily dose of ICS is being considered (except for short periods), the patient should be referred for expert assessment and advice, where possible (Section 8, p.139).

GINA recommends that all adults and adolescents and all children 6–11 years should receive ICS-containing medication, incorporated in their maintenance and/or anti-inflammatory reliever treatment as part of personalized asthma management. For adults and adolescents, treatment options are shown in Box 4-6 (p.77) and, for children aged 6–11 years, in Box 4-12 (p.96). Clinicians should check local eligibility and payer criteria before prescribing.

Adjusting ongoing asthma treatment in adults, adolescents, and children aged 6–11 years

Once asthma treatment has begun (Box 4-4, Box 4-5, Box 4-10 and Box 4-11, p.75), 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, asthma medication can be adjusted up or down in a stepwise approach (adults and adolescents: Box 4-6, p.77, children 6–11 years, Box 4-12, p.96) to achieve good symptom control and minimize future risk of exacerbations, persistent airflow limitation and medication side-effects. When good asthma control has been maintained for 2–3 months, treatment may be stepped down to find the patient's minimum effective treatment (Box 4-13, p.102).

People's ethnic and racial backgrounds may be associated with different responses to treatment. These are not necessarily associated with genetic differences.[318] The contributors are likely to be multifactorial, including differences in exposures, social disadvantage, diet and health-seeking behavior.

If a patient has persisting uncontrolled symptoms and/or exacerbations despite 2–3 months of ICS-containing 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) nonsteroidal anti-inflammatory drugs (NSAIDs)
- Comorbidities that may contribute to respiratory symptoms and poor quality of life
- Incorrect diagnosis.

The evidence supporting treatment options at each step is summarized below, first for adults and adolescents, then for children 6–11 years.

ADULTS AND ADOLESCENTS: ASTHMA TREATMENT TRACKS

The steps below refer to the recommended asthma treatment options shown in Box 4-6 (p.77). Treatment recommendations for adults and adolescents are shown in two treatment Tracks (Box 4-3), for clarity. Suggested low, medium and high doses for a range of ICS formulations are shown in Box 4-2 (p.71). Medication options and doses for GINA Track 1 are listed in Box 4-8 (p.84). Details about treatment steps for children 6–11 years start on p.94.

Box 4-3. Asthma treatment tracks for adults and adolescents

Asthma treatment for adults and adolescents is in two Tracks

For adults and adolescents, the main treatment figure (Box 4-6, p.77), shows the options for ongoing treatment as two treatment "tracks". The key difference is the medication that is used for symptom relief. In Track 1 (preferred), the reliever is as needed low-dose ICS formoterol, and in Track 2, as-needed SABA or as-needed ICS-SABA.

The reasons for showing treatment in two tracks are:

- to show clinicians how treatment can be stepped up and down using the same reliever at each step
- because ICS-formoterol cannot be used as the reliever in patients prescribed a combination ICS with non-formoterol LABA, due to lack of evidence about efficacy and safety (p.69).[306]

Track 1: The reliever is as-needed low-dose ICS-formoterol

This is the preferred approach recommended by GINA for adults and adolescents, because using low-dose ICS formoterol (an anti-inflammatory reliever [AIR]) reduces the risk of severe exacerbations, compared with regimens that use SABA as reliever, with similar symptom control.

In addition, the treatment regimen is simpler, with patients using a single medication for reliever and for maintenance treatment if prescribed, across treatment steps:

- With this approach, when a patient at any treatment step has asthma symptoms, they use low-dose ICS-formoterol in a single inhaler for symptom relief. In Steps 1–2, this provides their anti-inflammatory therapy.
- In Steps 3–5, patients also take ICS formoterol as their daily maintenance treatment; together, this is called "maintenance-and-reliever therapy" (MART).

Medications and doses for GINA Track 1 are shown in Box 4-8 (p.84).

Track 2: The reliever is as-needed SABA or as-needed ICS-SABA

This is an alternative approach if Track 1 is not possible, or if a patient's asthma is stable with good adherence and no exacerbations on their current therapy. However, before prescribing a regimen with SABA reliever, consider whether the patient is likely to adhere to their maintenance therapy, as poor adherence will increase the risk of exacerbations.

In Step 1, the patient takes a SABA and a low-dose ICS together for symptom relief when symptoms occur (in a combination inhaler, or with the ICS taken immediately after the SABA).

In Steps 2–5, a SABA (alone) or combination ICS-SABA is used for symptom relief, and the patient takes maintenance ICS-containing medication regularly every day. If the reliever and maintenance medication are in different devices, make sure that the patient can use each inhaler correctly.

If changing between steps requires a different inhaler device, train the patient how to use the new inhaler.

Stepping up and down

Treatment can be stepped up or down along one track, using the same reliever at each step, or it can be switched between tracks, according to the individual patient's needs and preferences. 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.47).

Additional controller options

The additional controller options, shown below the two treatment tracks, have either limited indications or less evidence for their safety and/or efficacy, compared with the treatments in Tracks 1 and 2.

ICS: inhaled corticosteroid; SABA: short-acting beta$_2$-agonist

INITIAL ASTHMA TREATMENT FOR ADULTS AND ADOLESCENTS

Box 4-4. Initial asthma treatment for adults and adolescents with a diagnosis of asthma

These recommendations are based on evidence, where available, and on consensus.

Presenting symptoms	Preferred INITIAL treatment (Track 1)	Alternative INITIAL treatment (Track 2)
Infrequent asthma symptoms, e.g., 1–2 days/week or less	**As-needed low-dose ICS-formoterol** (Evidence A)	**Low-dose ICS taken whenever SABA is taken**, in combination or separate inhalers (Evidence B). Such patients are highly unlikely to be adherent with daily ICS if prescribed.
Asthma symptoms less than 3–5 days/week, with normal or mildly reduced lung function		**Low-dose ICS (i.e., daily treatment) plus as-needed SABA** (Evidence A). Before choosing this option, consider likely adherence to daily ICS.
Asthma symptoms most days (e.g., 4+ days/week); or waking due to asthma once a week or more, or with reduced lung function. See p.81 for additional considerations.	**Low-dose ICS-formoterol maintenance-and-reliever therapy** (MART) (Evidence A)	**Low-dose ICS-LABA plus as-needed SABA** (Evidence A) or plus as-needed ICS-SABA (Evidence B), **OR** Medium-dose ICS plus as-needed SABA (Evidence A) or plus as-needed ICS-SABA (Evidence B). Consider probability of adherence to daily maintenance treatment.
Daily asthma symptoms or waking at night with asthma once a week or more, and with low lung function or recent exacerbation.	**Medium-dose ICS-formoterol maintenance-and-reliever therapy** (MART) (Evidence D).	**Medium-dose ICS-LABA** (Evidence D) **plus as-needed SABA or plus as-needed ICS-SABA**. Consider probability of adherence to daily maintenance treatment. High-dose ICS plus as-needed SABA is another option (Evidence A) but adherence is worse than with combination ICS-LABA.
Initial asthma presentation is during an acute exacerbation	Treat as for exacerbation (Box 9-4, p.168 and Box 9-6, p172), including short course of OCS if severe; commence medium-dose MART (Evidence D).	Treat as for exacerbation (Box 9-4, p.168 and Box 9-6, p.172), including short course of OCS if severe; commence medium-dose ICS-LABA plus as-needed SABA (Evidence D).

Before starting initial controller treatment

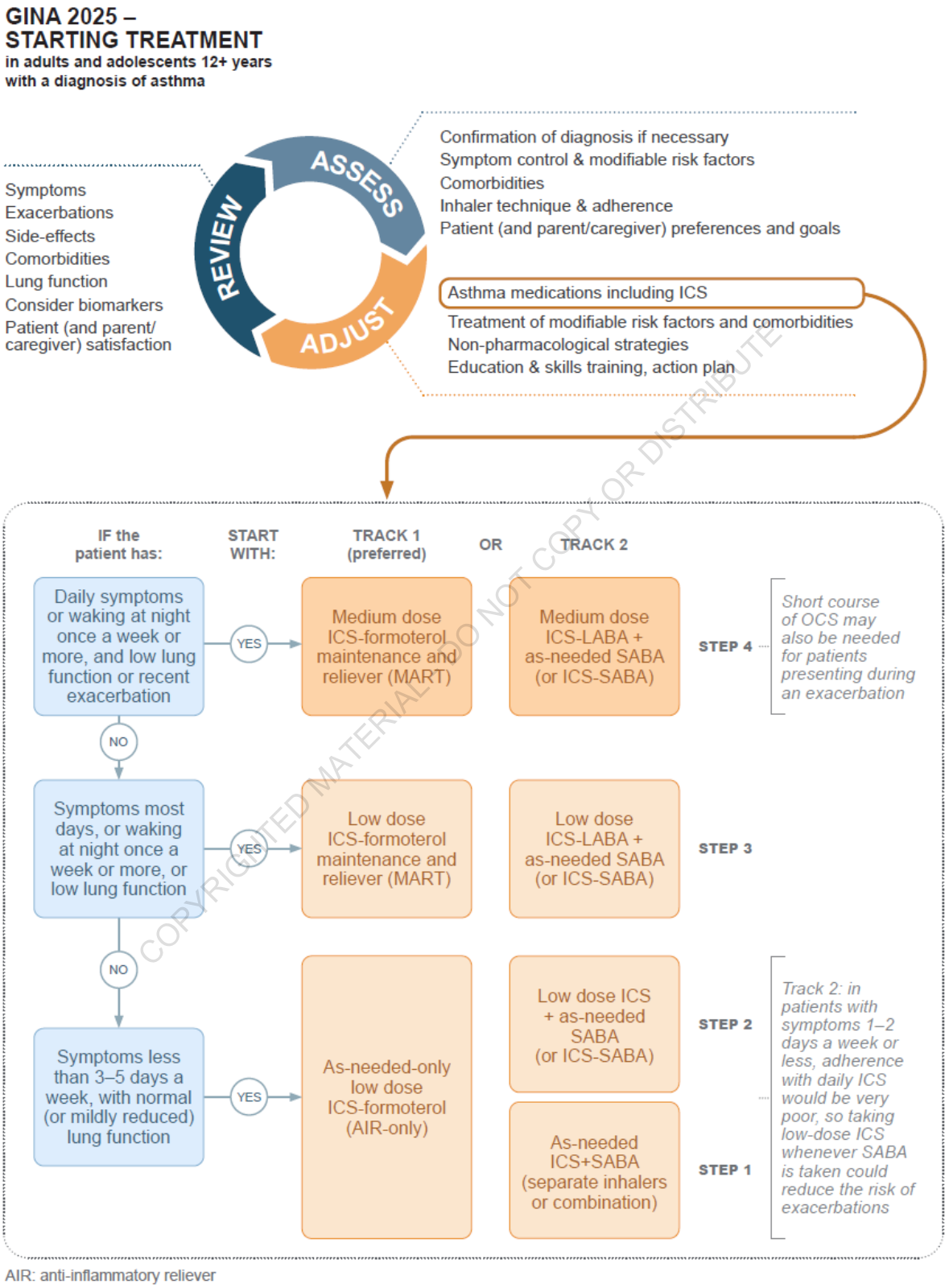
- Record evidence for the diagnosis of asthma.
- Record the patient's level of symptom control and risk factors, including lung function (Box 2-2, p.37).
- Consider factors influencing choice between available treatment options (Box 3-4, p.54), including whether patients likely to adhere to daily ICS-containing treatment, particularly if the reliever is SABA.
- Choose a suitable inhaler (Box 5-1, p.109) and ensure that the patient can use the inhaler correctly. If separate inhalers are needed, try to avoid devices that require different techniques.
- Schedule an appointment for a follow-up visit.

After starting initial controller treatment

- Review patient's response (Box 2-2, p.37) after 2–3 months, or earlier depending on clinical urgency.
- See Box 4-6 (p.77) for recommendations for ongoing treatment and other key management issues.
- Check adherence and inhaler technique frequently.
- Step down treatment once good control has been maintained for 3 months (Box 4-13, p.102).

Also consider cost and probability of adherence to maintenance treatment, and check local eligibility/payer criteria. See Box 4-2 (p.71) for low, medium and high ICS doses, and Box 4-8 (p.84) for Track 1 medications and doses. See list of abbreviations (p.11).

Box 4-5. Flowchart for selecting initial treatment in adults and adolescents with a diagnosis of asthma

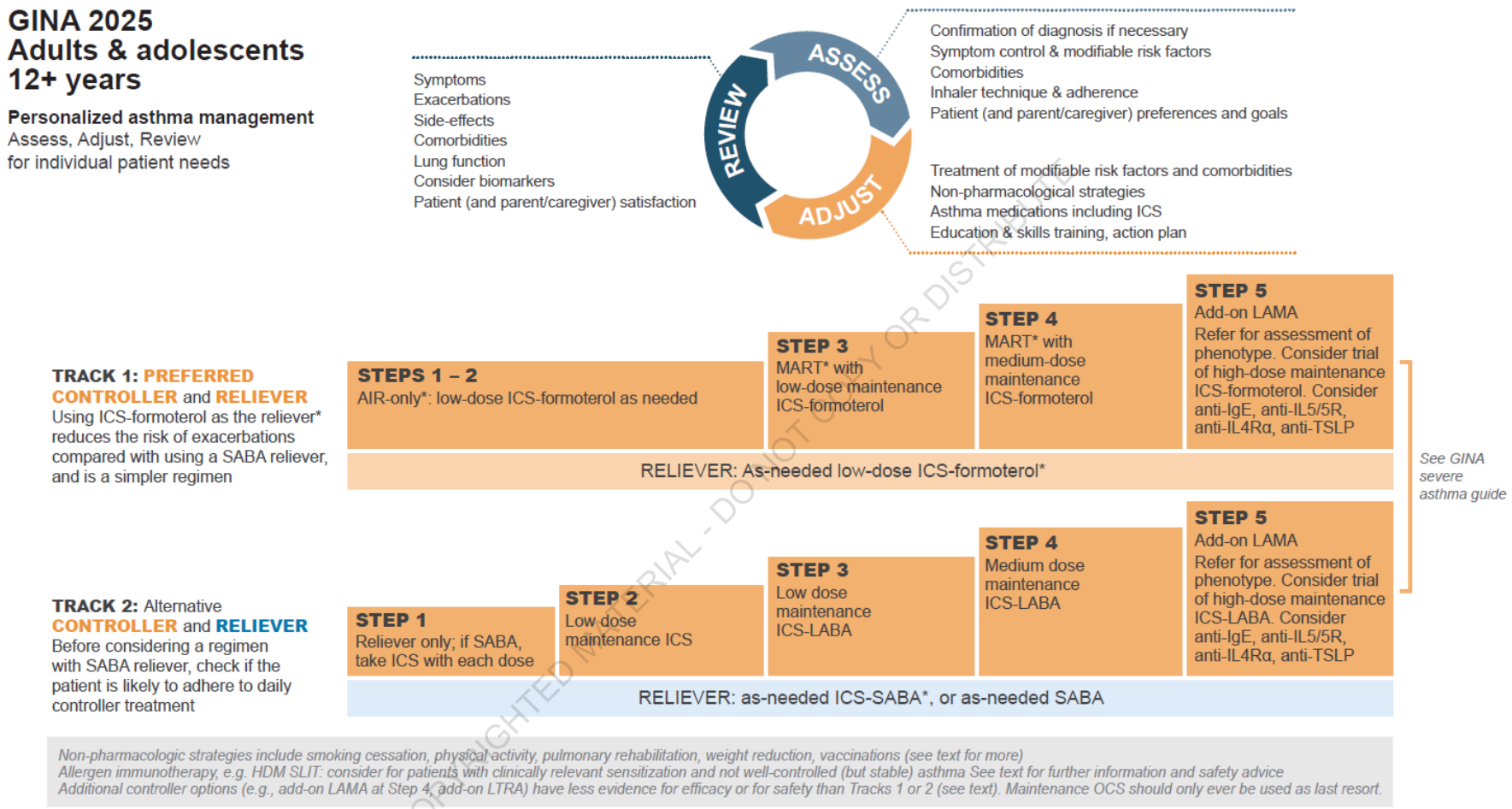


AIR: anti-inflammatory reliever

These recommendations are based on evidence, where available, and on consensus. See list of abbreviations (p.11). See Box 4-2 (p.71) for low, medium and high ICS doses for adults and adolescents. See Box 4-6 (p.77), for Track 1 medications and doses. Check local payer criteria.

ASTHMA TREATMENT STEPS IN ADULTS AND ADOLESCENTS

Box 4-6. Personalized management for adults and adolescents to control symptoms and minimize future risk



*AIR: Anti-inflammatory reliever; Ig: immunoglobulin; ICS: inhaled corticosteroids; HDM: house dust mits; IL: interleukin; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; MART: maintenance-and reliever therapy with ICS-formoterol; OCS: oral corticosteroid; SLIT: sublingual immunotherapy; TSLP: thymic stromal lymphopoietin. †If prescribing LTRA, advise patient/caregiver about risk of neuropsychiatric adverse effects.

For recommendations about initial asthma treatment in adults and adolescents, see Box 4-4 (p.75) and Box 4-5 (p.76). See Box 4-2 (p.71) for low, medium and high ICS doses for adults and adolescents. See Box 4-8 (p.84) for Track 1 medications and doses.

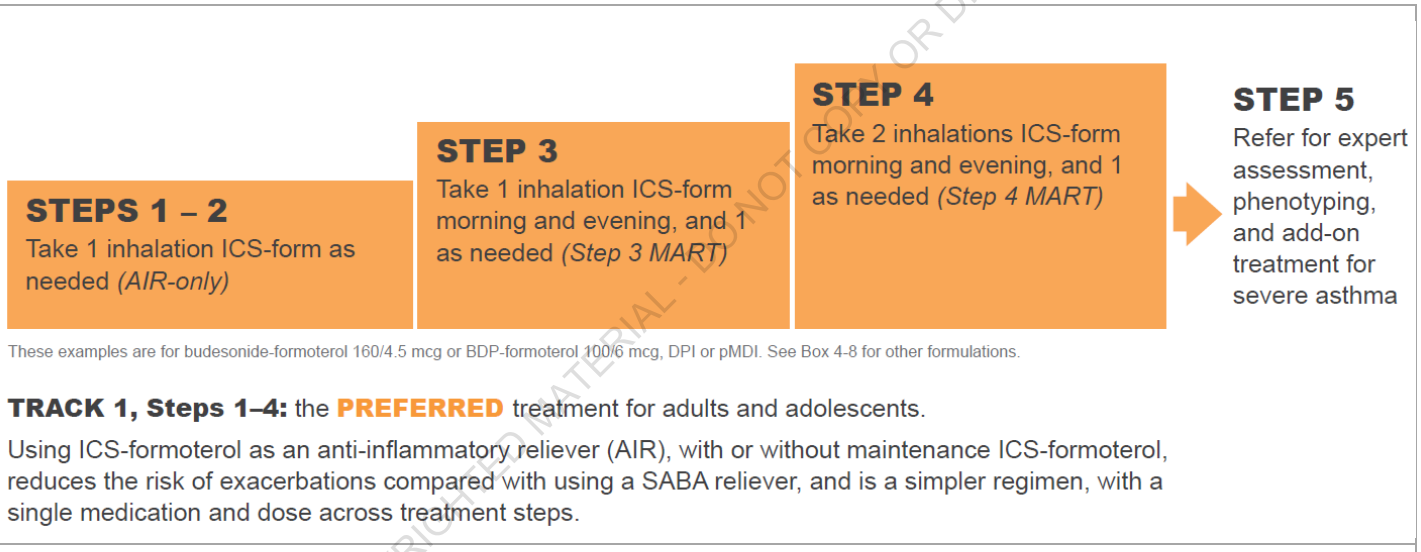
TRACK 1 (PREFERRED): TREATMENT STEPS 1–4 FOR ADULTS AND ADOLESCENTS USING ICS-FORMOTEROL RELIEVER

Track 1 is the preferred approach recommended by GINA for adults and adolescents with asthma, because using low-dose ICS formoterol (an anti-inflammatory reliever; AIR) reduces the risk of severe exacerbations, compared with regimens that use SABA as reliever, with similar symptom control and lung function. In addition, the treatment regimen is simpler, with patients using a single medication for reliever and for maintenance treatment (if prescribed), across treatment steps.

With the AIR approach, when a patient at any treatment step has asthma symptoms, they use low-dose ICS-formoterol in a single inhaler for symptom relief. In Steps 1–2, this provides their anti-inflammatory therapy. In Steps 3–5, patients also take ICS formoterol as their daily maintenance treatment; together, this is called "maintenance-and-reliever therapy" (MART). Details about medications and doses for Track 1 are in Box 4-8, p.84.

Details below are for Track 1, Steps 1–4. In Step 5, treatment options for Tracks 1 and 2 are similar, so the information is shown for both Tracks together, starting on p.91 and in Section 8, p.139.

Box 4-7. Track 1 (preferred) treatment Steps 1–4 for adults and adolescents



See Box 4-8 (p.84) for details of medications and doses. AIR: anti-inflammatory reliever; ICS: inhaled corticosteroid; MART: maintenance-and-reliever therapy with ICS-formoterol; SABA: short-acting beta$_2$-agonist

Check local eligibility and payer criteria for doses and formulations.

For symptom relief with ICS-formoterol, take 1 inhalation whenever needed. If symptoms persist after a few minutes, another dose can be taken. Seek medical care if more than 12 inhalations (total of reliever doses and maintenance doses, if prescribed) are needed in any 24-hour period.

Use 1 inhalation of ICS-formoterol before exercise, if needed, or before expected allergen exposure.

Track 1 (preferred) Step 1–2 treatment for adults and adolescents: as-needed low-dose combination ICS-formoterol

In Track 1, Steps 1–2, low-dose combination ICS-formoterol is used as needed for symptom relief, and before exercise or before expected allergen exposure.

Information about Steps 1 and 2 below is combined, because the recommended treatment (as-needed low-dose ICS-formoterol) is the same.

In Track 1, Step 1–2 treatment with as-needed-only low-dose combination ICS-formoterol is recommended for:

- Step-down treatment for patients whose asthma is well controlled on low-dose maintenance-and-reliever therapy with ICS-formoterol (Evidence D) or on regular low-dose ICS with as-needed SABA (Evidence A)
- Initial treatment for patients previously using SABA alone (or with newly diagnosed asthma), with normal or mildly reduced lung function. Some clinical factors, outlined below, may prompt consideration of starting treatment instead at Step 3, with low-dose ICS-formoterol maintenance-and-reliever therapy.

Populations studied

The populations studied in the large randomized controlled trials of as-needed low-dose ICS-formoterol[195,196,315,316] included almost 10,000 adults and adolescents with asthma that was considered to be mild, and was either uncontrolled on SABA alone, or controlled on low-dose ICS or LTRA. In the two largest studies, post-bronchodilator forced expiratory volume in 1 second (FEV_1) was required to be ≥80% predicted at baseline.[315,316]

Evidence

Use of low-dose ICS-formoterol as needed for symptom relief (an anti-inflammatory reliever) for adults and adolescents (Evidence B) is supported by evidence from four randomized controlled trials, and by systematic review and meta-analysis of all four studies for several outcomes.[191] The two largest studies were double-blind, and two were pragmatic and open-label, intended to evaluate the treatment as it would be used in clinical practice, without patients required to take a twice-daily maintenance inhaler.

The key findings with as-needed low-dose ICS-formoterol, as follows, support the Step 1–2 recommendations:

- A large double-blind study found a 64% reduction in severe exacerbations requiring OCS, compared with SABA-only treatment,[315] with a similar finding in an open-label study in patients previously taking SABA alone (Evidence A).[195] In the Cochrane meta-analysis, as-needed low-dose ICS-formoterol reduced the risk of severe exacerbations requiring OCS by 55%, and reduced the risk of emergency department visits or hospitalizations by 65%, compared with SABA alone (Evidence A).[191]
- Two large double-blind studies showed as-needed budesonide-formoterol was non-inferior for severe exacerbations, compared with regular ICS.[315,316] In two open-label randomized controlled trials, representing the way that patients with mild asthma would use as-needed ICS-formoterol in real life, as-needed budesonide-formoterol was superior to maintenance ICS in reducing the risk of severe exacerbations (Evidence A).[195,196]
- A Cochrane review provided moderate to high certainty evidence that as-needed ICS-formoterol was clinically effective in adults and adolescents with mild asthma, significantly reducing important clinical outcomes including need for oral corticosteroids, severe exacerbation rates, and emergency department visits or hospital admissions, compared with daily ICS plus as-needed SABA (Evidence A).[191]
- In all four studies, the as-needed low-dose ICS-formoterol strategy was associated with a substantially lower average ICS dose than with maintenance low-dose ICS.[195,196,315,316]
- Clinical outcomes with as-needed ICS-formoterol were similar in adolescents as in adults.[319]
- A post hoc analysis of one study[315] found that a day with >2 doses of as-needed budesonide-formoterol reduced the short-term (21 day) risk of severe exacerbations, compared with as needed terbutaline alone, suggesting that timing of use of ICS-formoterol is important.[134]
- No new safety signals were seen with as-needed budesonide-formoterol in these studies.[195,196,315,316,320]

Considerations for recommending as-needed-only low-dose ICS-formoterol as preferred treatment for Steps 1–2

The most important considerations for GINA were:

- The need to prevent severe exacerbations in patients with mild or infrequent symptoms; these can occur with unpredictable triggers such as viral infection, allergen exposure, pollution or stress.

- The desire to avoid the need for daily ICS in patients with mild asthma, who in clinical practice are often poorly adherent with prescribed ICS, leaving them exposed to the risks of SABA-only treatment.[321]
- The greater reduction in severe exacerbations with as-needed ICS-formoterol, compared with daily ICS, among patients previously taking SABA alone, with no significant difference for patients with well-controlled asthma on ICS or LTRA at baseline.[195,322]
- The very small differences in FEV_1, (approximately 30–50 mL), symptom control (difference in 5-question Asthma Control Questionnaire [ACQ-5] score of approximately 0.15 versus minimal clinically important difference 0.5), and symptom-free days (mean difference 10.6 days per year),[315,316] compared with regular ICS were considered to be less important. These differences did not increase over the 12-month studies. The primary outcome variable of one study[315] was "well-controlled asthma weeks", but this outcome was not considered reliable because it was based on an older concept of asthma control, and was systematically biased against the as-needed ICS-formoterol treatment group because much less ICS was permitted in a week for patients on ICS-formoterol than those on maintenance ICS before the week was classified as not well controlled.
- The similar reduction in FeNO with as-needed budesonide-formoterol as with maintenance ICS, and the lack of significant difference in treatment effect with as-needed budesonide-formoterol by patients' baseline eosinophils or baseline FeNO.[195,196]

Considerations for the GINA recommendation against SABA-only treatment of asthma

There were several important considerations for extending the recommendation for as-needed-only low-dose ICS-formoterol to adults and adolescents with infrequent asthma symptoms (i.e., eliminating SABA-only treatment):[6]

- Patients with few interval asthma symptoms can still have severe or fatal exacerbations.[188] GINA recommends assessing and addressing risk factors for exacerbations as well as symptom control (Box 2-2, p.37).
- The historic distinction between so-called "intermittent" and "mild persistent" asthma is arbitrary, with no evidence of difference in response to ICS.[190] A large reduction in risk of severe exacerbations with as-needed ICS-formoterol, compared with as-needed SABA, was seen even in patients with SABA use twice a week or less at baseline.[195]
- A post hoc analysis of one study found that a single day with increased as-needed budesonide-formoterol reduced the short-term (21-day) risk of severe exacerbations compared to as needed SABA alone, suggesting that timing of use of ICS-formoterol is important.[134]
- In patients with infrequent symptoms, adherence to prescribed daily ICS is very poor,[323] exposing them to risks of SABA-only treatment if they are prescribed daily ICS plus as-needed SABA.
- There is a lack of evidence for the safety or efficacy of SABA-only treatment. Historic recommendations for SABA-only treatment were based on the assumption that patients with mild asthma would not benefit from ICS.[190]
- Taking SABA regularly for as little as one week significantly increases exercise-induced bronchoconstriction, airway hyperresponsiveness and airway inflammation, and decreases bronchodilator response.[324,325]
- Even modest over-use of SABA (indicated by dispensing of 3 or more 200-dose canisters a year) is associated with increased risk of severe exacerbations[92] and, in one study, asthma mortality.[93]
- GINA places a high priority on avoiding patients becoming reliant on SABA, and on avoiding conflicting messages in asthma education. Previously, patients were initially provided only with SABA for symptom relief, but later, despite this treatment being effective from the patient's perspective, they were told that to reduce their SABA use, they needed to take a daily maintenance treatment, even when they had no symptoms. Recommending that all patients should be provided with ICS-containing treatment (including, in mild asthma, the option of as-needed ICS-formoterol) 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.

Considerations for starting treatment with low-dose maintenance-and-reliever therapy (Step 3 MART) instead of as-needed-only ICS-formoterol (Steps 1–2)

There is no specific evidence to guide this decision, but by consensus, we suggest starting with Step 3 MART (if permitted by local regulators) if the patient has symptoms most days or is waking at night due to asthma more than once a week (to rapidly reduce symptom burden), or if they are currently smoking, have impaired perception of bronchoconstriction (e.g., low initial lung function but few symptoms), a recent severe exacerbation or a history of a life-threatening asthma exacerbation, have severe airway hyperresponsiveness, or are currently exposed to a seasonal allergic trigger.

Anti-inflammatory reliever treatment with as-needed-only ICS-formoterol ('AIR-only') is the preferred treatment for Steps 1 and 2 in adults/adolescents, so these steps have been combined in the treatment figure (Track 1, Box 4-6, p.77) to avoid confusion.

Practice points for as-needed-only ICS-formoterol in mild asthma

The usual dose of as-needed budesonide-formoterol in mild asthma is a single inhalation of 200/6 mcg (delivered dose 160/4.5 mcg), taken whenever needed for symptom relief. The maximum recommended dose of as-needed budesonide-formoterol in a single day corresponds to a total of 72 mcg formoterol (54 mcg delivered dose). However, in randomized controlled trials (RCTs) in mild asthma, such high usage was rarely seen, with average use around 3–4 doses per week.[195,315,316] For more details about medications and doses for as-needed-only ICS-formoterol, see Box 4-8 (p.84).

Rinsing the mouth is not generally needed after as-needed doses of low-dose ICS-formoterol, as this was not required in any of the mild asthma studies (or in MART studies), and there was no increase in risk of oral candidiasis.[320]

Other ICS-formoterol formulations have not been studied for as-needed-only use, but beclometasone-formoterol may also be suitable, as it is well-established for as-needed use within maintenance-and-reliever therapy in GINA Steps 3–5.[233] Combinations of ICS with non-formoterol LABA cannot be used as-needed for symptom relief.

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 exercise.[246] This suggests that patients with mild asthma who are prescribed as-needed low-dose ICS-formoterol to prevent exacerbations and control symptoms can use the same medication before exercising, if needed, and do not need to be prescribed a SABA for pre-exercise use (Evidence B).

Patient preferences: from qualitative research, the majority of patients in a pragmatic open-label study preferred as-needed ICS-formoterol for ongoing treatment rather than regular daily ICS with a SABA reliever. They reported that shared decision-making would be important in choosing between these treatment options.[326]

Asthma action plan: Simple action plans for AIR-only and MART are available online.[327,328]

Track 1 (preferred) Step 3 treatment for adults and adolescents: low-dose ICS-formoterol maintenance-and-reliever therapy (MART)

For adults and adolescents, the preferred Step 3 option is low-dose ICS-formoterol as both maintenance and reliever treatment (MART). In this regimen, low-dose ICS-formoterol, either budesonide-formoterol or beclometasone-formoterol, is used as both the daily maintenance treatment and as an anti-inflammatory reliever for symptom relief. The low-dose ICS-formoterol can also be used before exercise, and before expected allergen exposure.

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, p.47).

Populations studied

Double-blind studies included adult and adolescent patients with ≥1 exacerbation in the previous year despite maintenance low-dose ICS or ICS-LABA treatment, with poor symptom control. Open-label studies were in patients taking at least low-dose ICS or ICS-LABA, with suboptimal asthma control; they did not require a history of exacerbations.[235]

Evidence

Low-dose ICS-formoterol maintenance-and-reliever therapy reduced severe exacerbations and provided 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 SABA (Evidence A).[235,329-333] In a meta-analysis, switching patients with uncontrolled asthma from Step 3 treatment plus SABA reliever to MART was associated with a 29% reduced risk of severe exacerbation, compared with stepping up to Step 4 ICS-LABA maintenance plus SABA reliever, and a 30% reduced risk, compared with staying on the same treatment with SABA reliever.[334] In open-label studies that did not require a history of severe exacerbations, maintenance-and-reliever therapy with ICS-formoterol also significantly reduced severe exacerbations with a lower average dose of ICS, compared with conventional best practice including SABA reliever.[235,335]

The benefit of the MART regimen in reducing the risk of severe exacerbations requiring OCS appears to be due to the increase in doses of both the ICS and the formoterol at a very early stage of worsening asthma. As for patients using as-needed-only ICS-formoterol (p.79), this reduces the risk of progressing to a severe exacerbation in the next 3 weeks.[132-134]

Other considerations

Use of ICS-formoterol as an anti-inflammatory reliever across treatment steps provides a simple regimen with easy transition if treatment needs to be stepped up (e.g., from Step 1–2 to Step 3, or Step 3 to Step 4), without the need for an additional medication or different prescription, or a different inhaler type (see Box 4-8, p.84).

Practice points for maintenance-and-reliever therapy (MART) with low-dose ICS-formoterol

Medications: ICS-formoterol maintenance-and-reliever therapy for Step 3 treatment can be prescribed with low-dose budesonide-formoterol (≥12 years) or low-dose beclometasone-formoterol (≥18 years). The usual dose for MART with budesonide-formoterol is 200/6 mcg metered dose (160/4.5 mcg delivered dose) and the usual dose for MART with beclometasone-formoterol is 100/6 metered dose (delivered dose 84.6/5 mcg for pMDI and 81.9/5 mcg for DPI). Each of these combinations is prescribed as one inhalation twice daily plus one inhalation whenever needed for symptom relief.

Doses: For MART with budesonide-formoterol, the maximum recommended total dose of formoterol in a single day (total of maintenance-and-reliever doses) gives 72 mcg metered dose (54 mcg delivered dose) of formoterol, with extensive evidence from large studies for its safety and efficacy up to this dose in a single day,[233,235] with or without ICS.[320,336,337] Based on this evidence, GINA suggests that the same maximum total dose of formoterol in a single day should also apply for MART with beclometasone-formoterol (maximum total 12 inhalations, total metered dose 72 mcg). Most patients need far fewer doses than this. For a summary of medications and doses, see Box 4-8 (p.84).

ICS-formoterol should not be used as the reliever for patients taking a different ICS-LABA maintenance treatment, since clinical evidence for safety and efficacy is lacking. Use of ICS-formoterol with other LABAs may be associated with increased adverse effects.[306]

Rinsing the mouth is not generally needed after as-needed doses of ICS-formoterol, as this was not required in any of the MART studies, and there was no increase in risk of oral candidiasis.[233]

Additional practice points can be found in an article describing how to use MART, including a customizable **written asthma action plan** for use with this regimen.[327] Other action plans for MART are available online.[327,328]

Track 1 (preferred) Step 4 treatment for adults and adolescents: medium-dose ICS-formoterol maintenance-and-reliever therapy (MART)

At a population level, most benefit from ICS is obtained at low dose, but individual ICS responsiveness varies, and some patients whose asthma is uncontrolled on low-dose ICS-LABA despite good adherence and correct inhaler technique may benefit from increasing the maintenance dose to medium, usually by taking twice the number of inhalations (see Box 4-8, p.84). High-dose ICS-formoterol is not recommended in Track 1 Step 4.

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.47).

Patients prescribed MART use low-dose ICS-formoterol as needed for symptom relief, and before exercise or allergen exposure if needed.

For adult and adolescent patients, combination ICS-formoterol as maintenance-and-reliever therapy (MART) is more effective in reducing exacerbations than the same dose of maintenance ICS-LABA or higher doses of ICS[332] or ICS-LABA[233] (Evidence A). The greatest reduction in risk was seen in patients with a history of severe exacerbations,[233] but MART was also significantly more effective than conventional best practice with as-needed SABA in open-label studies in which patients were not selected for greater exacerbation risk.[235]

In Step 4, the MART regimen can be prescribed with medium-dose maintenance budesonide-formoterol or beclometasone-formoterol treatment, by increasing the maintenance dose of low-dose ICS-formoterol to 2 inhalations twice-daily. The reliever dose remains 1 inhalation of low-dose ICS-formoterol, taken as needed.

The usual dose for MART with budesonide-formoterol is 200/6 mcg metered dose (160/4.5 mcg delivered dose) and the usual dose for MART with beclometasone-formoterol is 100/6 mcg metered dose (delivered dose 84.6/5 mcg for pMDI and 81.9/5 mcg for DPI). For Step 4, each of these combinations is prescribed as two inhalations twice-daily plus one inhalation whenever needed for symptom relief.

As in Step 3, the maximum recommended total dose of budesonide-formoterol in a single day (total of maintenance-and-reliever doses) gives 72 mcg metered dose (54 mcg delivered dose) of formoterol, with extensive evidence from large studies for its safety[320,336,337] and efficacy[233,235] up to this dose in a single day. Based on this evidence, GINA suggests that the same maximum total dose of formoterol in a single day should also apply for MART with beclometasone-formoterol (maximum total 12 inhalations, total metered dose 72 mcg). Most patients need far fewer doses than this.

For practice points, see information for GINA Step 3 and an article for clinicians.[327] For a summary of medications and doses, see Box 4-8 (p.84).

Box 4-8. Preferred medications and doses for GINA Track 1: anti-inflammatory reliever (AIR) therapy

GINA Track 1 – general principles

In GINA Track 1, the reliever inhaler is low-dose ICS-formoterol, with or without maintenance ICS-formoterol. This is the preferred treatment approach for adults and adolescents with asthma, because (i) it reduces severe exacerbations and OCS exposure across treatment steps, compared with using a SABA reliever, (ii) it uses a single medication for both reliever and maintenance treatment (less confusing for patients), and (iii) the patient's treatment can be stepped up and down if needed without changing the medication or inhaler device. This cannot be done with any other ICS-LABA. ICS-formoterol can also be used before exercise and before allergen exposure.

Low-dose ICS-formoterol is called an **anti-inflammatory reliever (AIR)** because it relieves symptoms and reduces inflammation. AIR with ICS-formoterol significantly reduces the risk of severe exacerbations across treatment steps, compared with using a SABA reliever, with similar symptom control, lung function and adverse effects.

Steps 1–2 (AIR-only): low-dose ICS-formoterol is used as needed for symptom relief without any maintenance treatment. It reduces the risk of severe exacerbations and ED visits/hospitalizations by 65%, compared with SABA alone, and reduces ED visits/hospitalizations by 37%, compared with daily ICS plus as-needed SABA.[191] Starting treatment with as-needed ICS-formoterol avoids training patients to regard SABA as their main asthma treatment.

Steps 3–5 (MART): maintenance-and-reliever therapy with ICS-formoterol reduces the risk of severe exacerbations by 32% compared with the same dose of ICS-LABA,[233] by 23% compared with a higher dose of ICS-LABA,[233] and by 17% compared with usual care.[235] MART is also an option for children 6–11 years in Steps 3–4.

Asthma action plan: Simple action plans for AIR-only and MART are available online.[327,328]

Which medications can be used in GINA Track 1, and how often?

Most evidence for AIR is with budesonide-formoterol DPI, usually 200/6 mcg metered dose (160/4.5 mcg delivered dose) for adults/adolescents, and 100/6 mcg (80/4.5 mcg delivered dose) for MART in children 6–11 years. Beclometasone dipropionate (BDP)-formoterol 100/6 mcg (84.6/5.0) is also effective for MART in adults. Other low-dose combination ICS-formoterol products may be suitable but have not been studied.

For as-needed use, patients should take either 1 or 2 inhalations (based on the formulation; see below and next page) whenever needed for symptom relief, or before exercise or allergen exposure, instead of a SABA reliever.

Patients do not need to wait a certain number of hours before taking more reliever doses (unlike SABA), but in a single day, they should not take more than the maximum total number of inhalations shown below and over (total as-needed plus maintenance doses, if used). Most patients need far less than this.

Age	Inhalers: mcg/inhalation metered dose *[delivered dose]* and maximum in any day	Dosing frequency by age group and treatment step (see next page for additional inhaler options and doses)
6–11 years	Budesonide-formoterol 100/6 **DPI** [80/4.5] (maximum total 8 inhalations in any day)	Step 1–2 AIR-only: no evidence to date Step 3 MART: 1 inhalation once daily plus 1 as needed Step 4 MART: 1 inhalation twice daily plus 1 as needed Step 5 MART: not recommended
12–17 years	Budesonide-formoterol 200/6 [160/4.5] **DPI** or **pMDI** (maximum total 12 inhalations in any day)	Step 1–2 (AIR-only): 1 inhalation as needed Step 3 MART: 1 inhalation twice (or once) daily plus 1 as needed Step 4 MART: 2 inhalations twice daily plus 1 as needed Step 5 MART: 2 inhalations twice daily plus 1 as needed
≥18 years	Budesonide-formoterol 200/6 [160/4.5] or BDP-formoterol 100/6, **pMDI** or **DPI** (maximum total 12 inhalations in any day†)	Step 1–2 (AIR-only): 1 inhalation as needed† Step 3 MART: 1 inhalation twice (or once) daily plus 1 as needed Step 4 MART: 2 inhalations twice daily plus 1 as needed Step 5 MART: 2 inhalations twice daily plus 1 as needed

Check local eligibility/payer criteria for medications and doses. †For BDP-formoterol, GINA suggests that the maximum total dose in any day should be 12 inhalations, based on the extensive safety data with budesonide-formoterol; it has not been studied as-needed only but may be suitable. More details, see p.82. BDP-formoterol 100/6 mcg: delivered dose 84.6/5 mcg for pMDI, 81.9/5 mcg for DPI.

Box 4-8. Medications and doses for GINA Track 1 anti-inflammatory reliever (AIR) therapy (continued)

Medications: mcg/inhalation metered dose [delivered dose] (maximum total inhalations in any day*)	**Dosing frequency for ICS-formoterol formulations suitable for AIR therapy, by age group and treatment step**
Children 6–11 years	
Budesonide-formoterol **DPI** 100/6 [80/4.5] (maximum total 8 inhalations in any day*)	Step 1–2 AIR-only: no evidence to date Step 3 MART: 1 inhalation once daily plus 1 as needed Step 4 MART: 1 inhalation twice daily plus 1 as needed Step 5 MART: not recommended
Budesonide-formoterol **pMDI** 50/3 [40/2.25] (maximum total 16 inhalations in any day*) ***These doses ONLY for pMDIs with 3 [2.25] mcg formoterol***	***These doses ONLY for pMDIs with 3 [2.25] mcg formoterol*** Step 1–2 AIR-only: no evidence to date Step 3 MART: 2 inhalations once daily plus 2 as needed Step 4 MART: 2 inhalations twice daily plus 2 as needed Step 5 MART: not recommended
Adolescents 12–17 years	
Budesonide-formoterol **DPI** or **pMDI** 200/6 [160/4.5] (maximum total 12 inhalations in any day*)	Step 1–2 (AIR-only): 1 inhalation as needed Step 3 MART: 1 inhalation twice (or once) daily plus 1 as needed Step 4 MART: 2 inhalations twice daily plus 1 as needed Step 5 MART: 2 inhalations twice daily plus 1 as needed
Budesonide-formoterol **pMDI** 100/3 [80/2.25] (maximum total 24 inhalations in any day*) ***These doses ONLY for pMDIs with 3 [2.25] mcg formoterol***	***These doses ONLY for pMDIs with 3 [2.25] mcg formoterol*** Step 1–2 (AIR-only): 2 inhalations as needed Step 3 MART: 2 inhalations twice (or once) daily plus 2 as needed Step 4 MART: 4 inhalations twice daily plus 2 as needed Step 5 MART: 4 inhalations twice daily plus 2 as needed
Adults 18 years and older	
Budesonide-formoterol **DPI** or **pMDI** 200/6 [160/4.5] (maximum total 12 inhalations in any day*)	Step 1–2 (AIR-only): 1 inhalation as needed Step 3 MART: 1 inhalation twice (or once) daily plus 1 as needed Step 4 MART: 2 inhalations twice daily plus 1 as needed Step 5 MART: 2 inhalations twice daily plus 1 as needed
Budesonide-formoterol **pMDI** 100/3 [80/2.25] (maximum total 24 inhalations in any day*) ***These doses ONLY for pMDIs with 3 [2.25] mcg formoterol***	***These doses ONLY for pMDIs with 3 [2.25] mcg formoterol*** Step 1–2 (AIR-only): 2 inhalations as needed Step 3 MART: 2 inhalations twice (or once) daily plus 2 as needed Step 4 MART: 4 inhalations twice daily plus 2 as needed Step 5 MART: 4 inhalations twice daily plus 2 as needed
Beclometasone-formoterol **pMDI** or **DPI** 100/6 (GINA suggests maximum total 12 inhalations in any day*†)	Step 1–2 (AIR-only): 1 inhalation as needed Step 3 MART: 1 inhalation twice (or once) daily plus 1 as needed Step 4 MART: 2 inhalations twice daily plus 1 as needed Step 5 MART: 2 inhalations twice daily plus 1 as needed

For abbreviations, see p.11. *Maximum total inhalations in any day is the sum of as-needed doses and maintenance doses, if used. Check local payer criteria, if relevant, for medications and doses. For ICS-formoterol with pMDI, use of a spacer is recommended.

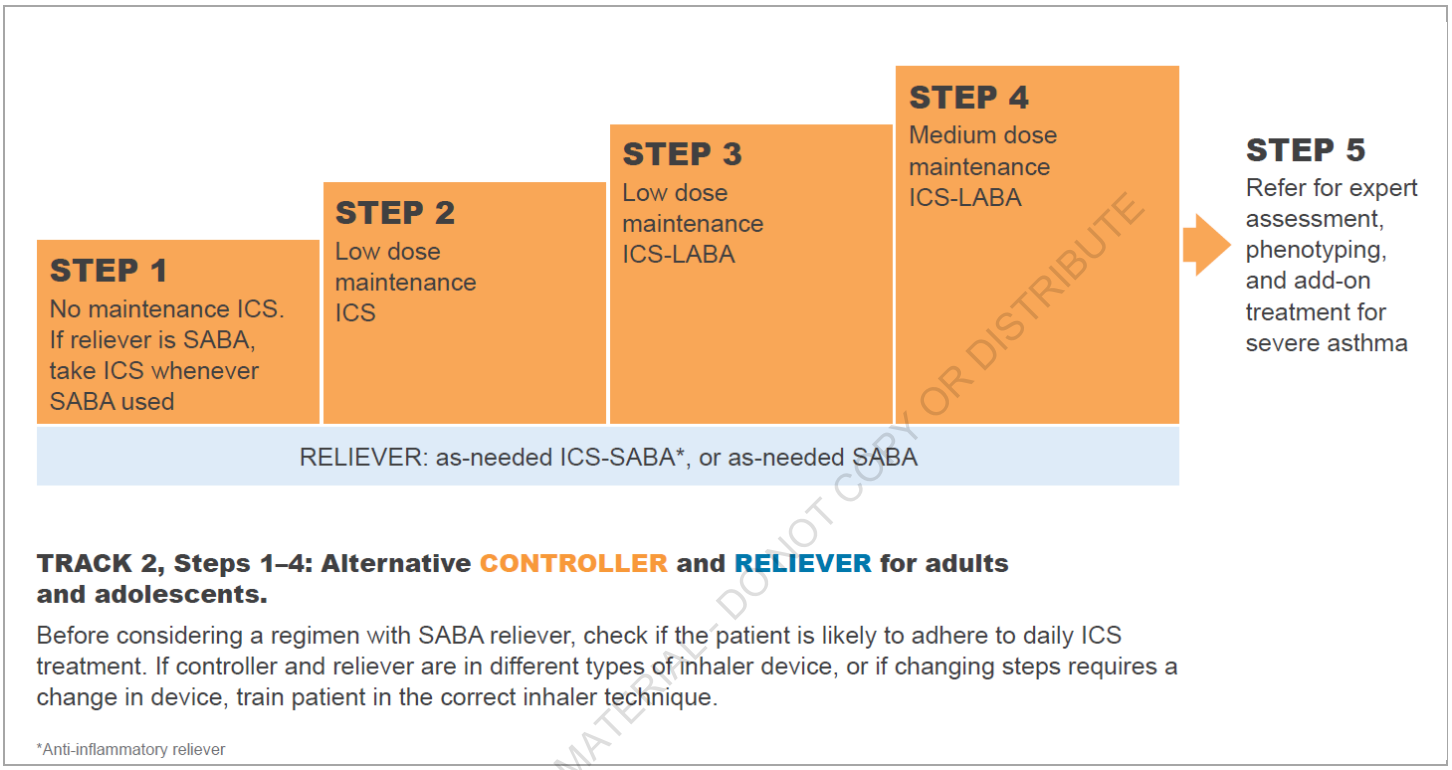
† Beclometasone (BDP)-formoterol has not been studied for as-needed-only use (Steps 1–2), but it may be suitable given its efficacy for MART in moderate-severe asthma.[330] GINA suggests that the maximum total dose of BDP-formoterol in any day should also be 12 inhalations, based on extensive safety data with budesonide-formoterol.[336] For more details, see p.82.

Budesonide-formoterol 400/12 [320/4.5] mcg should **not** be used as an anti-inflammatory reliever. For adults/adolescents, GINA does not suggest use of budesonide-formoterol 100/6 [80/4.5] as an anti-inflammatory reliever, since most evidence is with budesonide-formoterol 200/6 [160/4.5] mcg.

TRACK 2 (ALTERNATIVE): TREATMENT STEPS 1–4 FOR ADULTS AND ADOLESCENTS USING SABA OR ICS-SABA RELIEVER

This is an alternative approach if Track 1 is not possible, or if a patient's asthma is stable with good adherence and no exacerbations on their current therapy. However, before prescribing a regimen with SABA reliever, consider whether the patient is likely to adhere to their maintenance therapy; if not, they will be at higher risk of exacerbations.

Box 4-9. Track 2 (alternative) treatment Steps 1–4 for adults and adolescents



ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; SABA: short-acting beta$_2$-agonist

Track 2 (alternative) STEP 1 treatment options for adults and adolescents: low-dose ICS taken whenever SABA is taken

Low-dose ICS taken whenever SABA is used (in combination or separate ICS and SABA inhalers) is an option if as-needed ICS-formoterol is not available, and the patient is unlikely to take regular ICS. This regimen avoids SABA-only treatment, and may also be useful in regions where the cost of ICS-formoterol is currently prohibitive.

Populations studied

All the evidence for taking ICS whenever SABA is taken is from studies in patients whose asthma was controlled or partly controlled on daily low-dose ICS, i.e., it has been evaluated as a step-down treatment option.

Evidence

The evidence for taking ICS whenever SABA is taken is from two small studies in adults and two small studies in children and adolescents, with separate or combination ICS and SABA inhalers.[338-341] These studies showed no difference in exacerbations, compared with daily ICS but, in the two studies that included a SABA-only arm, SABA alone was the worst option for treatment failure.

All four studies used beclometasone dipropionate (BDP). One study of as-needed combination ICS-SABA used a medium dose (250 mcg BDP+100 mcg salbutamol [albuterol]), and the three studies with separate inhalers used 2 inhalations of BDP 50 mcg [40 mcg delivered dose] for each 2 inhalations of 100 mcg salbutamol (albuterol).

Other considerations

In making this recommendation, the most important considerations were reducing the risk of severe exacerbations, and the difficulty of achieving good adherence to regular ICS in patients with infrequent symptoms. For definitions of low-dose ICS see Box 4-2 (p.71).

Patients with symptoms less than 1–2 days a week are extremely unlikely to take ICS regularly even if prescribed, leaving them exposed to the risks of SABA-only treatment, so taking ICS whenever SABA is taken is likely to be a better option in such patients.

SABA-only treatment is not recommended by GINA for adults, adolescents or children 6–11 years with asthma. Although inhaled SABAs are highly effective for the quick relief of asthma symptoms,[342] patients whose asthma is treated with SABA alone (compared with ICS) are at increased risk of asthma-related death, compared with use of any ICS (Evidence A)[93,343] and of urgent asthma-related healthcare (Evidence A),[344] even if they have good symptom control.[345] The risk of severe exacerbations requiring urgent health care is substantially reduced in adults and adolescents by either as-needed ICS-formoterol,[191] or by regular low-dose ICS with as-needed SABA.[321] The risk of asthma exacerbations and mortality increases incrementally with higher SABA use, including in patients treated with SABA alone.[93] 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.[346] Starting treatment of asthma with SABA alone encourages patients to regard it as their main (and often only) asthma treatment, leading to poor adherence if ICS-containing therapy is prescribed.

Practice points

If combination ICS-SABA is not available, the patient needs to carry both ICS and SABA inhalers with them for as-needed use. See Box 4-2 (p.71) for ICS doses. There are no studies with daily maintenance low-dose ICS plus as-needed combination ICS-SABA.

Track 2 (alternative) Step 2 treatment options for adults and adolescents: low-dose maintenance ICS plus as-needed SABA

Regular daily low-dose ICS with as-needed SABA was standard of care for mild asthma for the past 30 years. Most guidelines recommended its use only for patients with asthma symptoms more than twice a week, based on an assumption that patients with less frequent symptoms did not need, and would not benefit, from ICS.[190]

Population studied

Most studies of daily low-dose ICS have included patients with symptoms 3–7 days per week.

Evidence

Regular daily low-dose ICS plus as-needed SABA is a long-established treatment for mild asthma. 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, compared with SABA alone; symptoms and exercise-induced bronchoconstriction are also reduced (Evidence A).[321,343,347-349] Severe exacerbations are halved with low-dose ICS even in patients with symptoms 0–1 days a week.[190] In a meta-analysis of long-term cohort studies, regular ICS was associated with a very small increase in pre-bronchodilator FEV_1% predicted, but there is insufficient evidence that it protects from development of persistent airflow limitation.[350]

Other considerations

Clinicians should be aware that adherence to maintenance ICS treatment in the community is extremely low. They should consider the high probability that patients with infrequent symptoms will not take daily ICS if prescribed, increasing their

risk of severe exacerbations. Over-use of SABA, indicated by dispensing of three or more 200-dose canisters of SABA in a year (i.e., average use more than daily), is associated with an increased risk of severe exacerbations[92,93] and, in one study, with increased mortality,[93] even in patients also taking ICS-containing treatment.

Track 2 (alternative) Step 3 treatment for adults and adolescents: maintenance low-dose ICS-LABA plus as-needed SABA or plus as-needed combination ICS-SABA

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, p.47).

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, mometasone-formoterol, and mometasone-indacaterol (see Box 4-2, p.71). A large real-world study showed that fluticasone furoate-vilanterol was more effective for symptom control compared with usual care, but there was no significant difference in risk of exacerbations.[351,352]

Maintenance ICS-LABA plus as-needed SABA

This is an alternative approach if MART is not possible, or if a patient's asthma is stable with good adherence and no exacerbations on their current therapy. For patients taking maintenance ICS, changing to maintenance combination ICS-LABA provides additional improvements in symptoms and lung function with a reduced risk of exacerbations, compared with the same dose of ICS (Evidence A),[353,354] but there is only a small reduction in reliever use.[355,356] In these studies, the reliever was as-needed SABA. However, before prescribing a regimen with SABA reliever, consider whether the patient is likely to adhere to their ICS-containing treatment, as poor adherence increase the risk of exacerbations.

Maintenance ICS-LABA plus as-needed combination ICS-SABA (≥18 years)

Population

In the double-blind MANDALA study,[357] the population relevant to Step 3 recommendations comprised patients with poor asthma control and a history of severe exacerbations who were taking maintenance low-dose ICS-LABA or medium-dose ICS. In this study, patients were randomized to as-needed ICS-SABA or as-needed SABA, and continued to take their usual maintenance treatment.

Evidence

In the sub-group taking Step 3 maintenance treatment, as-needed use of 2 inhalations of budesonide-salbutamol (albuterol) 100/100 mcg metered dose (80/90 mcg delivered dose), taken for symptom relief, increased the time to first severe exacerbation by 41%, compared with as-needed salbutamol (hazard ratio 0.59; CI 0.42–0.85). The proportion of patients with a clinically important difference in ACQ-5 was slightly higher with the budesonide-salbutamol reliever. A formulation with a lower ICS dose did not significantly reduce severe exacerbations.[357]

Other considerations

There are no head-to-head comparisons between this regimen and ICS-formoterol maintenance-and-reliever therapy (MART), both of which include an anti-inflammatory reliever (AIR). However, ICS-SABA is not recommended for regular use, and its use as the reliever in Steps 3–5 requires the patient to have different maintenance and reliever inhalers. This regimen is therefore more complex for patients, and increases the risk of incorrect inhaler technique or selective poor adherence, than GINA Track 1 with ICS-formoterol, in which the same medication is used for both maintenance and reliever doses. Transition between treatment steps with as-needed ICS-SABA may also be more complex than with as-needed ICS-formoterol.

Practice points

A maximum number of 6 as-needed doses (each 2 puffs of 100/100 mcg budesonide-salbutamol [80/90 mcg delivered dose]) can be taken in a day. It is essential to educate patients about the different purpose of their maintenance and

reliever inhalers, and to train them in correct inhaler technique with both devices if they are different; this also applies to SABA relievers.

Track 2 (alternative) Step 4 treatment for adults and adolescents: medium-dose ICS-LABA plus as-needed SABA or plus as-needed ICS-SABA

Maintenance medium-dose ICS-LABA plus as-needed SABA

This is an alternative approach if MART is not possible, or if a patient's asthma is stable with good adherence and no exacerbations on their current therapy. As above, individual ICS responsiveness varies, and some patients whose asthma is uncontrolled or who have frequent exacerbations on low-dose ICS-LABA despite good adherence and correct inhaler technique may benefit from maintenance medium-dose ICS-LABA (Evidence B)[358] plus as-needed SABA, if MART is not available. However, before prescribing a regimen with SABA reliever, consider whether the patient is likely to adhere to their ICS-containing treatment, as poor adherence will increase the risk of exacerbations.

Occasionally, high-dose ICS-LABA may be needed, but if possible it should be limited to 3–6 months, to reduce the risk of adverse effects.

Maintenance ICS-LABA plus as-needed combination ICS-SABA (≥18 years)

Population

In the double-blind MANDALA study,[357] the population relevant to Step 4 recommendations comprised patients with poor asthma control and a history of severe exacerbations who were taking maintenance medium-dose ICS-LABA or high-dose ICS.

Evidence

In the sub-population of patients who were taking maintenance medium-dose ICS-LABA or high-dose ICS (Step 4 treatment), there was no significant increase in time to first severe exacerbation with as-needed budesonide-salbutamol (albuterol) 2 inhalations of 100/100 mcg metered dose (80/90 mcg delivered dose), compared with as-needed salbutamol (hazard ratio 0.81; CI 0.61–1.07). More studies in this population are needed.

Other considerations

There are no head-to-head comparisons between this regimen and ICS-formoterol MART, both of which include an anti-inflammatory reliever. However, as ICS-SABA is not recommended for regular use, and its use as the reliever in Steps 3–5 requires the patient to have different maintenance and reliever inhalers, this regimen is more complex for patients than GINA Track 1 with ICS-formoterol in which the same medication is used for both maintenance and reliever doses.

Practice points

A maximum number of 6 as-needed doses (each 2 puffs of 100/100 mcg budesonide-salbutamol [80/90 mcg delivered dose]) can be taken in a day. It is essential to educate patients about the different purpose of their maintenance and reliever inhalers, and to train them in correct inhaler technique with both devices if they are different; this also applies to SABA relievers.

OTHER MEDICATIONS FOR ADULTS AND ADOLESCENTS (TRACKS 1 AND 2)

Other medications that have been studied for Step 1 or 2 in adults and adolescents

The medications below have limited indications, or less evidence for efficacy or safety, than the medications shown in the two treatment tracks.

Specific allergen immunotherapy (see p.104): For adult patients sensitized to house dust mite, with suboptimally controlled asthma despite low- to high-dose ICS, consider adding sublingual allergen immunotherapy (SLIT), provided FEV_1 is >70% predicted.[359,360]

Leukotriene receptor antagonists (LTRAs): LTRAs, which include montelukast, zafirlukast and zileuton, are less effective than ICS,[361] particularly for exacerbations (Evidence A). Before prescribing montelukast, healthcare providers should consider its benefits and risks, and patients or parents/caregivers should be counselled about the risk of neuropsychiatric events.[309]

Daily low-dose ICS-LABA as initial treatment: Regular daily combination low-dose ICS-LABA as the initial maintenance controller treatment (including in patients previously treated with SABA alone) reduces symptoms and improves lung function, compared with low-dose ICS.[362] However, it is often more expensive and does not further reduce the risk of exacerbations, compared with ICS alone (Evidence A).[362]

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

Other medications that have been studied for Step 3 in adults and adolescents

The medications below have limited indications, or less evidence for efficacy or safety, than the medications shown in the two treatment tracks.

Specific allergen immunotherapy (see p.104): For adult patients sensitized to house dust mite, with suboptimally controlled asthma despite low- to high-dose ICS, consider adding SLIT, provided FEV_1 is >70% predicted.[359,360]

Medium-dose ICS: Another option for adults and adolescents is to increase ICS to medium dose[174] (see Box 4-2, p.71) but, at population level, this is less effective than adding a LABA (Evidence A).[363,364] Other less efficacious options are low-dose ICS-containing therapy plus either LTRA[361] (Evidence A for lower efficacy than ICS) or low-dose, sustained-release theophylline[365] (lack of efficacy, and safety concerns). Note the concerns about neuropsychiatric adverse effects with montelukast.[309]

Other medications that have been studied for Step 4 in adults and adolescents

The medications below have specific indications, or less evidence for efficacy or safety, than the medications shown in the two treatment tracks.

Long-acting muscarinic antagonists (LAMAs): LAMAs may be considered as add-on therapy to low-dose ICS-LABA in a separate inhaler for patients aged ≥6 years (tiotropium), or in a combination ('triple') inhaler for patients aged ≥18 years (beclometasone-formoterol-glycopyrronium; fluticasone furoate-vilanterol-umeclidinium; mometasone-indacaterol-glycopyrronium) if asthma is persistently uncontrolled despite medium or high-dose ICS-LABA. Adding a LAMA to medium or high-dose ICS-LABA modestly improved lung function (Evidence A)[310,366-370] but with no difference in symptoms. In some studies, adding LAMA to ICS-LABA modestly reduced exacerbations, compared with some medium- or high-dose ICS-LABA comparators.[310,367,370] In meta-analyses, there was a 17% reduction in risk of severe exacerbations with addition of LAMA to medium- or high-dose ICS-LABA; sub-group analysis suggested that this benefit was mainly in patients with a history of exacerbations in the previous year.[371,372]

However, for patients experiencing exacerbations despite low-dose ICS-LABA, the ICS dose should be increased to at least medium, or treatment switched to maintenance-and-reliever therapy with ICS-formoterol, before considering adding a LAMA. In one study, the severe exacerbation rate was lower in patients receiving high-dose fluticasone furoate-vilanterol

(ICS-LABA) than with low- to medium-dose fluticasone furoate-vilanterol-umeclidinium (ICS-LABA-LAMA).[368] For patients prescribed an ICS-LABA-LAMA with a non-formoterol LABA, the appropriate reliever is SABA or ICS-SABA.

In Step 4, there is insufficient evidence to support ICS-LAMA over low- or medium-dose ICS-LABA combination; all studies were with ICS and tiotropium in separate inhalers.[366] In one analysis, response to adding LAMA to medium-dose ICS, as assessed by FEV_1, ACQ, and exacerbations, was not modified by baseline demographics, body-mass index, FEV_1, FEV_1 responsiveness, or smoking status (past smoking versus never).[373]

Allergen immunotherapy (see p.104): Consider adding sublingual allergen immunotherapy (SLIT) for adult patients with sensitization to house dust mite, with suboptimally controlled asthma despite low- to high-dose ICS, but only if FEV_1 is >70% predicted.[359,360]

Other medications with less evidence for efficacy and/or safety: For medium- or high-dose budesonide, efficacy may be improved with dosing four times daily (Evidence B),[374,375] but adherence may be an issue. For other ICS, twice-daily dosing is appropriate (Evidence D). Other medications for adults or adolescents that have been added to a medium or high-dose ICS, but that are less efficacious than adding LABA, include LTRA (Evidence A),[376-380] or low-dose sustained-release theophylline (Evidence B),[381] but neither of these has been compared with maintenance-and-reliever therapy with ICS-formoterol. Note the concern about potential neuropsychiatric adverse effects with montelukast.[309]

STEP 5 (TRACKS 1 AND 2) IN ADULTS AND ADOLESCENTS

Preferred treatment at Step 5 in adults and adolescents: refer for expert assessment, phenotyping, and add-on therapy (for more details, see Section 8, p.139)

Patients of any age with persistent symptoms or exacerbations despite correct inhaler technique and good adherence on Step 4 treatment, and in whom other controller options have been considered, should be referred promptly to a specialist with expertise in investigation and management of severe asthma, if available (Evidence D).[183]

In severe asthma, as in mild–moderate asthma,[382] participants in randomized controlled trials may not be representative of patients seen in clinical practice. For example, a registry study found that over 80% of patients with severe asthma would have been excluded from major regulatory studies evaluating biologic therapy.[383]

Recommendations from the **GINA Short Guide and decision tree** on Diagnosis and Management of difficult-to-treat and severe asthma in adolescent and adult patients are included in Section 8 (p.139). These recommendations emphasize the importance of first optimizing existing therapy and treating modifiable risk factors and comorbidities (see Box 8-2, p.142). If the patient still has uncontrolled symptoms and/or exacerbations, additional treatment options that may be considered may include the following (**always check local eligibility and payer criteria**).

Combination high-dose ICS-LABA

Combination high-dose ICS-LABA may be considered in adults and adolescents, but for most patients, the increase in ICS dose generally provides little additional benefit (Evidence A),[168,174,364] and there is an increased risk of side-effects, including adrenal suppression.[384] A high dose is recommended only on a trial basis for 3–6 months when good asthma control cannot be achieved with medium-dose maintenance-and-reliever therapy (MART) with ICS-formoterol or medium-dose ICS plus LABA and/or a third controller (e.g., LTRA or sustained-release theophylline with a SABA reliever (Evidence B).[379,381] Note safety concerns with montelukast.[309]

Maintenance-and-reliever therapy (MART) with ICS-formoterol

If a patient treated with medium-dose MART requires addition of biologic therapy, it is not logical to switch them from MART to conventional ICS-LABA plus as-needed SABA, as this may increase the risk of exacerbations. There is little evidence about initiating MART in patients receiving add-on treatment such as LAMA or biologic therapy.[385] However, in one study,[385] patients with severe eosinophilic asthma that was well controlled on benralizumab and high-dose ICS-LABA were randomized to budesonide-formoterol, either as high dose maintenance plus as-needed SABA, or as medium-dose MART with subsequent 8-weekly options for down-titration. Asthma remained stable after the switch from high-dose ICS-

formoterol to medium-dose MART, supporting the safety of MART in this population on Step 5 treatment. Most patients randomized to MART were able to further reduce their ICS-formoterol dose, but there was an increase in FeNO and decrease in FEV_1 in those who stepped down to as-needed-only ICS-formoterol,[385] suggesting that maintenance doses of ICS-formoterol should not be stopped.

Add-on long-acting muscarinic antagonists

Add-on long-acting muscarinic antagonists (LAMA) can be prescribed in a separate inhaler (tiotropium), or in a combination ('triple') inhaler for patients aged ≥18 years (beclometasone-formoterol-glycopyrronium; fluticasone furoate-vilanterol-umeclidinium; mometasone-indacaterol-glycopyrronium) if asthma is not well controlled with medium or high-dose ICS-LABA. Adding LAMA to ICS-LABA modestly improves lung function (Evidence A),[310,366-369,371,373,386] but not quality of life, with no clinically important change in symptoms.[371,372] Some studies showed a reduction in exacerbation risk; in meta-analyses, overall, there was a 17% reduction in risk of severe exacerbations requiring oral corticosteroids (Evidence A),[310,366,367,370,371,386] with subgroup analysis suggesting that this benefit was primarily in patients with a history of exacerbations in the previous year.[372] For patients with exacerbations despite ICS-LABA, it is essential that sufficient ICS is given (i.e., at least medium-dose ICS-LABA) before considering adding a LAMA. For patients prescribed an ICS-LABA-LAMA with a non-formoterol LABA, the appropriate reliever is SABA or ICS-SABA; patients prescribed ICS-formoterol-LAMA can continue ICS-formoterol reliever.

Azithromycin

Add-on azithromycin (three times a week) can be considered after specialist referral for adult patients with persistent symptomatic asthma despite high-dose ICS-LABA. Before considering add-on azithromycin, sputum should be checked for atypical mycobacteria, ECG should be checked for long QTc (and re-checked after a month on treatment), and the risk of increasing antimicrobial resistance should be considered.[387] Diarrhea is more common with azithromycin 500 mg 3 times per week.[388] Treatment for at least 6 months is suggested, as a clear benefit was not seen by 3 months in the clinical trials.[388,389] The evidence for this recommendation includes a meta-analysis of two clinical trials[388,389] in adults with persistent asthma symptoms that found reduced asthma exacerbations among those taking medium or high-dose ICS-LABA who had either an eosinophilic or non-eosinophilic profile and in those taking high-dose ICS-LABA (Evidence B).[390] The option of add-on azithromycin for adults is recommended only after specialist consultation because of the potential for development of antibiotic resistance at the patient or population level.[388]

Add-on biologic therapy

Options recommended by GINA for patients with uncontrolled severe asthma despite optimized maximal therapy (see more details in Section 8, p.139) include:

- *Add-on anti-immunoglobulin E (anti-IgE)* (subcutaneous (SC) omalizumab) for patients aged ≥ 6 years with severe allergic asthma (Evidence A)[391,392]
- *Add-on anti-interleukin-5/5Rα* (SC mepolizumab for ages ≥ 6 years, SC benralizumab for ages ≥12 years, or IV reslizumab for ages ≥18 years) for patients with severe eosinophilic asthma (Evidence A).[392-397]
- *Add-on anti-interleukin-4Rα* (SC dupilumab) for patients aged ≥ 6 years with severe eosinophilic/Type 2 asthma, or those requiring treatment with maintenance OCS (Evidence A)[392,398-401]
- *Add-on anti-thymic stromal lymphopoietin (anti-TSLP)* (SC tezepelumab) for patients aged ≥12 years with severe asthma (Evidence A).[402-404]

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 ICS (Evidence A),[405] but few clinicians currently have access to routine sputum testing.

Bronchial thermoplasty

Add-on treatment with bronchial thermoplasty may be considered for some adult patients with severe asthma (Evidence B).[183,406] Evidence is limited and in selected patients (see Bronchial thermoplasty, p.106). Long-term effects compared with control, including on lung function, are unknown.

Oral corticosteroids

As a last resort, add-on low-dose OCS (≤7.5 mg/day prednisone equivalent) may be considered for some adults with severe asthma (Evidence D),[183] but maintenance OCS is associated with substantial cumulative side effects (Evidence A).[234,407-409] It should only be considered for adults with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence on Step 5 treatment, and after exclusion of other contributory factors and trial of other add-on treatments including biologics where available and affordable. Patients should be counseled about potential side-effects.[408,409] They should be assessed and monitored for risk of adrenal suppression and corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counseling and prescription of therapy for prevention of osteoporosis and fragility fractures (where appropriate).[410]

NON-RECOMMENDED BRONCHODILATORS

Fenoterol: This short-acting beta$_2$-agonist is not recommended because of its higher risk of adverse effects (including hypokalemia and cardiovascular effects), and its association with increased asthma mortality.[411]

Oral bronchodilators: Oral SABA and theophylline have a higher risk of side-effects than inhaled SABA and are not recommended. For clinicians in regions without access to inhaled therapies, advice on minimizing the frequency and dose of these oral medications has been provided elsewhere.[25] No long-term safety studies have been performed to assess the risk of severe exacerbations associated with oral SABA or theophylline use in patients not also taking ICS.

Anticholinergic agents in the absence of ICS: In adults, inhaled short-acting muscarinic antagonists (SAMA) like ipratropium are potential alternatives to SABA for routine relief of asthma symptoms; however, these agents have a slower onset of action than inhaled SABA. Like SABAs (p.87) they should not be used without ICS. Use of long-acting muscarinic antagonists (LAMA) in asthma without concomitant ICS is associated with an increased risk of severe exacerbations.[412]

Formoterol without ICS: The rapid-onset LABA, formoterol, is as effective as SABA as a reliever medication in adults and children,[413] and reduces the risk of severe exacerbations by 15–45%, compared with as-needed SABA,[337,414,415] but use of regular or frequent LABA without ICS is strongly discouraged because of the risk of exacerbations (Evidence A).[158,416]

ABOUT ASTHMA TREATMENT FOR CHILDREN 6–11 YEARS

For general principles of asthma treatment, and non-pharmacological strategies, see Section 3, p.48.

For flowchart on initial asthma treatment for children 6–11 years, see p.94.

For asthma treatment steps in children 6–11 years, see p.96.

INITIAL ASTHMA TREATMENT IN CHILDREN 6–11 YEARS

Box 4-10. Initial asthma treatment for children aged 6–11 years with a diagnosis of asthma

These recommendations are based on evidence, where available, and on consensus.

Presenting symptoms	Preferred INITIAL treatment
Infrequent asthma symptoms, e.g., 1–2 days/week or less	Low-dose ICS taken whenever SABA is taken (Evidence B), in separate inhalers or in combination (if available)
Asthma symptoms 2–5 days/week	Low-dose ICS plus as-needed SABA (Evidence A) Other, non-preferred options include taking ICS whenever SABA is taken in combination or separate inhalers (Evidence B), or daily LTRA* (Evidence A for ICS having greater effectiveness for exacerbations than LTRA). Consider the probability of adherence to maintenance treatment if reliever is SABA.
Asthma symptoms most days (e.g., 4–5 days/week); or waking due to asthma once a week or more	Low-dose ICS-LABA plus as needed SABA (Evidence A), OR Medium-dose ICS plus as-needed SABA (Evidence A), OR Very-low-dose ICS-formoterol maintenance-and-reliever (Evidence B) Other, non-preferred options include daily low-dose ICS and LTRA,* plus as-needed SABA.
Daily asthma symptoms, waking at night once or more a week, and low lung function	Medium-dose ICS-LABA plus as-needed SABA, OR low-dose ICS-formoterol maintenance-and-reliever (MART).
Initial asthma presentation is during an acute exacerbation.	Treat as for exacerbation (Box 9-4, p.168), including a short course of OCS if the exacerbation is severe; commence Step 3 or Step 4 treatment, and arrange follow-up.

Before starting initial controller treatment

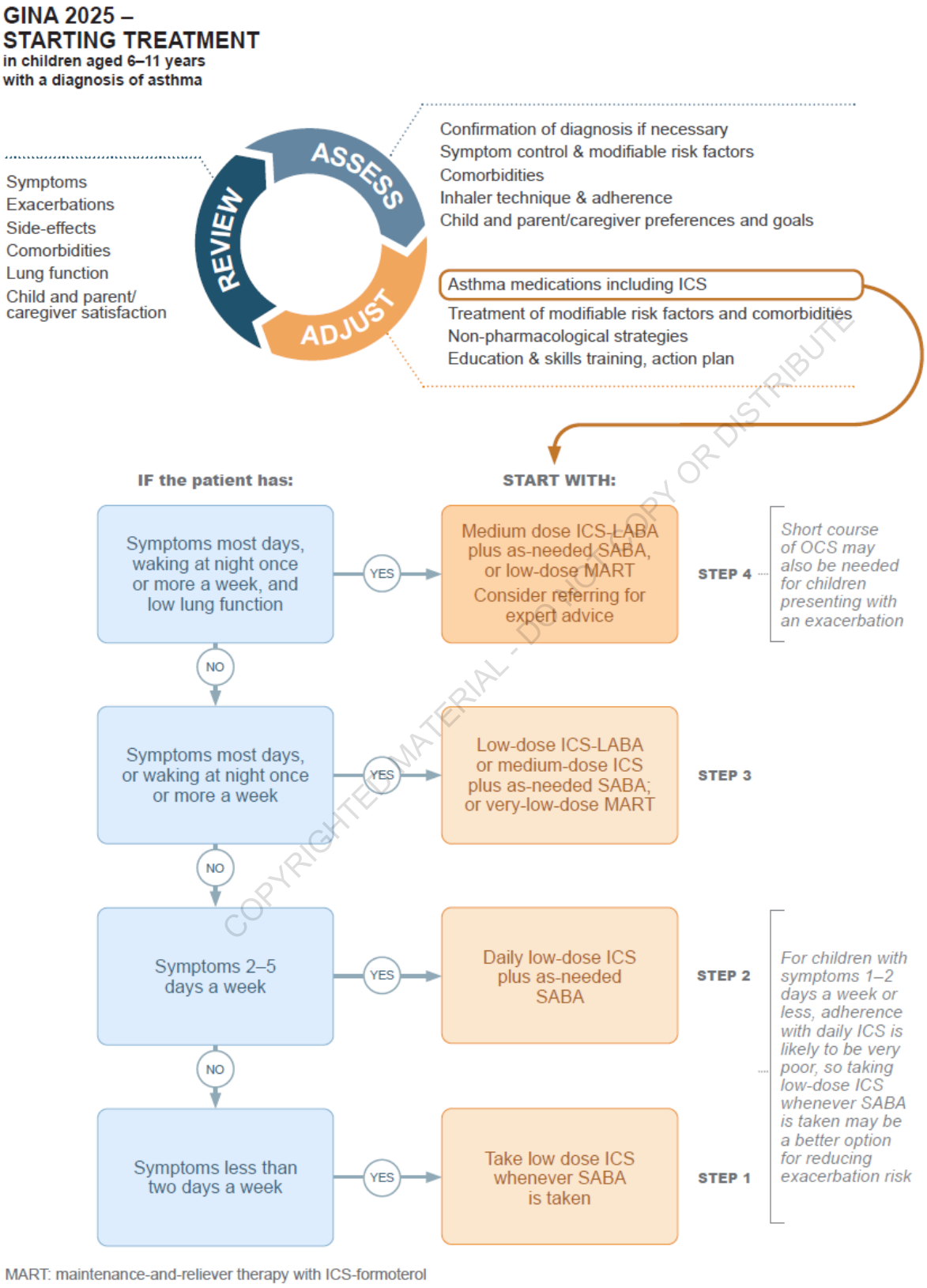
- Record evidence for the diagnosis of asthma, if possible.
- Record the child's level of symptom control and risk factors, including lung function (Box 2-2, p.37; Box 2-3, p.40).
- Consider factors influencing choice between available treatment options (Box 3-4, p.54).
- Choose a suitable inhaler (Box 5-1, p.109) and ensure that the child can use the inhaler correctly.
- Schedule an appointment for a follow-up visit.

After starting initial controller treatment

- Review child's response (Box 2-2, p.37) after 2–3 months, or earlier depending on clinical urgency.
- See Box 4-12 (p.96) for recommendations for ongoing treatment and other key management issues.
- Step down treatment once good control has been maintained for 3 months (Box 4-13, p.102).

This advice is based on evidence from available studies and from consensus, including considerations of cost. *If prescribing LTRA, advise about the risk of neuropsychiatric adverse effects.[309] See Box 4-2 (p.71) for low, medium and high ICS doses in children, and Box 4-8 (p.84) for MART doses in children. See list of abbreviations (p.11).

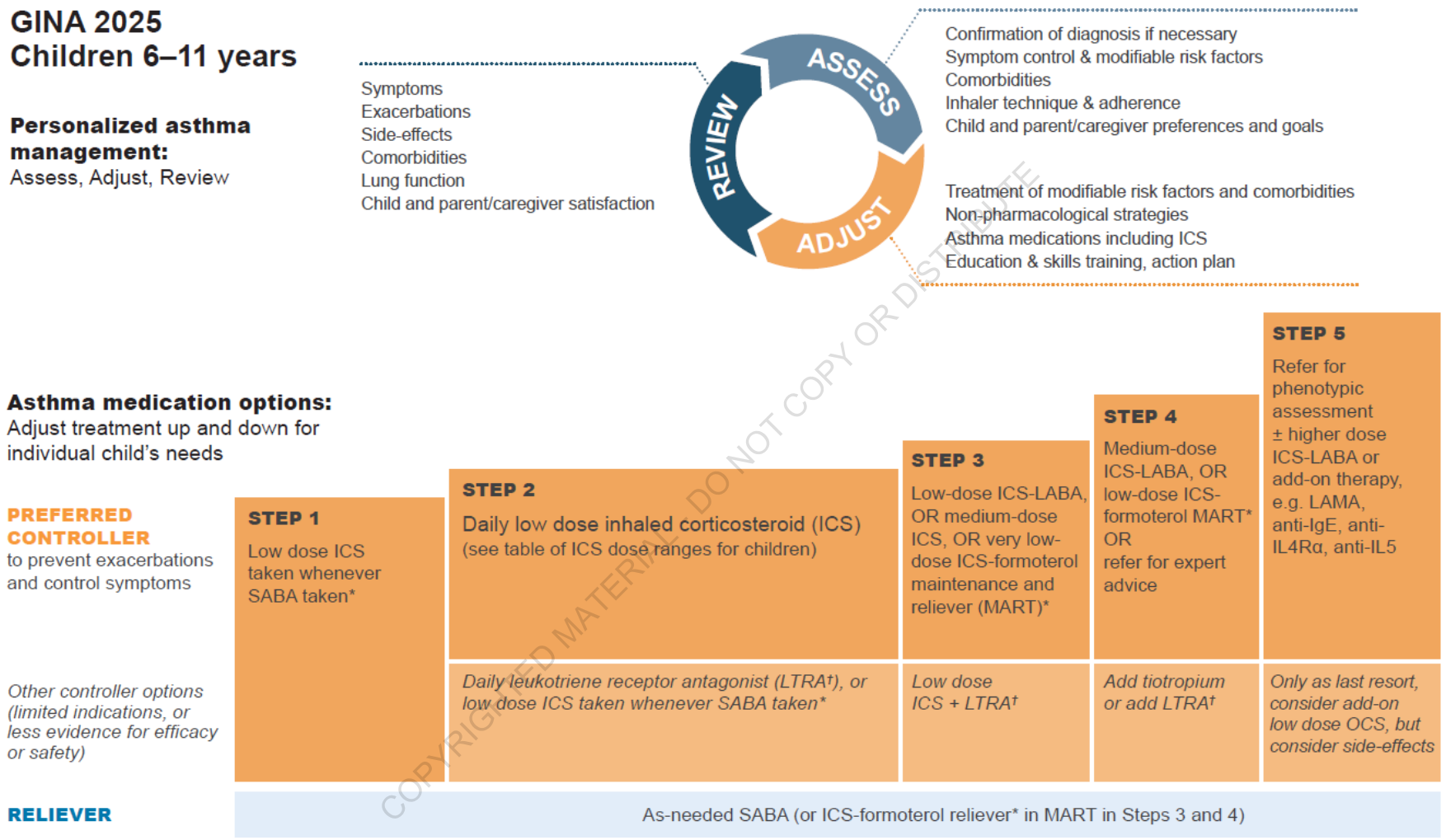
Box 4-11. Flowchart for selecting initial treatment in children aged 6–11 years with a diagnosis of asthma



These recommendations are based on evidence, where available, and on consensus. See list of abbreviations (p.11). See Box 4-2 (p.71) for low, medium and high ICS doses in children. See Box 4-8 (p.84) for medications and doses for MART in children.

ASTHMA TREATMENT STEPS FOR CHILDREN 6–11 YEARS

Box 4-12. Personalized management for children 6–11 years to control symptoms and minimize future risk



See list of abbreviations (p.11). *Anti-inflammatory reliever therapy (AIR); see Box 4-8. †If prescribing leukotriene receptor antagonists, note concerns about potential neuropsychiatric adverse effects.[309] For initial asthma treatment in children aged 6–11 years, see Box 4-10 (p.94) and 4-11 (p.95). See Box 4-2 (p.71) for low, medium and high ICS doses in children. See Box 4-8 (p.84) for MART doses for children 6–11 years.

The steps below refer to the recommended asthma treatment options shown in Box 4-12 p.96.

Suggested low, medium and high doses for a range of ICS formulations are shown in Box 4-2 (p.71).

Preferred Step 1 treatment for children 6–11 years: taking ICS whenever SABA is taken

For children 6–11 years with asthma symptoms that are well controlled on low-dose ICS, or who are using SABA alone and have symptoms less than twice a week, the recommended treatment is taking ICS whenever SABA is taken.

Populations studied

The TREXA study[339] was in children 5–18 years, with mild persistent asthma that was well controlled during a 4-week run-in on low-dose ICS with as-needed SABA. The ASIST study[341] was in African-American children aged 6–17 years, whose asthma was well controlled on low-dose ICS with as-needed SABA in a run-in period of 2–4 weeks. Results for children 6–11 years have not been published separately.

Evidence

Both studies used separate salbutamol (albuterol) and beclometasone dipropionate (BDP) 50 mcg [40 mcg delivered dose] inhalers for the intervention, 2 puffs of BDP for each 2 puffs of salbutamol (albuterol), with the inhalers taped together, back-to-back, in the TREXA study. In the TREXA study, the comparators were as-needed SABA and as-needed ICS+SABA, each with or without regular ICS. The highest rate of exacerbations was among the children receiving SABA alone, and there was a significant reduction in treatment failures in the group that took ICS whenever SABA was taken, as well as in the other ICS-containing groups.[339] In the ASIST study, symptom-based adjustment of ICS dose was associated with similar outcomes as with physician-adjusted treatment, with lower average ICS dose (Evidence B).[341] Exacerbations and symptoms were similar with this regimen as with maintenance ICS plus as-needed SABA.

Other considerations

Neither of these studies was sufficiently powered to examine severe exacerbations as an outcome. In the TREXA study, there were no differences in asthma symptom control or airway hyperresponsiveness between the treatment groups. The children receiving daily ICS had lower linear growth than those receiving as-needed SABA or as-needed ICS+SABA.[339] In the ASIST study, interviews with parents/caregivers indicated that those whose children were randomized to as-needed ICS-SABA felt more in control of their child's asthma than those whose children were randomized to physician-based adjustment.[341]

Concerns around SABA-only treatment are also relevant to children, and should be considered when initiating Step 1 treatment (see other controller options for children in Step 2, below). Studies of as needed-only ICS-formoterol in children aged 6–11 years are underway.

Not recommended

SABA-only treatment is not recommended in children 6–11 years, as for adults and adolescents. Although inhaled SABAs are highly effective for the quick relief of asthma symptoms,[342] children whose asthma is treated with SABA alone (compared with ICS) are at increased risk of asthma-related death, compared with use of any ICS (Evidence A)[93,343] and urgent asthma-related health care (Evidence A),[344] even if they have good symptom control.[345] In children, dispensing of three or more SABA inhalers in a year is associated with a doubling of risk of emergency department presentation.

Oral SABA and theophylline are not recommended because of the higher risk of side-effects and lower efficacy. For clinicians in regions without access to inhaled therapies, advice on minimizing the frequency and dose of these oral medications has been provided elsewhere.[25] No long-term safety studies have been performed to assess the risk of severe exacerbations associated with oral SABA or theophylline use in children not also taking ICS.

The rapid-onset LABA, formoterol, is as effective as SABA as a reliever medication in children as well as in adults,[413] and reduces the risk of severe exacerbations by 15–45%, compared with as-needed SABA,[337,414,415] but use of regular or frequent LABA without ICS is strongly discouraged because of the risk of exacerbations (Evidence A).[158,416]

Preferred Step 2 treatment for children 6–11 years: regular low-dose ICS plus as-needed SABA

The preferred controller option for children at Step 2 is regular low-dose ICS plus as-needed SABA (see Box 4-2, p.71 for ICS dose ranges in children). This reduces the risk of serious exacerbations, compared with SABA-only treatment.[321]

Evidence

Evidence in children includes the large long-term START study, in which patients aged 6–66 years with newly diagnosed asthma were provided with placebo or low-dose budesonide (200 mcg/day for children <11 years) for 3 years. Low-dose ICS reduced the risk of severe exacerbations requiring emergency room visit or hospitalization by 40%, improved lung function, increased symptom-free days and decreased days lost from school years).[417]

Alternative Step 2 treatment option for children 6–11 years: taking low-dose ICS whenever SABA is taken

This has been evaluated in studies with separate ICS and SABA inhalers, showing similar asthma outcomes as with daily ICS.[339,341]

Another alternative option at Step 2 is daily LTRA, which, overall, is less effective than ICS,[361] and there are concerns about potential neuropsychiatric adverse events.[309]

Not recommended

Sustained-release theophylline has only weak efficacy in asthma (Evidence B)[381,418,419] and side-effects are common, and may be life-threatening at higher doses.[420] Chromones (nedocromil sodium and sodium cromoglycate) have been discontinued globally.

Preferred Step 3 treatment options for children 6–11 years: regular medium dose ICS or low-dose ICS-LABA plus SABA reliever, or MART with very low-dose ICS-formoterol

In children, after checking inhaler technique and adherence, and treating modifiable risk factors, there are three preferred options at a population level:

- Increase ICS to medium dose (see Box 4-2, p.71) plus as-needed SABA reliever (Evidence A),[421] or
- Change to combination low-dose ICS-LABA plus as-needed SABA reliever (Evidence A),[422] or
- Switch to maintenance-and-reliever therapy (MART) with a very low dose of ICS-formoterol (Evidence B).[423] For a summary of medications and doses, see Box 4-8 (p.84).

Evidence

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.[424] In children, a single study of maintenance-and-reliever therapy (MART) with very low-dose budesonide-formoterol (100/6 metered dose, 80/4.5 mcg delivered dose for both maintenance and reliever) showed a large reduction in exacerbations, compared with the same dose of budesonide-formoterol plus SABA reliever, or compared with higher-dose ICS.[423]

Individual children's responses vary, so try the other controller options above before considering Step 4 treatment.[425]

Other Step 3 treatment options for children 6–11 years

A 2014 systematic review and meta-analysis did not support the addition of LTRA to low-dose ICS in children.[426] Note concerns about the risk of neuropsychiatric adverse effects.[309]

Preferred Step 4 treatment options for children 6–11 years: refer for expert advice, or increase treatment to medium-dose ICS-LABA plus as-needed SABA, or MART with low-dose ICS-formoterol

For children whose asthma is not adequately controlled by low-dose maintenance ICS-LABA with as-needed SABA, consider referral for expert advice. Alternatively, treatment may be increased to medium-dose ICS-LABA (Evidence B).[424] For maintenance-and-reliever therapy (MART) with budesonide-formoterol, the maintenance dose may be increased to 100/6 mcg twice daily (metered dose; 80/4.5 mcg delivered dose) (Evidence D); this is still a low-dose regimen. For a summary of medications and doses, see Box 4-8 (p.84).

If asthma is not well controlled on medium-dose ICS (Box 4-2B, p.71), refer the child for expert assessment and advice.

Other Step 4 options for children 6–11 years that may be considered after referral include:

Increasing ICS-LABA dose: Increasing the ICS-LABA dose to a high pediatric ICS dose (Box 4-2B, p.71) can be considered, but adverse effects must be considered.

Tiotropium: Tiotropium (a 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 exacerbations (Evidence A),[386] largely independent of baseline IgE or blood eosinophils.[427]

LTRA: If not trialed before, LTRA could be added (but note the concern about risks of neuropsychiatric adverse effects with montelukast).[309] Add-on theophylline is not recommended for use in children due to lack of efficacy and safety data.

Preferred treatment at Step 5 in children 6–11 years: refer for expert assessment, phenotyping, and add-on therapy

Children with persistent asthma symptoms or exacerbations despite correct inhaler technique and good adherence on 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 asthma, if available (Evidence D).[183]

In severe asthma, as in mild–moderate asthma,[382] participants in randomized controlled trials may not be representative of patients seen in clinical practice. For example, a registry study found that over 80% of patients with severe asthma would have been excluded from major regulatory studies evaluating biologic therapy.[383]

Add-on long-acting muscarinic antagonists

Tiotropium, a long-acting muscarinic antagonists (LAMA), can be prescribed as an add-on treatment in a separate inhaler for patients aged ≥6 years if asthma is not well controlled with medium or high-dose ICS-LABA.[386,427]

Add-on biologic therapy

Options recommended by GINA for children aged 6–11 years with uncontrolled severe asthma despite optimized maximal therapy (see Section 8 for more details) include:

- *Add-on anti-immunoglobulin E (anti-IgE)* (omalizumab) for patients aged ≥6 years with severe allergic asthma (Evidence A)[391]
- *Add-on anti-interleukin-5/5Rα* (subcutaneous mepolizumab for patients aged ≥6 years with severe eosinophilic asthma (Evidence A).[396,397]
- *Add-on anti-interleukin-4Rα* (subcutaneous dupilumab) for patients aged ≥6 years with severe eosinophilic/Type 2 asthma.[401]

Maintenance-and-reliever therapy (MART) with ICS-formoterol

There is no direct evidence about initiating MART in children receiving add-on treatment such as LAMA or biologic therapy. Switching a patient from MART to conventional ICS-LABA plus as-needed SABA may increase the risk of exacerbations.

REVIEWING RESPONSE AND ADJUSTING TREATMENT – ADULTS, ADOLESCENTS AND CHILDREN 6–11 YEARS

How often should asthma be reviewed?

Each patient's asthma should be reviewed regularly to monitor symptom control, risk factors and occurrence of exacerbations, and to document response to any treatment changes. For most controller medications, improvement in symptoms and lung function begins within days of initiating treatment, but the full benefit may only be reached after 3–4 months,[428] or even later in patients with severe and chronically under-treated asthma.[429]

All healthcare 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.[430] 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 scheduled (Evidence D).[431]

Stepping up asthma treatment

Asthma is a variable condition, and adjustments of controller treatment by the clinician and/or the patient may be needed.[432]

Day-to-day adjustment using an anti-inflammatory reliever (AIR)

For patients whose reliever inhaler is combination budesonide-formoterol or beclometasone-formoterol (with or without maintenance ICS-formoterol), the patient adjusts the number of as needed doses of ICS-formoterol from day to day according to their symptoms. This strategy reduces the risk of developing a severe exacerbation requiring OCS within the next 3–4 weeks.[132-134] As-needed combination budesonide-salbutamol is an anti-inflammatory reliever option that has been studied in Steps 3–5.[357]

Short-term step-up (for 1–2 weeks)

A short-term increase in maintenance ICS dose for 1–2 weeks may be necessary (e.g., during viral infections or seasonal allergen exposure). This increase may be initiated by the patient according to their written asthma action plan (Box 9-2, p.163), or by the healthcare provider.

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; 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 4-6, p.77) after confirming that the symptoms are due to asthma, inhaler technique and adherence are satisfactory, and modifiable risk factors such as smoking have been addressed (Box 3-5, p.56). Any step-up should be regarded as a therapeutic trial; if there is no response after 2–3 months, treatment should be reduced to the previous level, and alternative treatments or referral considered.

Stepping down treatment when asthma is well controlled

Once good asthma control has been achieved and maintained for 2–3 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 ICS-containing treatment. Patients prescribed maintenance controller treatment in either Track often experiment with intermittent treatment through concern about the risks or costs of daily treatment.[433] For patients prescribed GINA Track 1 MART, the ICS-formoterol reliever provides a safety net during planned step-down or if adherence to maintenance doses is poor. However, for patients prescribed maintenance

controller with a SABA reliever (GINA Track 2, Steps 2–5), poor adherence leaves them exposed to the risks of SABA-only treatment. Step-down options for patients on different treatment steps are shown in Box 4-13 (p.102).

Before stepping down

The optimal approach to stepping down will differ between patients, depending on their current treatment, risk factors and preferences. There are few data on the optimal timing, sequence and magnitude of treatment reductions in asthma. Factors associated with a greater risk of exacerbation after step-down include a history of exacerbations and/or emergency department visit for asthma in the previous 12 months,[434,435] and a low baseline FEV_1.[435] Other predictors of loss of control during dose reduction include airway hyperresponsiveness and sputum eosinophilia,[436] but these tests are not readily available in primary care.

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

How to step asthma treatment down

Decisions about treatment step-down should be based on individual assessment. 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.[437]

If treatment is stepped down too far or too quickly, the risk of exacerbations may increase even if symptoms remain reasonably controlled (Evidence B).[438] Higher baseline FeNO has not been demonstrated to predict exacerbations following step-down of ICS dose.[439,440] A meta-analysis suggested that greater reduction in ICS dose may be able to be achieved in patients with baseline FeNO <50 ppb, but the authors point to the need for further research.[440] Complete cessation of ICS is associated with a significantly increased risk of exacerbations (Evidence A).[441]

Stepping down from daily low-dose ICS plus as-needed SABA to as needed-only ICS-formoterol provides similar or greater protection from severe exacerbations and need for urgent health care, with similar symptom control and lung function and a much lower average daily ICS dose, compared with treatment with daily low-dose ICS plus as-needed SABA.[191] Step-down strategies for different controller treatments are summarized in Box 4-13 (p.102); these are based on current evidence, but more research is needed. Few step-down studies have been performed in children.

Box 4-13. Options for stepping down treatment in adults and adolescents 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 at least 3 months (Evidence D). If the patient has risk factors for exacerbations (Box 2-2, p.37), for example a history of exacerbations in the past year,[434] or persistent airflow limitation, step down only with 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, p.37), provide clear instructions, provide a written asthma action plan (Box 9-2, p.163) 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 patients (Evidence A).[442]

Current step	Current medication and dose	Options for stepping down if asthma is well controlled and lung function stable for ≥3 months	Evidence
Step 5	High-dose ICS-LABA plus oral corticosteroids (OCS)	If Type 2-high severe asthma, add biologic therapy if eligible and reduce OCS (see Box 8-4, p.144 for more details)	A
		Optimize inhaled therapy to reduce OCS dose	D
		Use sputum-guided approach to reducing OCS	B
		For low-dose OCS, use alternate-day dosing	D
	Biologic therapy plus high-dose ICS-LABA	Cease other add-on medications especially OCS, then consider reducing ICS-LABA dose[385] (see Box 8-5 (p.145) and p.145).	B
Step 4	Moderate- to high-dose ICS-LABA maintenance treatment	Continue combination ICS-LABA and reduce ICS component by 50%, by using available formulations	B
		Caution: Discontinuing LABA may lead to deterioration[443]	A
		Switch to maintenance-and-reliever therapy (MART) with ICS-formoterol, with lower maintenance dose[334]	A
	Medium-dose ICS-formoterol* as maintenance and reliever	Reduce maintenance ICS-formoterol* to low dose, and continue as-needed low-dose ICS-formoterol* reliever	D
	High-dose ICS plus second controller	Reduce ICS dose by 50% and continue second controller[442]	B
Step 3	Low-dose ICS-LABA maintenance	Reduce ICS-LABA to once daily	D
		Caution: Discontinuing LABA may lead to deterioration[443]	A
	Low-dose ICS-formoterol* as maintenance and reliever	Reduce maintenance ICS-formoterol* dose to once daily and continue as needed low-dose ICS-formoterol* reliever	C
		Consider stepping down to as-needed-only low-dose ICS-formoterol	D
	Medium- or high-dose ICS	Reduce ICS dose by 50%[442]	A
		Adding LABA may allow ICS dose to be stepped down[444]	B
Step 2	Low-dose maintenance ICS	Once-daily dosing (budesonide, ciclesonide, mometasone, fluticasone furoate)[445,446]	A
		Switch to as-needed-only low-dose ICS-formoterol[196,315,316,322]	A
		Switch to taking ICS whenever SABA is taken[338-341]	B
		Caution: Do not completely stop ICS, because the risk of exacerbations is increased with SABA-only treatment[322,441]	A

ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; SABA: short-acting beta$_2$-agonist; OCS: oral corticosteroid *MART: low-dose budesonide-formoterol or beclometasone-formoterol (p.69).

Other strategies for adjusting asthma treatment

Some alternative strategies for adjusting asthma maintenance ICS-containing treatment have been evaluated:

- *Treatment guided by sputum eosinophil count*: in adults with frequent exacerbations and moderate-severe asthma, this approach leads to a reduced risk of exacerbations and similar levels of symptom control and lung function, compared with guidelines-based treatment.[405] However, few clinics have routine access to induced sputum analysis. There is insufficient evidence to assess this approach in children.[405] 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 technique (Evidence A).[183,405]
- *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.[447] Results of FeNO measurement at a single point in time should be interpreted with caution.[51,313] The relationship between FeNO and other Type 2 biomarkers is lost or altered in obesity.[22,48]
  In a 2016 meta-analysis, FeNO-guided treatment in children and young adults with asthma 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; 95% –0.49 to –0.06 per year), compared with guidelines-based treatment (Evidence A);[448] FeNO-guided treatment was associated with similar benefits when compared with non-guidelines-based algorithms.[448] However, a subsequent good-quality multicenter clinical trial in children with asthma in secondary and primary care centers found that the addition of FeNO to symptom-guided treatment did not reduce severe exacerbations over 12 months.[449]
  In non-smoking adults with asthma, no significant reduction in risk of exacerbations and in exacerbation rates was observed with FeNO-guided treatment, compared with treatment strategies similar to those in most guidelines; a difference was seen only in studies with other (non-typical) comparator approaches to adjustment of treatment.[450] In a large study in pregnant women, there was no reduction in exacerbations with FeNO-guided treatment, compared with usual care.[451] In adults and in children, no significant differences were seen in symptoms or ICS dose with FeNO-guided treatment, compared with other strategies.[448,450]
- *Treatment guided by combination biomarkers*: An RCT in patients taking high-dose ICS-LABA compared a treatment adjustment strategy based on a composite of Type 2 biomarkers only with an algorithm based on ACQ-7 and history of recent exacerbation, but the findings were inconclusive because a substantial proportion of patients did not follow recommendations for treatment change.[452]
- *Selection of add-on treatment for patients with severe asthma*: The assessment of severe asthma includes identification of the inflammatory phenotype, based on blood or sputum eosinophils or FeNO, to assess the patient's eligibility for various add-on treatments including biologic therapy. A higher baseline blood eosinophil count and/or FeNO predicts a good asthma response to some biologic therapies (see Box 8-3, p.143 and Box 8-4, p.144).

Further studies are needed to identify the subpopulations of patients with asthma who are most likely to benefit from biomarker-guided adjustment of maintenance ICS-containing treatment, and the optimal frequency of monitoring, including for corticosteroid de-escalation strategies. Until more definitive evidence is available to support a specific strategy, GINA continues to recommend a comprehensive clinical evaluation that includes patient-reported symptoms as well as modifiable risk factors, environmental exposures comorbidities and patient preferences, when making treatment decisions for individual patients.

ALLERGEN IMMUNOTHERAPY

Allergen-specific immunotherapy may be considered as add-on therapy for adults and children with asthma who have clinically significant sensitization to aeroallergens, including in those with allergic rhinitis.[11,12,453,454] It involves the identification of clinically relevant allergens and the administration of extracts in precisely calculated doses to induce desensitization and/or tolerance. Allergen immunotherapy is currently the only intervention with both an immune modifying effect and long-term efficacy on the allergic response.

Few studies reporting effects of allergen immunotherapy on asthma have compared immunotherapy with pharmacological therapy, or used standardized outcomes such as exacerbations; furthermore, most studies have been performed in patients with mild asthma.[455] The allergens most often tested in allergen immunotherapy studies are house dust mite and grass pollens. There is insufficient evidence about the safety and efficacy of allergen immunotherapy in patients with asthma who are sensitized to mold.[456] More studies are needed to clarify the role of allergen immunotherapy in the development and progression of asthma, and in clinical asthma management.[455]

There are two approaches: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT).

Subcutaneous immunotherapy (SCIT)

SCIT involves the administration of extracts in progressively higher doses, usually over a period of 3–5 years. There is considerable variation in the specific SCIT regimens used in clinical practice.

Efficacy of SCIT for treatment of asthma

Systematic reviews and meta-analysis of SCIT in the treatment of adult and pediatric asthma concluded that addition of SCIT led to a reduction in ICS dose requirement and/or the proportion of patients requiring ICS (moderate strength of evidence) and may improve asthma-specific quality of life and lung function, while reducing reliever use and the need for systemic corticosteroids (low strength of evidence).[12,454] Few studies of SCIT to house dust mite have been conducted only in children, or report results for children separately.[454] A 2020 systematic review of allergen immunotherapy in children with asthma aged 18 years and younger reported that SCIT led to a reduction in ICS requirement (moderate strength of evidence), and improved asthma-related quality of life and lung function (low strength of evidence).[11]

Safety

Safety data, overall, suggest that severe allergic reactions occur in fewer than 0.5–0.7% of patients treated with SCIT.[457] Serious adverse effects of SCIT are rare, but may include life-threatening anaphylactic reactions. Asthma, especially severe or uncontrolled asthma, has been identified as a major risk factor for severe and fatal adverse reactions to SCIT.[458] Food allergy is also a risk factor for systemic reactions to SCIT.

Advice

When considering SCIT for adults or children with asthma, the potential benefits, compared with pharmacological treatment and allergen avoidance, must be weighed against the risk of adverse effects and the inconvenience and cost of the prolonged course of therapy (typically 3–5 years), including the minimum 30 minutes of monitoring required after each injection (Evidence D).

If allergen immunotherapy is considered for patients with severe asthma, the potential benefits and risks should be carefully identified and discussed as part of a shared decision-making process. To minimize the risk of severe reactions, SCIT should not be initiated until good asthma control (symptom control and risk factors for exacerbations) has been established.

For each patient, SCIT should be tailored to their specific pattern of allergic sensitization. Given the complexity of making up SCIT extracts, combined with the risk of serious adverse events, SCIT prescription and administration should be limited to practitioners who are specifically trained and experienced in allergy testing and in the formulation and administration of SCIT. Injections should be administered only in a healthcare setting with capability for, and personnel skilled in the management of, severe allergic reactions/anaphylaxis. SCIT should be administered only with high-quality extracts, and standardized extracts should be used, where available.

Healthcare providers who offer SCIT must establish effective safety protocols. The risk of severe adverse events is significantly reduced by systems that ensure appropriate supervision after injections, including training of office staff to track time after injections and monitor patient checkout.[458]

Sublingual immunotherapy (SLIT)

Sublingual immunotherapy involves the administration of extracts either as tablet or drops administered under the tongue, with an induction phase in which the dose is progressively increased. The duration of SLIT depends on the allergens used (house dust mite or grass pollen).

Efficacy of SLIT for treatment of asthma

Several systematic reviews have examined the effect of SLIT for asthma in adults and children,[459,460] but many of the studies were unblinded or used non-standardized outcomes. In general, there is limited evidence demonstrating effects of SLIT on important outcomes such as asthma exacerbations and quality of life,[460] and few RCTs have compared SLIT with pharmacological therapy for asthma. A 2020 Cochrane review of 66 trials of SLIT for allergic rhinitis, in which at least 80% of participants also had allergic asthma, concluded that addition of SLIT may reduce the risk of asthma exacerbation requiring OCS or healthcare visits (low strength of evidence), but only one study in adults and one in children reported effects on healthcare visits.[460] In a 2023 systematic review focusing on individuals (mainly adults) with allergic rhinitis and asthma, SLIT was associated with a significant reduction in asthma symptoms, compared with placebo, but there was no effect on ICS dose, FeNO, lung function or direct treatment cost.[461]

House dust mite SLIT**:** European Academy of Allergy & Clinical Immunology (EAACI) guidelines recommend HDM SLIT as add-on treatment in adults with controlled or partially controlled HDM-driven allergic asthma.[454] In a subsequent systematic review, addition of standardized HDM SLIT resulted in reduction in ICS dose in one RCT and improved asthma symptoms in two RCTs but there was no consistent effect on exacerbations in adolescents and adults with well or partly controlled asthma.[453] There is no separate evidence for adolescents, but no reason to suppose that effectiveness and/or safety would be different than in adults.

Ragweed SLIT**:** In children with allergic rhinoconjunctivitis and asthma who were sensitized to ragweed, ragweed SLIT reduced SABA use and nocturnal awakenings during peak ragweed season.[462]

Safety

The rate of serious adverse events associated with SLIT, as reported in RCTs, is estimated at ≤1% (moderate certainty of evidence)[460] with rare cases of anaphylaxis requiring epinephrine.[453] In a real-world study, the incidence of serious adverse events was lower among those receiving SLIT than among those receiving SCIT[463]. Adverse events due to SLIT for inhalant allergens are mainly limited to oral and gastrointestinal symptoms and usually reported to be transient and mild.[460,464-467]

Advice

For adult or adolescent patients with asthma who are sensitized to house dust mite, with persisting asthma symptoms despite low- to medium-dose ICS-containing therapy, consider adding HDM SLIT, but only if FEV_1 is >70% predicted (Evidence B).

For children with asthma sensitized to ragweed, consider adding SLIT before and during the ragweed season, provided FEV_1 is ≥80% predicted. There is insufficient evidence to make a recommendation about HDM SLIT in children with asthma.

As for any treatment, the potential benefits of SLIT for individual patients should include shared decision making and be weighed against the risk of adverse events and the cost for the patient and the health system.

VACCINATIONS

Influenza

Influenza causes significant morbidity and mortality in the general population, and contributes to some acute asthma exacerbations. In 2020, the first year of the COVID-19 pandemic, many countries reported a reduction in influenza-related illness, likely due to the handwashing, masks and social/physical distancing introduced because of the pandemic.[468,469]

The risk of influenza infection itself can be reduced by annual vaccination. A 2013 systematic review of placebo-controlled randomized controlled trials of influenza vaccination showed no reduction in asthma exacerbations,[470] but no such studies had been performed since 2001. A 2017 systematic review and meta-analysis, which included observational studies with a wide range of study designs, suggested that influenza vaccination reduced the risk of asthma exacerbations, but bias could not be excluded for most of the studies.[471] There is no evidence for an increase in asthma exacerbations after influenza vaccination, compared with placebo.[471] A systematic review of studies in individuals aged 2–49 years with mild–moderate asthma found no significant safety concerns or increased risk for asthma-related outcomes after influenza vaccination with live attenuated virus.[472]

Respiratory syncytial virus

Respiratory syncytial virus (RSV) infection causes lower respiratory tract disease in infants, including bronchiolitis and pneumonia. It also causes lower respiratory tract infections in older children and adults, and may exacerbate asthma. Children and the elderly are more likely to experience severe disease with RSV infection. RSV vaccines prevent RSV-related acute respiratory infection; an adjuvanted RSV-subunit vaccine reduced upper and lower respiratory tract disease in adults 60 years or older, including in those with underlying coexisting conditions such as asthma.[473,474]

Other vaccines

People with asthma, particularly children and the elderly, are at higher risk of pneumococcal disease.[475] Pneumococcal vaccine protects against invasive pneumococcal infection, but asthma alone is not a specific indication for pneumococcal vaccination.[476] Pertussis infection may trigger or mimic asthma exacerbations, and pertussis vaccination reduces the risk of severe pertussis-related disease, but there is limited evidence on the efficacy and safety of vaccines in preventing asthma exacerbations in adults (and hence for an asthma-specific recommendation). For information about COVID-19 vaccines, see p.122.

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). Follow local immunization schedules.

Advise vaccination against pneumococcal, pertussis, influenza, RSV and COVID-1 for children, adults and the elderly with asthma, following their local immunization schedule. Advice about COVID-19 vaccination is on p.122.

Check local advice for information about co-administration of different vaccines on the same day.

OTHER THERAPIES

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.[157] The treatment is associated with a large placebo effect.[157] 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 control.[157] Extended follow-up of some treated patients reported a sustained reduction in exacerbations,

compared with pre-treatment.[477] However, there is a need for longer-term follow up of larger cohorts comparing effectiveness and safety, including for lung function, in both active and sham-treated patients.

Advice

For adult patients whose asthma remains uncontrolled despite optimization of asthma therapy and referral to a severe asthma specialty center, and who do not have access to biologic therapy or are not eligible for it, 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 FEV_1 <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.[183]

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.[478] Vitamin D supplementation may reduce the rate of asthma exacerbation requiring treatment with systemic corticosteroids or may improve symptom control in asthma patients with baseline 25(OH)D of less than approximately 25–30 nmol/L.[479,480] There is no good-quality evidence that Vitamin D supplementation leads to improvement in asthma control or reduction in exacerbations, particularly in preschool children and people with severe asthma.[481]

5. Guided asthma self-management education and skills training

KEY POINTS

As with other chronic diseases, people with asthma need education and skills training to manage it well. Effective self-management is achieved through a partnership between the patient/caregiver and their healthcare providers

Essential components of shared decision-making and self-management education include:

- Choosing the most appropriate inhaler for the patient's asthma treatment: consider available devices, cost, the ability of the patient to use the inhaler after training, environmental impact, and patient satisfaction
- Skills training to use inhaler devices effectively
- Encouraging adherence to medications, appointments and other advice, within an agreed management strategy
- Asthma information
- Training in guided self-management, with self-monitoring of symptoms or peak expiratory flow (PEF), a written asthma action plan to show how to recognize and respond to worsening asthma, and regular review by a healthcare provider or trained healthcare worker.

In developing, customizing and evaluating self-management interventions for different cultures, sociocultural factors should be considered.[482]

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, correct use of an inhaler device 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.[97] Most patients (up to 70–80%) do not use their inhaler correctly. Unfortunately, many healthcare providers are unable to correctly demonstrate how to use the inhalers they prescribe.[483] 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. The several factors that should be considered in the choice of inhaler device for an individual patient are described below and in Box 5-1 (p.109).

Strategies for ensuring effective use of inhaler devices are summarized in Box 5-2 (p.110).[484] These principles apply to all types of inhaler devices. For patients prescribed pressurized metered-dose inhalers (pMDIs), use of a spacer improves delivery of the medicine to the lungs. For inhaled corticosteroids (ICS) spacers also reduce the potential for local side-effects such as dysphonia and oral candidiasis.[485] 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[486,487] and older children[484] (Evidence A). A physical demonstration is essential to improve inhaler technique.[488] This is easiest if the healthcare provider has placebo inhalers and a spacer. After training, inhaler technique deteriorates 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. Attaching a pictogram[489,490] or a list of inhaler technique steps[491] to the inhaler substantially increases the retention of correct technique at follow-up. Pharmacists, nurses and trained lay health workers can provide highly effective inhaler skills training.[484,492-494]

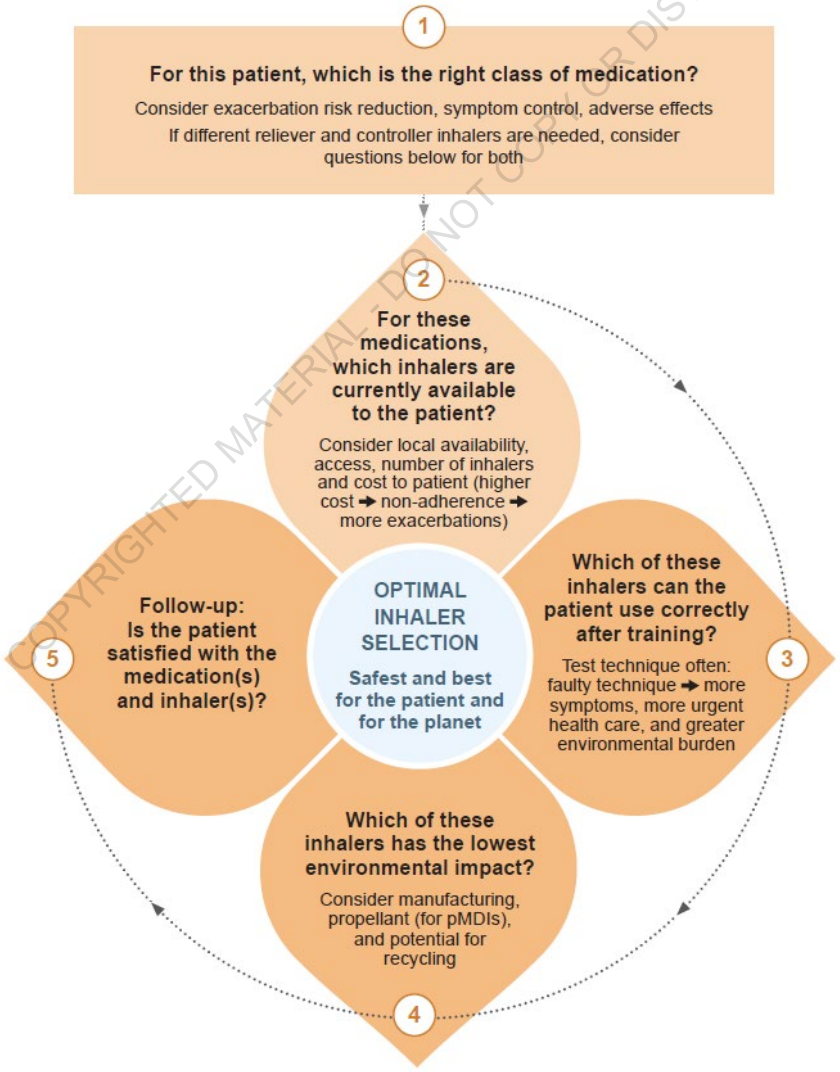
SHARED DECISION-MAKING FOR CHOICE OF INHALER DEVICE

Globally, multiple different devices are available for delivery of inhaled medication, including pMDIs, dry-powder inhalers (DPIs), mist inhalers and nebulizers, although the choice of inhaler device for each medication class in any country is often limited. Initiatives are underway to increase access to ICS-containing inhalers for people with asthma worldwide, with the goal of reducing the risk of severe exacerbations and asthma deaths. As these inhalers become universally available, an equally high priority is to ensure that patients/caregivers are trained to use them correctly.

There is also increasing interest in reducing the impact of asthma and its care (routine and urgent) on the environment, including those due to the manufacture and disposal of inhaler devices, and from the propellants in pMDIs, which are the inhalers most commonly used worldwide.[495-497] Strategies include recycling of devices and development of less polluting propellants.

For all age-groups, selecting the right inhaler for the individual patient is crucial to asthma care, not only to reduce patients' symptom burden, but also to reduce the need for emergency health care and hospitalization, which have even greater environmental impacts than use of pMDIs.[498,499]

Box 5-1. Shared decision-making between healthcare provider and patient about choice of inhalers



pMDI: pressurized metered dose inhaler.

Box 5-2. Choice and effective use of inhaler devices

CHOOSE

- Choose the most appropriate inhaler device for the patient before prescribing. Consider the preferred medication (Box 4-6, p.77 and Box 4-12, p.96), available devices, patient skills, environmental impact and cost (see Box 5-1, p.109).
- 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

- 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

- Show the patient how to use the device correctly with a physical demonstration, e.g., using a placebo inhaler, or using videos.[500]
- Check technique again, paying attention to problematic steps. You may need to repeat this process 2–3 times within the same session for the patient to master the correct technique.[486]
- Consider an alternative device only 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.[501]

CONFIRM

- Clinicians should be able to demonstrate correct technique for each of the inhalers they prescribe.
- Inhaler skills training provided by specially trained pharmacists and nurses is highly effective.[492,493]

ICS: inhaled corticosteroid; pMDI: pressurized metered-dose inhaler

Choosing the medication, inhaler and device

Several factors must be considered in shared decision-making about the choice of inhaler device for the individual patient (Box 5-1, p.109), starting with the choice of the medication itself:

- *Which medication class(es) or individual medication(s) does the patient need to relieve and control symptoms and to prevent asthma exacerbations?* The approach in GINA Track 1 (Box 4-3, p.74) is preferred, because the use of ICS-formoterol as an anti-inflammatory reliever reduces the risk of severe exacerbations and urgent healthcare utilization, compared with using a short-acting beta$_2$-agonist (SABA) reliever. The Track 1 approach also avoids the risks associated with SABA over-use, and allows simple adjustment across treatment steps with a single medication for both symptom relief and delivery of ICS-containing treatment. Most studies of maintenance-and-reliever therapy (MART) with ICS-formoterol, and all studies of as-needed-only ICS-formoterol have used a DPI.
- *Which inhaler devices are available to the patient for these medications?* The choice of device for any particular medication class in each country is often limited. Consider local availability, access, and cost to the patient. Where more than one medication is needed, a single (combination) inhaler is preferable to multiple inhalers. Also consider the patient's age, since DPIs are not suitable for most children aged ≤5 years and some elderly patients; pMDIs with spacers remain essential for such patients.

- *Can the patient use the available device(s) correctly after training?* This may be determined by factors including physical dexterity, coordination, inspiratory flow, and cognitive status. Different inhaler types require different inhalation techniques, so it is preferable to avoid prescribing a pMDI and DPI for the same patient. Incorrect inhaler technique increases risk of severe asthma exacerbations.
- *What are the environmental implications of the available inhaler(s)?* This has become an important part of inhaler selection, with particular consideration of carbon emissions due to the propellants in pMDIs, but also of environmental effects of inhaler manufacture and potential recycling. However, clinicians need to be aware of the potential to place the additional burden of "green guilt" on patients, as this could reduce adherence and increase the risk of exacerbations.
- *Is the patient satisfied with the medication and inhaler?* The best inhaler for each patient is likely to be the one that they prefer and can use correctly, as this promotes adherence and reduces risk of exacerbations and adverse effects.

In follow-up, review symptom control, asthma exacerbations and adverse events, and check the patient's ability to use their inhaler(s) correctly, ideally at each visit.

ADHERENCE TO MEDICATIONS AND TO 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 healthcare provider. There is increasing awareness of the importance of poor adherence in chronic diseases, and of the potential to develop interventions to improve adherence.[502] Approximately 50% of adults and children on long-term therapy for asthma fail to take medications as directed at least part of the time.[198]

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 5-3 (p.112) 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. Electronic inhaler monitoring has also been used in clinical practice to identify poor adherence in patients with difficult-to-treat asthma.[184,185]

In clinical studies assessing factors contributing to poor adherence, methods of measuring adherence include using short adherence behavior questionnaires, analysis of dispensing records, dose or pill counting, electronic inhaler monitoring,[503,504] and drug assay (e.g., for prednisolone).[505]

In patients with difficult-to-treat asthma, a FeNO suppression test (with high-dose ICS added to usual treatment for 1 week) can identify when high FeNO is due to poor adherence (with or without incorrect inhaler technique), and can help to distinguish this from relatively corticosteroid-refractory Type 2 inflammation.[236,506] In almost two-thirds of adults with uncontrolled asthma and high FeNO despite prescription of high-dose ICS-LABA, FeNO was significantly suppressed within a week of addition of high-dose ICS (electronically monitored); blood eosinophils also decreased. In patients with a positive FeNO suppression test, asthma symptom control and lung function improved when medium-dose ICS-LABA was taken with good adherence for one month.[236]

Factors contributing to poor adherence

To understand the reasons behind patients' medication-taking behavior, it is important to elicit their beliefs and concerns about asthma and asthma medications. Both intentional and unintentional factors contribute to poor adherence (Box 5-3, p.112). Issues of ethnicity,[507] health literacy,[508,509] and numeracy[210] are often overlooked. Patients may be concerned about known side-effects or about perceived harm.[433,510]

Box 5-3. Poor adherence to prescribed maintenance treatment in asthma

Factors contributing to poor adherence	How to identify poor adherence in clinical practice
Medication/regimen factors Difficulties using inhaler device (e.g., arthritis) Burdensome regimen (e.g., several times per day) Multiple different inhalers **Unintentional poor adherence** Misunderstanding about instructions Forgetfulness Absence of a daily routine Cost **Intentional poor adherence** 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 healthcare providers Stigmatization Cultural or religious issues Cost	For patients prescribed maintenance treatment, ask an empathic question Acknowledge the likelihood of incomplete adherence and encourage an open non-judgmental discussion. Examples are: '*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?*'[511] '*Do you find it easier to remember your inhaler in the morning or the evening?*' Check medication usage: • Check the date of the last 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.[197,512]
Examples of successful adherence interventions	
Shared decision-making for medication/dose choice[200,203] Inhaler reminders, either proactively or for missed doses[513-515] Prescribing low-dose ICS once-daily versus twice-daily[516] Home visits for a comprehensive asthma program by an asthma nurse[517] Electronic monitoring of adherence with feedback to patients.[518] In a systematic review, multidisciplinary care involving one-to-one advice and digitally enhanced communications appeared to offer the greatest benefit for improving adherence.[519]	

ICS: inhaled corticosteroid

Interventions that improve adherence in asthma

Few adherence interventions have been studied comprehensively in people with asthma. Some examples of successful interventions have been published:

- Shared decision-making for medication/dose choice improved adherence and asthma outcomes.[200]
- Electronic inhaler reminders, either proactively or for missed doses, improved adherence[513-515] and possibly reduced exacerbations and oral corticosteroid use.[513-515,520,521]
- 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.[517]
- 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.[522]
- 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.[523]

- In one study, directly observed administration of maintenance asthma treatment at school, combined with telemedicine oversight, was associated with more symptom-free days and fewer urgent visits than usual care.[524]
- In patients with difficult-to-treat asthma, electronic inhaler monitoring with feedback on adherence and inhaler technique led to improved adherence and reduced need for escalation of treatment.[518]

Digital interventions for adherence

A 2022 Cochrane review found that a variety of digital intervention strategies improved adherence to maintenance controller medications, especially in those with poor adherence, reduced exacerbations, and improved asthma control, in studies of up to 2 years' duration in adults and children.[520] Electronic monitoring of inhaler use,[521] and text messages sent to phones appear to be effective. No harms associated with these technologies were reported. The effects of digital interventions on quality of life, lung function and unscheduled healthcare utilization are unclear.

Improving adherence to maintenance ICS-containing medications may not necessarily translate to improved clinical outcomes.[525] Further studies are needed of adherence strategies that are feasible for implementation in primary care.

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 over several sessions or stages.

For young children, the focus of asthma education will be on the parent/caregiver, but young children can be taught simple asthma management skills. Adolescents may have unique difficulties with adherence, and peer support group education may help in addition to education provided by the healthcare provider.[526] 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.[527]

The key features and components of an asthma education program are provided in Box 5-4. Information alone improves knowledge but does not improve asthma outcomes.[528] 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[529,530] information about asthma and its treatment. Patients and their families should be encouraged to make a note of any questions about their asthma or its treatment, and should be given time to address these.

Asthma education and training, for both adults and children, can be delivered effectively by a range of healthcare providers including pharmacists and nurses (Evidence A).[492,493,531,532] Trained lay health workers (also known as community health workers) can deliver appropriately defined aspects of respiratory care such as asthma self-management education. Asthma education by trained lay health workers has been found to improve patient outcomes and healthcare utilization, compared with usual care,[494,533] and to a similar extent as nurse-led education in primary care (Evidence B).[534] These findings suggest the need for additional studies to assess applicability in other settings and populations.

Patients can be encouraged to contact national or local patient organizations to obtain peer support, information, and patient-centred resources.

Box 5-4. Asthma information

Goal: To provide the person with asthma, their family and other caregivers with suitable information and training to manage their asthma in partnership with their healthcare providers	
Approach 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.49). Fully discuss expectations, fears and concerns. Develop shared goals.	**Topics to include** Asthma diagnosis Rationale for treatment, and differences between relievers and maintenance treatments (if prescribed) Potential side-effects of medications Prevention of symptoms and flare-ups: importance of anti-inflammatory treatment 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 healthcare 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:[201]

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

Self-management education that includes these components dramatically reduces asthma morbidity, both in adults (Evidence A)[201,494,535] and children (Evidence A).[202,535] Benefits include reduction of one-third to two-thirds in asthma-related hospitalizations, emergency department visits and unscheduled doctor or clinic visits, missed work/school days, and nocturnal wakening.[201] 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.[201 536] Less intensive interventions that involve self-management education, but not a written action plan, are less effective,[537] and information alone is ineffective.[528] A systematic meta-review of 270 RCTs on supported self-management for asthma confirmed that it reduces unscheduled health care use, improves asthma control, is applicable to a wide range of target groups and clinical settings, and does not increase healthcare costs (Evidence A).[535]

Self-monitoring of symptoms and/or peak expiratory flow (PEF)

Patients/caregivers should be trained to keep track of symptoms (with or without a diary), recognize when symptoms start to worsen, and act when necessary.

PEF monitoring may sometimes be useful:

- In short-term monitoring
  - After an exacerbation, to monitor recovery
  - After a change in treatment, to help in assessing whether the patient has responded
  - When 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

- In long-term monitoring
  - For earlier detection of exacerbations, mainly in patients with poor perception of airflow limitation[159]
  - For patients with a history of sudden severe exacerbations
  - For patients who have difficult-to-control or severe asthma.

For patients carrying out PEF 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.[182] One such chart is available for download from www.woolcock.org.au/resources/asthma-peak-flow-chart.

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 asthma (Evidence B).[538]

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.[539,540] "Written" action plans include printed, digital or pictorial plans (i.e., the patient is given a record of the instructions).

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 oral corticosteroids (OCS) and, for PEF-based plans, when they are based on personal best rather than percent predicted PEF (Evidence A).[540]

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 doctor (Evidence A).[537] Thus, patients who cannot self-manage can still benefit from a structured program of regular medical review.

Action plans for patients using SABA as their reliever

Examples of written asthma action plan templates for asthma treatment with a SABA reliever, including for adult and pediatric 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.[541,542]

Action plan for patients using as-needed ICS-formoterol as their reliever

A different type of action plan is needed for patients using as-needed ICS-formoterol as their reliever in GINA Track 1, because the initial action when asthma worsens is for the patient to increase their as-needed doses of ICS-formoterol, rather than taking a SABA and/or increasing their maintenance treatment. An example of such a customized template can be found in a review article about practical use of maintenance-and reliever-therapy (MART).[327] A similar action plan template can be used for patients using as-needed-only ICS-formoterol.[328]

Healthcare providers should become familiar with action plans that are relevant to their local healthcare 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 Section 9 (Box 9-2, p.163).

REGULAR REVIEW BY A HEALTHCARE PROVIDER OR TRAINED HEALTHCARE WORKER

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

- **Ask the patient if they have any questions or concerns**
  - Discuss issues, and provide additional educational messages as necessary.
  - If available, refer the patient to someone trained in asthma education.
- **Assess asthma control, risk factors for exacerbations, and comorbidities**
  - Review the patient's level of symptom control and risk factors (Box 2-2, p.37).
  - 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 5-2, p.110).
  - Assess medication adherence and ask about adherence barriers (Box 5-3, p.112).
  - Ask about adherence to other interventions (e.g., smoking cessation).
  - Review the asthma action plan and update it if level of asthma control or treatment have changed.[543]

A single-page prompt to clinicians has been shown to improve the provision of preventive care to children with asthma during office visits.[544] Follow-up by telehealthcare is unlikely to benefit patients with asthma that is well controlled at a low treatment step, but may benefit those with severe disease at risk of hospital admission.[538]

SCHOOL-BASED PROGRAMS FOR CHILDREN

A systematic review found that school-based studies (most conducted in the US and Canada) that included self-management skills for children aged 5–18 years was associated with a 30% decrease in emergency department visits, and a significant decrease in hospitalizations and in days of reduced activity.[545]

6. Managing asthma with multimorbidity and in specific populations

KEY POINTS

Multimorbidity is common in patients with chronic diseases such as asthma. It is important to identify and manage multimorbidity, as it contributes to impaired quality of life, increased healthcare utilization, and adverse effects of medications.

Some comorbidities, such as rhinosinusitis, obesity, anxiety and/or depression, and gastro-esophageal reflux disease (GERD), may also contribute to respiratory symptoms, and some contribute to poor asthma control. These conditions or treatable traits should be managed as part of comprehensive, personalized care for the individual patient.

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
- Recommend pulmonary rehabilitation where appropriate.

All adolescents and adults with asthma should receive inhaled corticosteroid (ICS)-containing treatment to reduce their risk of severe exacerbations. It should be taken every day or, as an alternative in patients with mild asthma, by as-needed ICS-formoterol for symptom relief.

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 8, p.139).

Women with asthma who are pregnant or planning pregnancy should be advised to not stop ICS-containing therapy, as exacerbations increase the risk of adverse perinatal outcomes. The advantages of actively treating asthma in pregnancy with ICS-containing therapy markedly outweigh any potential risks of these medications.

MANAGING MULTIMORBIDITY

Multimorbidity is a common problem in patients with chronic diseases such as asthma. It is associated with worse quality of life, increased healthcare utilization and increased adverse effects of treatment.[199] Multimorbidity is particularly common among those with difficult-to-treat or severe asthma.[99] Active management of comorbidities such as rhinosinusitis, anxiety and/or depression, obesity and GERD is important, as these conditions may also contribute to respiratory symptom burden and lead to medication interactions. Some comorbidities also contribute to poor asthma control.[546] The advice below covers some of the most common comorbidities of asthma, but is not an exhaustive list.

Obesity

Clinical features

Being overweight or obese is a risk factor for childhood asthma and wheeze, particularly in girls.[547] Asthma is more difficult to control in obese patients.[276,548-550] This may be due to a different type of airway inflammation, contributory comorbidities such as obstructive sleep apnea and 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 expiratory airflow (Box 1-2, p.25). Asthma is more common in obese than non-obese patients,[79] but both over- and under-

diagnosis of asthma occur in obesity.[55,80] The relationship between biomarkers of Type 2 inflammation is lost in the obese.[22,48]

Management

As for other patients with asthma, ICS treatment is essential in obese patients (Evidence B), although their response may be reduced.[276] 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).[283] Weight loss can improve asthma control, lung function, health status and reduces medication needs in obese patients,[278,279] but the studies have generally been small, quality of some studies is poor, and the interventions and results have been variable.[277] The most striking results have been observed after bariatric surgery,[280,281,551] but even 5–10% weight loss can lead to improved asthma control and quality of life.[283] For patients with comorbid obstructive sleep apnea, one study showed a significant reduction in moderate exacerbations with 6 months of continuous positive airway pressure (CPAP) therapy.[552]

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,[546] but this may be in part due to cough being attributed to asthma; in addition, some asthma medications such as beta$_2$-agonists and theophylline cause relaxation of the lower esophageal sphincter. Asymptomatic gastroesophageal reflux is not a likely cause of poorly controlled asthma.[546]

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 reflux symptoms persist, specific investigations such as 24-hour pH monitoring or endoscopy may be considered.

Management

Clinical trials of proton pump inhibitors in patients with confirmed asthma, most of whom had a diagnosis of GERD, showed small benefits for lung function, but no significant benefit for other asthma outcomes.[553,554] 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.[555] In general, benefits of proton pump inhibitors in asthma appear to be limited to patients with both symptomatic reflux and night-time respiratory symptoms.[556] 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).[554] Few data are available for children with asthma symptoms and symptoms of GERD.[557,558]

Anxiety and depression

Clinical features

Anxiety symptoms and psychiatric disorders, particularly depressive and anxiety disorders, are more prevalent among people with asthma.[559,560] Psychiatric comorbidity is also associated with worse asthma symptom control and medication adherence, and worse asthma-related quality of life.[561] Anxious and depressive symptoms have been associated with increased asthma-related exacerbations and emergency visits.[548] 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. A 2006 systematic review of 15 randomized controlled trials of psychological interventions for adults with asthma included cognitive behavior therapy, psychoeducation, relaxation, and biofeedback.[549] Results for anxiety were conflicting, and none of the studies found significant treatment differences for depression. A 2024 systematic review found limited RCT evidence to support psychological interventions in children or adolescents with asthma, due to substantial heterogeneity, small sample sizes, and non-standardized outcomes of available trials. Drug treatments and cognitive behavior therapy[550] have shown some benefit for patients with asthma and anxiety, and analysis of 3 placebo-controlled trials of anti-depression medications in patients with asthma and a major depressive disorder showed reduction in oral corticosteroid usage.[562] However, current evidence is limited in volume and quality.

Food allergy and anaphylaxis

Clinical features

Rarely, food allergy is a trigger for asthma symptoms (<2% of people with asthma). However, 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.[100] 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.[563] 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.[564]

Diagnosis

Patients with confirmed food allergy should be assessed for asthma. Children with food allergy have a four-fold increased likelihood of having asthma compared with children without food allergy.[565] 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 immunoglobulin E (IgE). On occasion, carefully supervised food challenges may be needed.

Management

Patients who are at risk for anaphylaxis due to confirmed food allergy must have an epinephrine auto-injector available at all times, and be trained how to use it. 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.

Allergic rhinitis

Clinical features

Evidence clearly supports a link between diseases of the upper and lower airways.[566] Most patients with asthma, either allergic or non-allergic, have concurrent rhinitis, and 10–40% of patients with allergic rhinitis have asthma.[567] Depending on sensitization and exposure, allergic rhinitis may be seasonal (e.g., ragweed or grass pollen), or perennial (e.g., house dust mite allergens, furred pets in the home), or intermittent (e.g., furred pets at other locations).[568] Rhinitis is defined as irritation and inflammation of the mucous membranes of the nose. Allergic rhinitis may be accompanied by ocular symptoms (conjunctivitis).

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 and/or occupational exposure (e.g., furred pets, house dust mite,

molds, pollens) suggests allergic rhinitis. Examination of the upper airway should be arranged for patients with severe asthma.

Management

International evidence-based guidelines[566,569] 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,[570] but a meta-analysis found improvement in asthma outcomes only in patients not also receiving ICS.[571] Allergen immunotherapy is a treatment option for some patients with allergic rhinitis and asthma (p.104).

Chronic rhinosinusitis with and without nasal polyps (CRSwNP and CRSsNP)

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).[572] 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 polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP).[573] The heterogeneity of chronic rhinosinusitis may explain the wide variation in prevalence rates in the general population, ranging from 1% to 10% without polyps and 4% with polyps. Chronic rhinosinusitis is associated with more severe asthma, especially in patients with nasal polyps.[574]

Diagnosis

Nasendoscopy and/or computed tomography (CT) of the sinuses can identify changes suggestive of chronic rhinosinusitis with or without nasal polyps. In severe asthma, presence of nasal polyps may help with choice of biologic therapy (see Box 8-4, p.144).

Management

Chronic rhinosinusitis, with or without nasal polyps, has a significant impact on patients' quality of life. Guidelines for the management of chronic rhinosinusitis with or without nasal polyps have been published.[575,576]

A 2022 systematic review of studies reporting treatment outcomes in patients with both asthma and chronic rhinosinusitis found that medical treatments (including intranasal saline irrigations, intranasal corticosteroids delivered by irrigation, drops (only one small study of each) or sprays, oral antibiotics (small studies with erythromycin), and oral corticosteroids) improved sinonasal-specific quality of life in patients with chronic rhinosinusitis (most commonly with nasal polyps) and comorbid asthma. However, people with chronic rhinosinusitis and asthma may have a lesser response to rhinosinusitis treatments than people who do not have asthma.[577] There was limited evidence for improvements in lung function and asthma control, and no data on the effect of intranasal corticosteroids on lung function or asthma control.[577]

The systematic review found strong RCT evidence that anti-IL4Rα and anti-IL5/5Rα receptor therapies improve rhinosinusitis, including reducing polyp counts, as well as improving asthma outcomes, in patients with asthma and CRSwNP who have experienced inadequate response to non-biologic therapy.[577] Biologics were less effective in managing chronic sinusitis without polyps in people with asthma.[577] The review found no studies that directly compared biologic therapy with endoscopic sinus surgery in patients with CRSwNP and asthma. There was moderate-to-strong evidence that endoscopic sinus surgery improves sinonasal-specific and asthma-specific quality of life in patients with chronic rhinosinusitis and asthma, and may improve asthma symptom control, but there was insufficient evidence for effects on lung function.[577]

Current evidence supports stepwise treatment to manage chronic rhinosinusitis in people with asthma, beginning with topical nasal saline irrigations and topical nasal steroids as the main treatment. Oral antibiotics can be used as needed after considering the risks and microbial resistance. Oral corticosteroid treatment is effective, but should be minimized due

to adverse effects (Box 9-3, p.166). In patients with CRSwNP, omalizumab,[578] mepolizumab[579,580] and dupilumab[581] improved subjective and objective assessments including nasal symptoms and polyp size, compared with placebo. Endoscopic sinus surgery can be considered in patients with asthma who have inadequate response to medical therapies for chronic rhinosinusitis, but it does not improve asthma outcomes.

Managing asthma during the COVID-19 pandemic

Are people with asthma at higher risk of COVID-19 or severe COVID-19?

People with asthma do not appear to be at increased risk of acquiring COVID-19, and systematic reviews have not shown an increased risk of severe COVID-19 in people with well-controlled mild-to-moderate asthma. Overall, studies to date indicate that people with well-controlled asthma are not at increased risk of COVID-19-related death,[582,583] and in one meta-analysis, mortality appeared to be lower than in people without asthma.[584] However, the risk of COVID-19 death was increased in people who had recently needed oral corticosteroids (OCS) for their asthma,[468,582] and in hospitalized patients with severe asthma.[468,585] Therefore, it is important to continue good asthma, with strategies to maintain good symptom control, reduce the risk of severe exacerbations and minimize the need for OCS. In one study of hospitalized patients aged ≥50 years with COVID-19, mortality was lower among those with asthma who were using ICS than in patients without an underlying respiratory condition.[585]

In 2020 and 2021, many countries recorded a reduction in asthma exacerbations and influenza-related illness. The reasons are not precisely known, but may be due to handwashing, masks and social/physical distancing that reduced the incidence of other respiratory infections, including influenza.[469]

During pandemic conditions, advise patients with asthma to continue taking their prescribed asthma medications, particularly inhaled corticosteroid (ICS)-containing medications, and OCS if prescribed

It is important for patients to continue taking their prescribed asthma medications as usual during the COVID-19 pandemic. This includes ICS-containing medications (alone or in combination with a long-acting beta$_2$-agonist (LABA), and add-on therapy including biologic therapy for severe asthma. Stopping ICS often leads to potentially dangerous worsening of asthma. See Section 4 (p.67) for information about asthma medications and regimens and non-pharmacologic strategies, and Section 5 (p.108) for guided asthma self-management education and skills training.

For a small proportion of patients with severe asthma, long-term OCS may sometimes be needed, and it is very dangerous to stop these suddenly. See Section 8 (p.139) for advice about investigation and management of difficult-to-treat and severe asthma, including addition of biologic therapy for minimizing use of OCS.

Advise patients to discuss with you before stopping any asthma medication.

Make sure that all patients have a written asthma action plan

A written action plan (printed, digital or pictorial) tells the patient how to recognize worsening asthma, how to increase their reliever and maintenance medications, and when to seek medical help. A short course of OCS may be needed during severe asthma flare-ups (exacerbations). See Box 9-2 (p.163) for more information about specific action plan options for increasing reliever medications (or reliever and maintenance medications), depending on the patient's usual therapeutic regimen.

At present, there is no clear evidence about how to distinguish between worsening asthma due to respiratory viral infections such as rhinovirus and influenza, and COVID-19.

If local risk of COVID-19 is moderate or high, avoid use of nebulizers where possible due to the risk of transmitting infection to other patients/family and to healthcare workers

Nebulizers can transmit respiratory viral particles across distances of at least 1 m.[586] Use of nebulizers for delivering bronchodilator therapy is mainly restricted to management of life-threatening asthma in acute care settings. Instead, to deliver short-acting beta$_2$-agonist for acute asthma in adults and children, use a pressurized metered-dose inhaler and spacer, with a tightly fitting face mask, if required. Check the manufacturer's instructions about whether a spacer can be autoclaved. If not (as is the case for many types of spacers), or if in doubt, spacers should be restricted to single patient

use. If use of a nebulizer is needed in settings where COVID-19 infection is possible, strict infection control procedures should be followed.

Remind patients not to share inhaler devices or spacers with family members, to avoid transmitting infection.

Avoid spirometry in patients with confirmed/suspected COVID-19

In healthcare facilities, follow local COVID-19 testing recommendations and infection control procedures if spirometry or peak flow measurement is needed.[31] Use of an in-line filter minimizes the risk of transmission during spirometry, but many patients cough after performing spirometry; before performing spirometry, coach the patient to stay on the mouthpiece if they feel the need to cough.

If spirometry is not available due to local infection control restrictions, and information about lung function is needed, consider asking patients to monitor lung function at home.

Follow infection control recommendations if any aerosol-generating procedures are needed

Other aerosol-generating procedures include oxygen therapy (including via nasal prongs), sputum induction, manual ventilation, non-invasive ventilation and intubation. Follow local health advice about hygiene strategies and use of personal protective equipment, as new information becomes available in your country or region.

The website of the World Health Organization (WHO) provides comprehensive advice for healthcare providers and health systems about prevention and management of COVID-19 here.

Management of asthma if the patient acquires COVID-19

People with asthma who acquire COVID-19 are not at higher risk of severe COVID-19. However, be aware that those with poorly controlled asthma (e.g., recent need for OCS) are at higher risk of hospitalization for severe disease if they acquire COVID-19.[468,582,585] Advise patients to continue taking their usual asthma medications. Patients with severe asthma should continue biologic therapy or OCS, if prescribed.

To reduce the risk of transmitting infection, as above, avoid use of nebulizers where possible (use a pressurized metered-dose inhaler [pMDI] and spacer instead), avoid spirometry, and instruct patients to avoid sharing of inhalers/spacers.

Before prescribing antiviral therapies, consult local prescribing guidelines. Check carefully for potential interactions between asthma therapy and COVID-19 therapy. For example, ritonavir-boosted nirmatrelvir (NMV/r) is a potent CYP3A4 inhibitor. While this is unlikely to cause clinically important corticosteroid-related adverse effects, because of the short duration of anti-COVID-19 treatment, be cautious if considering prescribing NMV/r for patients taking ICS-salmeterol or ICS-vilanterol, as the interaction may increase cardiac toxicity of the LABA.[165] Product information indicates that for patients taking ICS-salmeterol or ICS-vilanterol, concomitant treatment with CYP3A4 inhibitors is not recommended. Some drug interaction websites advise stopping ICS-salmeterol or ICS-vilanterol during NMV/r treatment and for a few days afterwards, but this may increase the risk of an asthma exacerbation. Instead, consider prescribing alternative antiviral therapy (if available) or switching to ICS alone or ICS-formoterol (if available) for the duration of NVM/r therapy and a further 5 days.[165] If switching to a different inhaler, remember to teach correct technique with the new inhaler.

Advise people with asthma to be up to date with COVID-19 vaccines

Many types of COVID-19 vaccines have been studied and are in use. New evidence about the vaccines, including in people with asthma, will emerge over time. In general, allergic reactions to the vaccines are rare. Patients with a history of severe allergic reaction to a COVID-19 vaccine ingredient (e.g., polyethylene glycol for Pfizer/BioNTech or Moderna, or polysorbate 80 for AstraZeneca or J&J/Janssen) should receive a different COVID-19 vaccine. However, people with anaphylaxis to foods, insect venom, or other medications can safely receive COVID-19 vaccines. As always, patients should speak to their healthcare provider if they have concerns. Follow local advice about monitoring patients after COVID-19 vaccination.

Usual vaccine precautions apply. For example, ask if the patient has a history of allergy to any components of the vaccine, and if the patient has a fever or another infection, delay vaccination until they are well.

For people with severe asthma, GINA suggests that, if possible, the first dose of biologic therapy and COVID-19 vaccine should not be given on the same day, to allow adverse effects of either to be more easily distinguished.

Remind people with asthma to have an annual influenza vaccination (p.106). Influenza vaccine and COVID-19 vaccine can be given on the same day.

MANAGING ASTHMA IN SPECIFIC POPULATIONS, SETTINGS OR CONTEXTS

This section includes brief advice about managing asthma in some of the specific populations, settings of contexts in which the usual treatment approach may need to be modified. See also How to make the diagnosis of asthma in other contexts (p.33).

Low- and middle-income countries

Clinical features

In 2019, 96% of asthma deaths and 84% of disease burden, measured in disability-adjusted life years (DALYs) were in low- and middle-income countries (LMICs).[2] Symptoms of asthma are similar world-wide, but patient language may differ, and comorbidities may vary depending on environmental exposures such as smoking and biomass fuel exposure and incidence of chronic respiratory infections from tuberculosis and HIV/AIDS.

Management

The fundamental principles and aims of asthma treatment are the same in LMICs as in high-income countries, but common barriers to effective long-term asthma care include the lack of availability and affordability of inhaled medicines, and prioritization of acute care over chronic care by healthcare systems.[2,5]

Recommendations by WHO and the International Union Against Tuberculosis and Lung Disease[587] form the basis of treatments offered in many LMICs.[5] The WHO Model List of Essential Medicines includes ICS, combination ICS-formoterol, and bronchodilators,[588] and the WHO Model List of Essential Medicines for Children includes ICS.[589] Spacers are included in the WHO list of essential technology, but are rarely available due to obstacles to their manufacture or purchase, practical issues of cleaning, and inconvenience for ambulatory use. Effective spacers can be made at no cost from plastic drink bottles.[590]

Medicines selected as "essential" are not necessarily the most effective or convenient, particularly for patients with more severe disease, and a limited choice does not allow for consideration of patient preferences and likelihood of adherence. However, ICS-containing medications, when provided for large populations, have achieved impressive reductions in mortality and morbidity,[591] including in LMICs. In Brazil, government policy ensuring nationwide easy access to ICS, at no cost to patients, was associated with a 34% reduction in hospitalizations for asthma.[192] Prescribing ICS-formoterol as the symptom reliever, with (GINA Steps 3–5) or without (Steps 1–2) maintenance ICS-formoterol, provides the safest and most effective asthma treatment for adolescents and adults,[191,233] and avoids the behavioral consequences of starting treatment with short-acting beta$_2$-agonist (SABA) alone.

Inclusion of essential asthma medicines in formularies and guidelines does not assure sustained and equitable supply to patients. The supply of medicines in many LMICs tends to be sporadic for a wide variety of reasons, sometimes determined by the ability of governments to pay for supplies, issues relating to procurement, poor administration and record keeping, and problems in the supply chain, particularly to remote dispensaries.[3,5]

Availability of asthma medicines varies widely between LMICs, with some having only oral bronchodilators (salbutamol and theophylline tablets/solutions), supplemented from time to time with oral corticosteroids.[25] Oral bronchodilators have a slow onset of action and more adverse effects than inhaled SABA, and even occasional courses of OCS are associated with a significant risk of short-term adverse effects such as pneumonia and sepsis,[592] and, in adults, with long-term adverse effects including osteoporosis and fragility fractures, cataract and diabetes.[234] The largest (52 countries) survey of the accessibility and affordability of inhaled asthma medicines, conducted in 2011, reported that salbutamol was available in only half of public hospitals; ICS was available in fewer than one in five public pharmacies and not at all in 14 countries.[593]

Obtaining asthma medicines often represents a catastrophic household expense. A recent systematic review of published data on the availability, cost and affordability of essential medicines for asthma and chronic obstructive pulmonary disease (COPD) in LMICs found these to be largely unavailable and unaffordable particularly for ICS and combination ICS-LABA.[594] This means that the essential cornerstone of treatment that achieves substantial reductions in morbidity and mortality is out of reach for the great majority of the world's children, adolescents and adults living with asthma.

It is not acceptable in 2023 for clinicians to have to manage asthma with SABAs and oral corticosteroids instead of preventive ICS-containing treatments. The research community must develop and evaluate approaches designed to obviate barriers to care in resource-constrained settings. A World Health Assembly Resolution on equitable access to affordable care, including inhaled medicines, for children, adolescents and adults with asthma, wherever they live in the world, would be a valuable step forward – as was achieved in 2021 for the supply of insulin for diabetes.[595] GINA strongly supports this initiative.[3]

In the meantime, in general, Track 2 treatment, although less effective in reducing asthma exacerbations, may be considered preferable in settings where current availability or affordability constrains the ability to implement Track 1 treatment. The "other controller options" in Box 4-6 (p.77), though potentially less costly, may be considerably less effective (e.g., leukotriene receptor antagonists [LTRAs]) or more harmful (e.g., maintenance OCS), or not well supported by evidence, especially in the low-resource setting (e.g., use of a low-dose ICS inhaler whenever a SABA is taken for symptom relief). Of these three other controller options, the third would be closest to the preferred recommendations in Tracks 1 and 2, as it would ensure that an ICS was provided, at least during symptomatic periods.[25]

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.[596] Exploratory and risk-taking behaviors such as smoking occur at a higher rate in adolescents with chronic diseases than in healthy adolescents.

In a large meta-analysis of adherence to ICS treatment among adolescents and young adults,[198] overall adherence was 28%, and slightly higher in those <18 years (36%). However, pharmacy refill data provided lower estimates of adherence than self-report measures. Predictors of adherence included personality, illness perceptions, and treatment beliefs.

Management

General principles for managing chronic disease in adolescents have been published by WHO.[597] Adolescents and their parent/caregivers should be encouraged in the transition towards asthma self-management by the adolescent.[598] This may involve the transition from a pediatric to an adult healthcare facility. Transitioning should not be based on chronological age but on developmental stage and readiness, using formal tools to assess readiness at around 11–13 years (ideal timing/age not based on evidence). Clinicians should aim to increase self-management, focusing consultations on areas in which the young person is not confident. Consider using technology to assist with adherence and guide young people to web-based apps and tools to improve knowledge of asthma. Awareness of asthma should be promoted to communities and peers.

During consultations, the adolescent should be seen separately from the parent/caregiver 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. In adolescents with mild asthma, use of as-needed low-dose ICS formoterol

reduced risk of severe exacerbations, compared with SABA alone, and without the need for daily treatment. Change in height from baseline in younger adolescents was significantly greater with as-needed ICS-formoterol than with daily low-dose ICS plus as-needed SABA.[319]

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.[61,69]

Management

Regular treatment with ICS significantly reduces EIB (Evidence A).[69] Training and sufficient warm-up reduce the incidence and severity of EIB (Evidence A).[69] 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).[69] 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.[246] More studies are needed, but this suggests that patients with mild asthma who are prescribed as-needed low-dose 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). Chromone pMDIs have been discontinued globally.

Breakthrough EIB often indicates poorly controlled asthma, and stepping up ICS-containing 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.[70]

Management

Preventive 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 beta$_2$-agonists will help to avoid the development of tolerance.[69] 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 Global Allergy and Asthma European Network (GA(2)LEN)[599] and on the World Anti-Doping Agency (WADA) website (www.wada-ama.org). The International Olympic Committee (IOC) and WADA allow use of ICS-formoterol by competitive athletes up to a formoterol dose of 72 mcg metered dose (54 mcg delivered dose) in a day.

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.[600] Exacerbations are common in pregnancy, particularly in the second trimester.[101] 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 healthcare provider. Pregnant women appear to be particularly susceptible to the effects of viral respiratory infections,[601] 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).[101] Risk factors for asthma exacerbations during pregnancy include severe asthma, multiparity, black ethnicity, depression and anxiety, current smoking, age >35 years and obesity. Addressing these risk factors may not only reduce the risk of exacerbations, but also the risk of adverse perinatal outcomes.[602] If asthma is well controlled throughout pregnancy there is little or no increased risk of adverse maternal or fetal complications.[71]

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 asthma medications (Evidence A).[71] 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, beta$_2$-agonists, montelukast or theophylline is not associated with an increased incidence of fetal abnormalities.[603]

Women with asthma who are pregnant or planning pregnancy should be advised to not stop ICS-containing therapy. Importantly, ICS reduce the risk of exacerbations of asthma during pregnancy (Evidence A),[71,604,605] and cessation of ICS during pregnancy is a significant risk factor for exacerbations,[101] (Evidence A). One study reported that a treatment algorithm in non-smoking pregnant women based on monthly measurement of fractional concentration of exhaled nitric oxide (FeNO) and symptoms using the Asthma Control Questionnaire (ACQ) was associated with significantly fewer exacerbations and better fetal outcomes than an algorithm based only on ACQ.[606] However, the ACQ-only algorithm did not reflect current clinical recommendations, as LABA was introduced only after ICS had been increased to medium dose, and ICS could be stopped; 58% of women in the ACQ-only group were being treated without ICS by the end of pregnancy. In a subsequent large randomized controlled trial in pregnant women, there was no reduction in exacerbations with FeNO-guided treatment, compared with usual care.[451]

Use of ICS during pregnancy by women with asthma may also be protective for asthma in their children. A study using administrative data reported that uncontrolled maternal asthma increased the risk of early-onset asthma in the offspring.[607] In an intervention study with follow-up for 4–6 years, the prevalence of asthma was over 50% lower in children of women with asthma who took ICS during pregnancy than in children of women who did not take ICS, with the largest reduction in asthma prevalence seen in children whose mothers took ICS in early pregnancy (before weeks 12–20).[608]

On balance, given the evidence in pregnancy and infancy for adverse outcomes from exacerbations during pregnancy (Evidence A),[71] including due to lack of ICS or poor adherence,[101] and evidence for safety of usual doses of ICS and LABA (Evidence A),[603] **a low priority should be placed on stepping down treatment (regardless of the method used to assess control) until after delivery** (Evidence D), and **ICS should not be stopped in preparation for pregnancy or during pregnancy** (Evidence C).

Despite lack of evidence for adverse effects of asthma treatment in pregnancy, many women and healthcare providers remain concerned about medication.[609] 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 may provide additional reassurance.[610] During pregnancy, monitoring of asthma every 4–6 weeks is recommended.[610] It is feasible for this to be achieved by pharmacist-clinician collaboration, with monthly telephone monitoring of asthma symptom control.[611] One observational study found that pregnant women

whose asthma was well controlled without controller therapy and who had no history of previous exacerbations were at low risk for exacerbations during pregnancy.[612] However, such women should still be closely monitored.

For women with severe asthma, evidence on use of **biologic therapies** during pregnancy is scarce.[613] A registry study found no evidence of an increased risk of major congenital malformations when mothers received omalizumab during pregnancy. Women should be counselled that the potential risks associated with biologic exposure during pregnancy need to be balanced against the risks for themselves and their children caused by uncontrolled asthma.[614]

During **acute asthma exacerbations**, pregnant women may be less likely to be treated appropriately than non-pregnant patients.[101] To avoid fetal hypoxia, it is important to manage acute asthma exacerbations during pregnancy aggressively with SABA, oxygen, and early administration of systemic corticosteroids. Respiratory infections should be monitored and managed appropriately during pregnancy.[601]

During labor and delivery, usual maintenance 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.[615]

A review of asthma guidelines for the management of asthma during pregnancy highlighted the need for greater clarity in current recommendations and the need for more RCTs among pregnant asthma patients.[616]

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 BMI, a longer duration of asthma, and a greater likelihood of aspirin-exacerbated respiratory disease (AERD). They more often have dysmenorrhea, premenstrual syndrome, shorter menstrual cycles, and longer menstrual bleeding. The role of hormone levels and systemic inflammation remains unclear.[617]

Management

In addition to the usual strategies for management of asthma, oral contraceptives and/or leukotriene receptor antagonists may be helpful (Evidence D).[617] Further research is needed.

Occupational asthma

Clinical features

In people with allergen exposure in the workplace, rhinitis often precedes the development of asthma (see p.33 for information on making the 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 non-responsive airflow limitation may result.[65]

Management

Detailed information is available in evidence-based guidelines about management of occupational asthma.[65,68] 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.[65] Cost-effective minimization of latex sensitization can be achieved by using non-powdered low-allergen gloves instead of powdered latex gloves.[65] 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.[618-620] Among the elderly, there is no increased risk of cardiovascular disease among those with asthma, compared with those without asthma, except in current or former smokers.[621] 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.[619]

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.[618,619] Data on efficacy of asthma medications in the elderly are limited because these patients are often excluded from major clinical trials. Side-effects of beta$_2$-agonists such as cardiotoxicity, and corticosteroid side-effects such as skin bruising, osteoporosis and fragility fractures,[622] and cataracts, are more common in the elderly than in younger adults.[618] Clearance of theophylline is also reduced.[618] 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,[619,623] 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 features of both asthma and COPD, see Section 7 (p.131).

Aspirin-exacerbated respiratory disease (AERD)

Clinical features

The clinical picture and course of AERD (previously called aspirin-induced asthma) are well established.[249] 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 and nonsteroidal anti-inflammatory drugs (NSAIDs) develop subsequently. Following ingestion of aspirin or 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.[624,625] AERD is more likely to be associated with low lung function and severe asthma,[626,627] and with increased need for emergency care[627]. The prevalence of AERD is 7% in general adult asthma populations, and 15% in severe asthma.[627,628]

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[629,630] 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.[629,630] Bronchial (inhalational) and nasal challenges with lysine aspirin are safer than oral challenges and may be safely performed in allergy centers.[629,631]

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,[632,633] with appropriate healthcare provider supervision and observation for at least 2 hours after administration (Evidence B).[634] ICS treatment is the mainstay of asthma management in patients with AERD, but OCS treatment is sometimes required;

LTRA may also be useful (Evidence B),[624,634] but note the concern about potential neuropsychiatric adverse effects with montelukast.[309] See section 8 (p.139) for treatment options for patients with severe asthma. An additional option is aspirin desensitization, which may be conducted under specialist care in a clinic or hospital.[635] Desensitization to aspirin followed by daily aspirin treatment can significantly improve upper respiratory symptoms and overall quality of life, decrease recurrence of nasal polyps, reduce the need for OCS and sinus surgery, and improve nasal and asthma scores, but few double-blind studies have examined asthma outcomes.[629,636,637] Aspirin desensitization is associated with a significantly increased risk of adverse effects such as gastritis and gastrointestinal bleeding.[637]

Allergic bronchopulmonary aspergillosis (ABPA)

Clinical features

Allergic bronchopulmonary aspergillosis (ABPA) is a complex pulmonary disease due to a hypersensitivity response to *Aspergillus fumigatus*, a common indoor and outdoor mold. It is 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 diagnosed in people with asthma or cystic fibrosis.

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.[638] 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., a 4-month tapering course), with itraconazole reserved for those with exacerbations or requiring long-term OCS.[639-641] Clinicians should be aware of the potential for drug interactions between itraconazole (a cytochrome P450 inhibitor) and asthma medications. These interactions may lead to increased risk of ICS adverse effects such as adrenal suppression and Cushing’s syndrome, and may increase the risk of cardiovascular adverse effects of some LABAs (salmeterol and vilanterol).[165] Concomitant use is not recommended, so it may be appropriate to switch ICS-LABA treatment to an alternative product such as budesonide-formoterol or mometasone-formoterol for the duration of treatment with itraconazole.[165]

A randomized double-blind placebo-controlled study in patients with severe asthma and ABPA found significantly fewer exacerbations with omalizumab (anti-IgE) than placebo.[642] A systematic review and meta-analysis that included this trial and others, but with a total of only 450 patients in the analysis, provides evidence of moderate quality that patients with ABPA who do not respond to treatment with oral corticosteroids have a favorable response to omalizumab without substantial side effects.[643] Small case series and case reports of treatment of ABPA with other biologic therapies have been published.[644] Information about use of biologic therapies in severe asthma is covered in Section 8 (p.139).

In patients with ABPA and bronchiectasis, regular physiotherapy and daily drainage are recommended. Patients with ABPA should be referred for specialist investigation and care if available.

Surgery and asthma

Clinical features

There is no evidence of increased peri-operative risk for the general asthma population.[645] However, there is an increased risk for patients with COPD,[645] and this may also apply to asthma patients with reduced FEV_1. The incidence of severe peri-operative bronchospasm in people with asthma is low, but it may be life threatening.[646]

Management

For elective surgery, meticulous attention should be paid pre-operatively to achieving good asthma control, especially for patients with more severe asthma, uncontrolled symptoms, exacerbation history, or persistent airflow limitation (Evidence B).[646] 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 surgery (Evidence B).[647] More immediate intra-operative issues relating to asthma management are reviewed in detail elsewhere.[646] For all patients, maintaining their prescribed ICS-containing therapy throughout the peri-operative period is important.

Air travel and asthma

Practical advice for air travel by people with respiratory disease was published by the British Thoracic Society (BTS) in 2022.[648] The advice for people with asthma included pre-flight optimization of treatment, carrying all asthma medications and spacer (if used) in the cabin to allow immediate access during the flight (and in case checked luggage is mislaid), and carrying a copy of the patient's asthma action plan.

Extreme weather and asthma

Background

The increasing frequency and intensity of extreme weather events (including extreme heat, cold, rainfall, drought) poses a growing risk to vulnerable populations such as children, the elderly, and people with asthma.[649,650] The health impacts of climate change are complex, but the impact on asthma is likely to fall into two broad categories. First, catastrophic weather events impact infrastructure and disrupt care for people living with chronic conditions such as asthma.[651] Second, increased levels of air pollution (for example, from wildfires), enhanced survival of respiratory viruses, and increased concentration of allergens like mold and pollen, together with extreme temperatures, may worsen asthma morbidity and contribute to healthcare costs.[301,652] Thunderstorms can also trigger asthma exacerbations, including acute asthma epidemics (see p.160).

Asthma outcomes

Extreme weather events can increase hospitalizations, increased emergency department (ED) visits and asthma mortality. A systematic review and meta-analysis found that extreme weather increased the rate of asthma ED visits by 34%, that heat waves increased hospitalization rates by 39%,and that cold spells increased hospitalization rates by 35%. A 2023 meta-analysis suggested that heatwaves elevate the risk of asthma-related ED visits by approximately 7%, while cold spells may raise this risk by 20%.[653] This analysis found that the effects of extreme heat on hospital visits showed a short-term lag effect, appeared to be relatively acute and lasted for a week, whereas extreme cold showed a long-term lag effect, lasting from 3 to 30 days.[653] Extreme weather events are also associated with 2.3-fold increased risk of acute asthma exacerbations requiring outpatient visits.[654] There is emerging evidence that extreme weather can increase asthma mortality rates.[654,655]

Mitigation strategies

There is limited evidence about mitigation strategies to prevent asthma exacerbations during extreme weather events. Practical interventions include the use of face masks to reduce PM2.5 exposure during wildfires,[656] and sheltering in temperature-controlled environments such as shopping malls. Other interventions, such as the use of mobile phone alerts prompting behavioral change to mitigate against extreme events or high exposure levels, have been found to improve asthma outcomes.[657] Automated health-related weather alerts can also help with health system readiness.

7. Diagnosis and initial treatment in adults with features of asthma, COPD or both

KEY POINTS

Asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous and overlapping conditions

"Asthma" and "COPD" are umbrella labels for heterogeneous conditions characterized by chronic airway and/or lung disease. Asthma and COPD each include several different clinical phenotypes, and are likely to have several different underlying mechanisms, some of which may be common to both asthma and COPD.

Symptoms of asthma and COPD may be similar, and the diagnostic criteria overlap.

Why are the labels "asthma" and "COPD" still important?

There are extremely important differences in evidence-based treatment recommendations for asthma and COPD. For example, treatment with a long-acting beta$_2$-agonist (LABA) and/or long-acting muscarinic antagonist (LAMA) alone (i.e., without inhaled corticosteroids [ICS]) is recommended as initial treatment in COPD but contraindicated in asthma due to the risk of severe exacerbations and death.

These risks are also seen in patients who have diagnoses of both asthma and COPD, making it important to identify adult patients who, for safety, should not be treated with long-acting bronchodilators alone. ICS reduce mortality and hospitalizations in patients with asthma, including in those with concomitant COPD.

Many patients have features of both asthma and COPD

Distinguishing asthma from COPD can be difficult, particularly in smokers and older adults, and some patients may have features of both asthma and COPD.

The terms "asthma-COPD overlap" or "asthma+COPD" are simple descriptors for patients who have features of both asthma and COPD. These terms do *not* refer to a single disease entity. They include patients with several clinical phenotypes that are likely caused by a range of different underlying mechanisms.

More research is needed to better define these phenotypes and mechanisms, but in the meantime, safety of pharmacologic treatment is a high priority.

Diagnosis

Diagnosis in patients with chronic respiratory symptoms involves a stepwise approach: first identifying chronic airways disease, then categorizing by syndrome (typical asthma, typical COPD, features of both, and the presence/absence other conditions such as bronchiectasis).

Lung function testing is essential for confirming persistent airflow limitation, but variable airflow obstruction can be detected with serial peak flow measurements and/or measurements before and after bronchodilator.

Initial treatment for safety and clinical efficacy

For asthma: ICS treatment is essential, either alone or in combination with a LABA, to reduce the risk of severe exacerbations and death. Do not treat with LABA and/or LAMA alone (i.e., without ICS).

For patients with features of both asthma and COPD, treat as asthma. ICS-containing therapy is important to reduce the risk of severe exacerbations and death. Do not give LABA and/or LAMA alone without ICS.

For COPD: Treat according to current recommendations from the Global Initiative for Chronic Obstructive Lung Disease (GOLD):[76] initial treatment with LAMA and LABA, plus as-needed SABA; add ICS for patients with hospitalizations, ≥2 exacerbations/year requiring oral corticosteroids (OCS), or blood eosinophils ≥300/μL. Avoid high-dose ICS because of risk of pneumonia.

All patients: provide structured education especially focusing on inhaler technique and adherence; assess for, and treat, other clinical problems, including advice about smoking cessation, immunizations, physical activity, and management of multimorbidity.

Specialist referral for additional investigations in patients with asthma+COPD is encouraged, as they often have worse outcomes than patients with asthma or COPD alone.

OBJECTIVES

The objectives of this section of the GINA Strategy Report are:

- To assist primary care clinicians to identify typical asthma and typical COPD and to recognize when patients have features of both. This is particularly relevant in patients aged 40 years and older.
- To provide advice about safe and effective initial treatment
- To provide guidance on indications for referral for specialist assessment.

BACKGROUND TO DIAGNOSING ASTHMA AND/OR COPD IN ADULT PATIENTS

Why are the labels "asthma" and "COPD" still important?

Asthma and COPD are heterogeneous conditions characterized by airway obstruction. Each of these "umbrella" labels covers several different patterns of clinical features (phenotypes) that may overlap. Each may also include different inflammatory patterns and different underlying mechanisms, some of which may be common to both asthma and COPD.[658]

The most easily recognized phenotypes of asthma and COPD such as allergic asthma in children/young adults and emphysema in older smokers are clearly distinguishable. Regulatory studies of pharmacotherapy in asthma and COPD are largely restricted to patients with very clearly defined asthma or COPD. However, in the community, the features of asthma and COPD may overlap, especially in older adults.

There are extremely important differences in treatment recommendations for asthma and COPD. In particular, treatment with long-acting bronchodilators alone (i.e., without ICS) is recommended for initial treatment in COPD[76] but is contraindicated in asthma due to the risk of severe exacerbations and death.[158,416,659,660] Several studies have also shown that patients with diagnoses of both asthma and COPD are at increased risk of hospitalization or death if they are treated with LABA or LABA-LAMA, compared with ICS-LABA (or ICS-LABA-LAMA).[661-663]

Challenges in clinical diagnosis of asthma and COPD

Although asthma is characterized by variable expiratory airflow, at least initially (Box 1-2, p.25), and COPD is characterized by persistent airflow limitation,[76] the definitions of asthma and COPD are not mutually exclusive (Box 7-1, p.133). This means that clinical features are also important in making a diagnosis and treating appropriately.

In children and young adults with chronic or recurrent respiratory symptoms, the differential diagnosis is different from that in older adults (see Box 1-3, p.27). After excluding infectious disease and nonpulmonary conditions (e.g., congenital heart disease, inducible laryngeal obstruction), the most likely chronic airway disease in children and young adults is asthma.

However, in adults with a history of longstanding asthma,[664,665] persistent airflow limitation may be found.[666-670] Distinguishing this from COPD is problematic, especially if they are smokers or have other risk factors for COPD.[671-674] On the other hand, patients with COPD may show evidence of bronchodilator response, a feature more strongly associated with asthma. In medical records, such patients often are assigned both diagnoses.[78,675]

In keeping with common usage of the term “overlap” in other contexts, e.g., for the association between COPD with sleep disorders, and in overlap syndromes of collagen vascular disease, the descriptive term “asthma-COPD overlap” was often used.

“Asthma-COPD overlap” is a descriptor for patients often seen in clinical practice, who comprise a heterogeneous group. It does not refer to a single disease entity. To avoid confusion, the term “asthma+COPD” is now preferred.

Box 7-1. Current definitions of asthma and COPD, and clinical description of asthma+COPD

Asthma (GINA)
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.
COPD (GOLD)
Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.[76]
Asthma+COPD, also called asthma-COPD overlap (descriptive term)
“Asthma-COPD overlap” and “asthma +COPD” are terms used to collectively describe patients who have persistent airflow limitation together with clinical features that are consistent with both asthma and COPD. This is **not** a definition of a single disease entity, but a descriptive term for clinical use that includes several different clinical phenotypes reflecting different underlying mechanisms.

Prevalence and morbidity of asthma+COPD

In epidemiological studies, reported prevalences of asthma+COPD among patients with either diagnosis have ranged between 9% and 55%, with variation by sex and age.[669,676-678] This wide range reflects differences between criteria used by investigators. Concurrent doctor-diagnosed asthma and COPD has been reported in between 15 and 32% of patients with one or other diagnosis.[675,679,680]

There is broad agreement that patients with features of both asthma and COPD have a greater burden of symptoms,[681] experience frequent exacerbations,[78,667,681] have poor quality of life,[78,676,681] a more rapid decline in lung function,[681] higher mortality,[667,675] and greater use of healthcare resources,[78,682] compared with patients with asthma or COPD alone.

ASSESSMENT AND MANAGEMENT OF CHRONIC RESPIRATORY SYMPTOMS

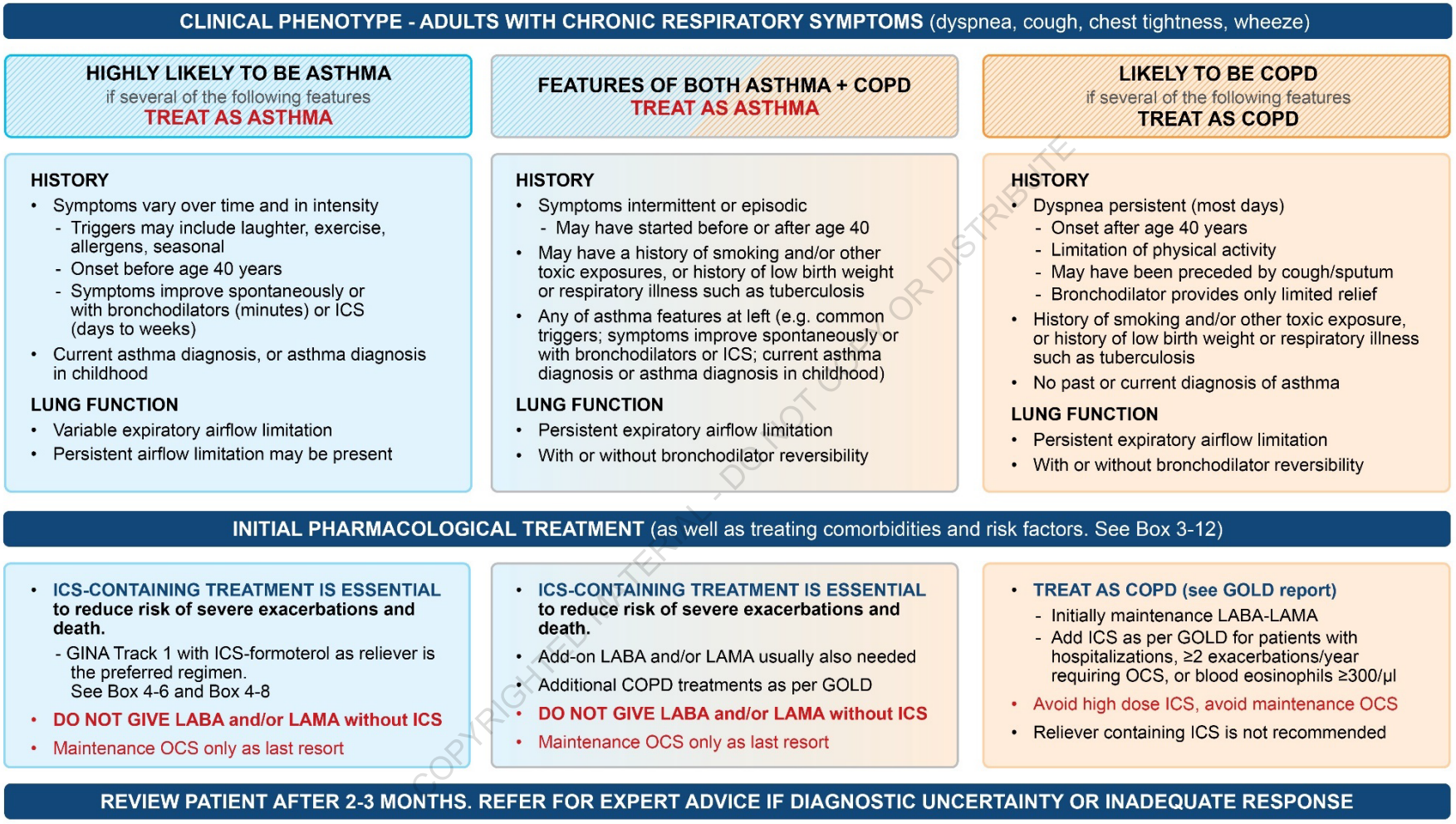
1: History and clinical assessment

Establish:

- The nature and pattern of respiratory symptoms (variable and/or persistent)
- History of asthma diagnosis; childhood and/or current
- Exposure history: smoking and/or other exposures to risk factors for COPD.

The features that are most helpful in identifying and distinguishing asthma from COPD, and the features that should prompt a patient to be treated as asthma to reduce the risk of severe exacerbations and death, are shown in Box 7-2 (p.134).

Box 7-2. Syndromic approach to initial treatment in patients with asthma and/or COPD



COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung disease; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroid

Caution: Consider alternative diagnoses; other airways diseases, such as bronchiectasis and chronic bronchitis, and other forms of lung disease such as interstitial lung disease may present with some of the above features. The above approach to diagnosis does not replace the need for a full assessment in patients presenting with respiratory symptoms, to first exclude non-respiratory diagnoses such as heart failure. Physical examination may provide supportive information.

2: Lung function testing is essential

Use lung function testing to confirm:

- Persistent expiratory airflow limitation
- Variable expiratory airflow.

Spirometry should be performed at the initial assessment, where possible. In cases of clinical urgency, it may be delayed to a subsequent visit, but confirmation of diagnosis may be more difficult after the patient has started ICS-containing therapy (see Box 1-4, p.30). Early confirmation (or exclusion) of the presence of persistent expiratory airflow limitation may avoid needless treatment trials or delays in initiating other investigations. Spirometry can confirm both persistent airflow limitation and bronchodilator responsiveness (Box 7-2, p.134 and Box 7-3, p.135).

Measurement of peak expiratory flow (PEF), performed repeatedly on the same meter over a period of 1–2 weeks, may help to confirm variable airflow limitation and the diagnosis of asthma by demonstrating excessive variability (Box 1-2, p.25). However, PEF is not as reliable as spirometry, and a normal PEF does not rule out either asthma or COPD.

Box 7-3. Spirometric measures in asthma and COPD

Spirometric variable	Asthma	COPD	Asthma+COPD
Normal FEV_1/FVC pre- or post BD	Compatible with asthma. If patient is symptomatic at a time when lung function is normal, consider alternative diagnosis.	Not compatible with COPD	Not compatible
Reduced post-BD FEV_1/FVC (< lower limit of normal, or <0.7)[76]	Indicates airflow limitation but may improve spontaneously or on treatment	Required for diagnosis of COPD	Required for diagnosis of asthma+COPD
Post-BD FEV_1 ≥80% predicted	Compatible with diagnosis of asthma (good asthma control or interval between symptoms)	Compatible with mild persistent airflow limitation if post-BD FEV_1/FVC is reduced	Compatible with mild persistent airflow limitation if post-BD FEV_1/FVC is reduced
Post-BD FEV_1 <80% predicted	Compatible with diagnosis of asthma. Risk factor for asthma exacerbations	An indicator of severity of airflow limitation and risk of future events (e.g., mortality and COPD exacerbations)	As for COPD and asthma
Post-BD increase in FEV_1 ≧12% and ≥200 mL from baseline (indicates variable expiratory airflow).	Typical of untreated asthma, but may not be present when well controlled or on ICS-containing therapy	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 400 mL from baseline (marked response)	Indicates high probability of asthma	Unusual in COPD	Compatible with asthma+COPD

BD: bronchodilator; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

3: Select initial treatment according to diagnosis (see Box 7-2 (p.134)

For asthma

Commence treatment as described in Section 4, preferably with Track 1 anti-inflammatory reliever therapy with ICS-formoterol reliever (Box 4-4, p.75 and Box 4-5, p.76). Pharmacotherapy is based on ICS to reduce the risk of severe exacerbations and death and to improve symptom control, with add-on treatment (e.g., LABA and/or LAMA) as required.

For COPD

Commence treatment as in the current GOLD strategy report.[76] Pharmacotherapy starts with symptomatic treatment with long-acting bronchodilators (LABA and LAMA). Use of ICS is strongly recommended for patients with hospitalizations in the last year, ≥2 exacerbations/year requiring OCS, or blood eosinophils ≥300/μL, or with a history of asthma or concomitant asthma.[76] However, ICS should not be used alone without LABA and/or LAMA. Inhaled therapy should be optimized to reduce the need for OCS. In patients with features of COPD, high-dose ICS should be avoided because of the risk of pneumonia.[683,684]

For patients with features of asthma and COPD

Start treatment as for asthma (Box 4-4, p.75 and Box 4-5, p.76) until further investigations have been performed.

ICS treatment is essential 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.[685] For patients with asthma+COPD, ICS should be used initially in a low or medium dose (see Box 4-2, p.71), depending on level of symptoms and risk of adverse effects, including pneumonia.

Patients with features or diagnosis of both asthma and COPD will usually also require add-on treatment with LABA and/or LAMA to provide adequate symptom control.

Patients with any features of asthma should not be treated with LABA and/or LAMA alone, without ICS. 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.[661] In another large retrospective longitudinal population cohort study of patients aged ≥66 years, those recorded as having asthma with COPD had lower morbidity and hospitalizations if they received ICS treatment; a similar benefit was seen in those with COPD plus concurrent asthma.[663]

All patients with chronic airflow limitation

Provide advice on the following (see Sections 3, 5, and 6, and the GOLD report):[76]

- 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, pulmonary rehabilitation and vaccinations
- Appropriate self-management strategies
- Regular follow-up.

For most patients, asthma and COPD can initially be managed satisfactorily in primary care. However, referral is recommended for further diagnostic procedures when indicated (see below).[76] Referral may be particularly important for patients with features of both asthma and COPD, given that this is associated with worse outcomes and greater healthcare utilization.

4: Refer for specialized investigations (if necessary)

Referral for expert advice and further diagnostic evaluation (Box 7-4) is advised for patients with:

- Persistent symptoms and/or exacerbations despite treatment
- An uncertain diagnosis, especially when investigations are needed for an alternative diagnosis (e.g., bronchiectasis, post-tuberculous scarring, bronchiolitis, pulmonary fibrosis, pulmonary hypertension, cardiovascular diseases and other causes of respiratory symptoms)
- Suspected asthma or COPD with atypical or additional symptoms or signs (e.g., hemoptysis, significant weight loss, night sweats, fever, signs of bronchiectasis or other structural lung disease) suggest an additional pulmonary diagnosis; these should prompt early referral, without waiting for a trial of treatment for asthma or COPD.
- Suspected chronic airways disease but few syndromic features of either asthma or COPD
- Comorbidities that may interfere with the assessment and management of their airways disease, particularly cardiovascular disease.

Referral may also be appropriate for patients with issues arising during ongoing management of asthma, COPD or asthma+COPD.

Box 7-4. Specialized investigations sometimes used in patients with features of 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
Tests of airway hyperresponsiveness	Not useful on its own in distinguishing asthma from COPD, but marked hyperresponsiveness favors 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
Biomarkers (more details in Appendix A, p.217)		
Tests for atopy (specific IgE and/or skin prick test to aeroallergens)f	Positive test increases probability of allergic asthma; not essential for diagnosis of asthma	Conforms to background prevalence of allergic sensitization; positive test does not rule out COPD
FeNO	A high level (>50 ppb) in non-smokers moderately associated with eosinophilic airway inflammation	Usually normal Low in current smokers
Blood eosinophil count	Eosinophilia supports diagnosis of eosinophilic airway inflammation	Eosinophilia may be present in COPD including during exacerbations
Sputum inflammatory cell count	Role in differential diagnosis is not established in large populations.	

COPD: chronic obstructive pulmonary disease; CT: computed tomography; DLCO: diffusing capacity of the lungs for carbon monoxide; FeNO: fractional exhaled nitric oxide; Ig: immunoglobulin

Unanswered clinical questions

There is an urgent need for more research on this topic to guide better recognition and safe and effective treatment. 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, and from many mechanistic studies.

Future research should include study of clinical and physiological characteristics, biomarkers, outcomes and underlying mechanisms, among broad populations of patients with respiratory symptoms or with chronic airflow limitation. Meanwhile, this section provides interim advice about diagnosis and *initial* treatment, from the perspective of clinicians, particularly those in primary care and nonpulmonary 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.

8. Difficult-to-treat and severe asthma in adults and adolescents

KEY POINTS

What are difficult-to-treat asthma and severe asthma?

Difficult-to-treat asthma is asthma that is uncontrolled despite prescribing of medium or high-dose treatment with the combination of inhaled corticosteroid (ICS) and long-acting beta$_2$-agonist (LABA), or that requires high-dose ICS-LABA 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 to optimized high-dose ICS-LABA 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. It is often associated with multimorbidity.

How should these patients be assessed?

Assess all patients with difficult-to-treat asthma to confirm the diagnosis of asthma, and to identify and manage risk factors and multimorbidity 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-containing therapy (with good adherence and correct inhaler technique), the clinical or inflammatory phenotype should be assessed, as this can guide the selection of add-on treatment.

Management of severe asthma

Although most patients can achieve the goal of long-term well-controlled asthma, some patients' asthma will not be well controlled despite optimized treatment.

Depending on the inflammatory phenotype and other clinical features, add-on treatments for severe asthma include long-acting muscarinic antagonists (LAMAs), leukotriene receptor antagonists (LTRAs), low-dose azithromycin (adults), and biologic agents for severe asthma.

Low-dose maintenance oral corticosteroids (OCS) should be considered only as a last resort if no other options are available, because of their serious cumulative long-term side-effects.

Assess the response to any add-on treatment, stop ineffective treatments, and consider other options.

Utilize specialist multidisciplinary team care for severe asthma, if available. Optimize management of co-morbidities, such as allergic rhinitis, chronic rhinosinusitis with nasal polyps (CRSwNP), and obesity.

For patients with severe asthma, continue to optimize patient care in collaboration with the primary care clinician, and considering the patient's social and emotional needs.

Invite patients with severe asthma to enroll in a registry or clinical trial, if available and relevant, to help fill evidence gaps.

See Boxes 8-2 through 8-5 (starting on p.142) for the GINA severe asthma decision tree.

This section of the GINA report is published separately each year as a GINA short guide for healthcare providers. Other resources for severe asthma management 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 (≥2/year) requiring OCS, or severe exacerbations (≥1/year) requiring hospitalization.

Difficult-to-treat asthma is asthma that is uncontrolled despite prescribing of medium- or high-dose ICS with a second controller (usually a LABA) or with maintenance OCS, or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations.[183] It does not mean a "difficult patient". In many cases, poor control may be due to modifiable factors such as incorrect inhaler technique, poor adherence, smoking or comorbidities, or an incorrect diagnosis.

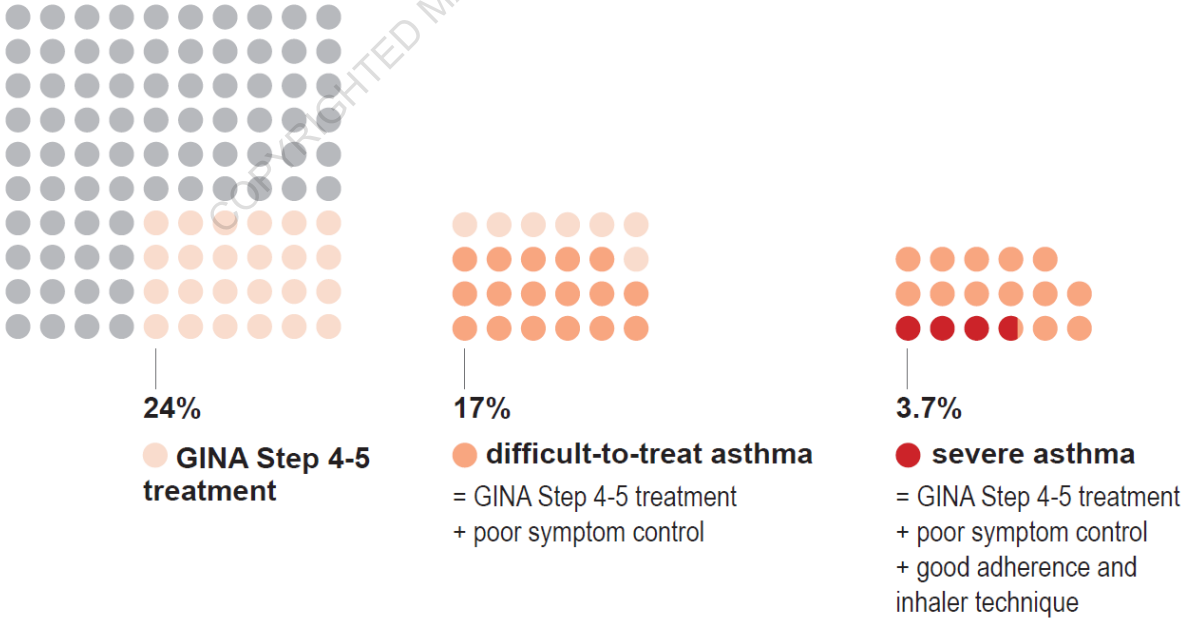
Severe asthma is a subset of difficult-to-treat asthma (Box 8-1). It means asthma that is uncontrolled despite good adherence to maximal optimized high-dose ICS-LABA treatment and management of contributory factors, or that worsens when high-dose treatment is decreased.[183] At present, therefore, "severe asthma" is a retrospective label. It is sometimes called "severe refractory asthma",[183] because 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.[183]

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 high-dose ICS-LABA, or medium or high-dose ICS-LABA plus long-term OCS, who had poor symptom control (by Asthma Control Questionnaire) despite good adherence and inhaler technique (Box 8-1).[686]

Box 8-1. What proportion of adults have difficult-to-treat or severe asthma?



Data from the Netherlands, reported by Hekking et al (2015)[686]

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,[408] which in the past were a mainstay of treatment for severe asthma. Adverse effects of long-term or frequent OCS include obesity, diabetes, osteoporosis and fragility fractures,[622] cataracts, hypertension and adrenal suppression; psychological side-effects such as depression and anxiety are particularly concerning for patients.[687] Even short-term use of OCS is associated with sleep disturbance, and increased risk of infection, fracture and thromboembolism.[592] 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.[687]

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. Severe asthma in adolescents may improve over 3 years in approximately 30% of males and females.[688] The only reported predictor of asthma becoming non-severe is higher baseline blood eosinophils.[688] Studies with longer follow-up time are needed.

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).[689] In a Canadian study, severe uncontrolled asthma was estimated to account for more than 60% of asthma costs.[690]

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.

OVERVIEW OF DECISION TREE FOR ASSESSMENT AND MANAGEMENT OF DIFFICULT-TO-TREAT AND SEVERE ASTHMA

The clinical decision tree (from p.142), summarizes a stage-by-stage, evidence-based approach to investigating and managing difficult-to-treat asthma in adults and adolescents, assessing and treating severe asthma phenotypes, and monitoring/adjusting severe asthma treatment. The decision tree is divided into three broad stages:

Stages 1–4 (green) are for use in primary care and/or specialist care.

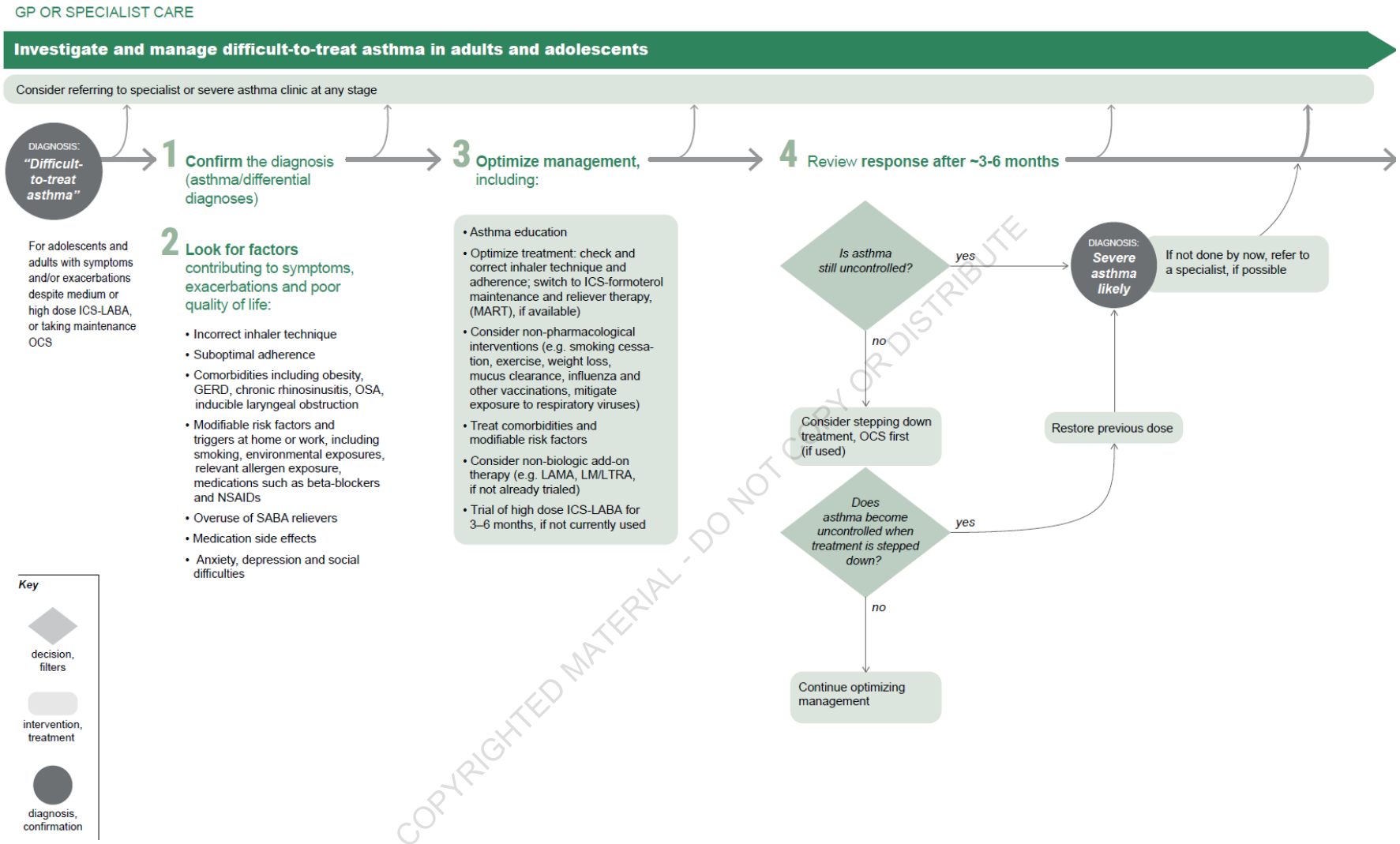
Stages 5–8 (blue) are mainly relevant to respiratory specialists.

Stages 9–10 (brown) are about maintaining ongoing collaborative care between the patient, primary care physician, specialist and other healthcare providers.

The Severe Asthma Guide and decision tree was designed in collaboration with experts in the translation of complex health information into visual formats.

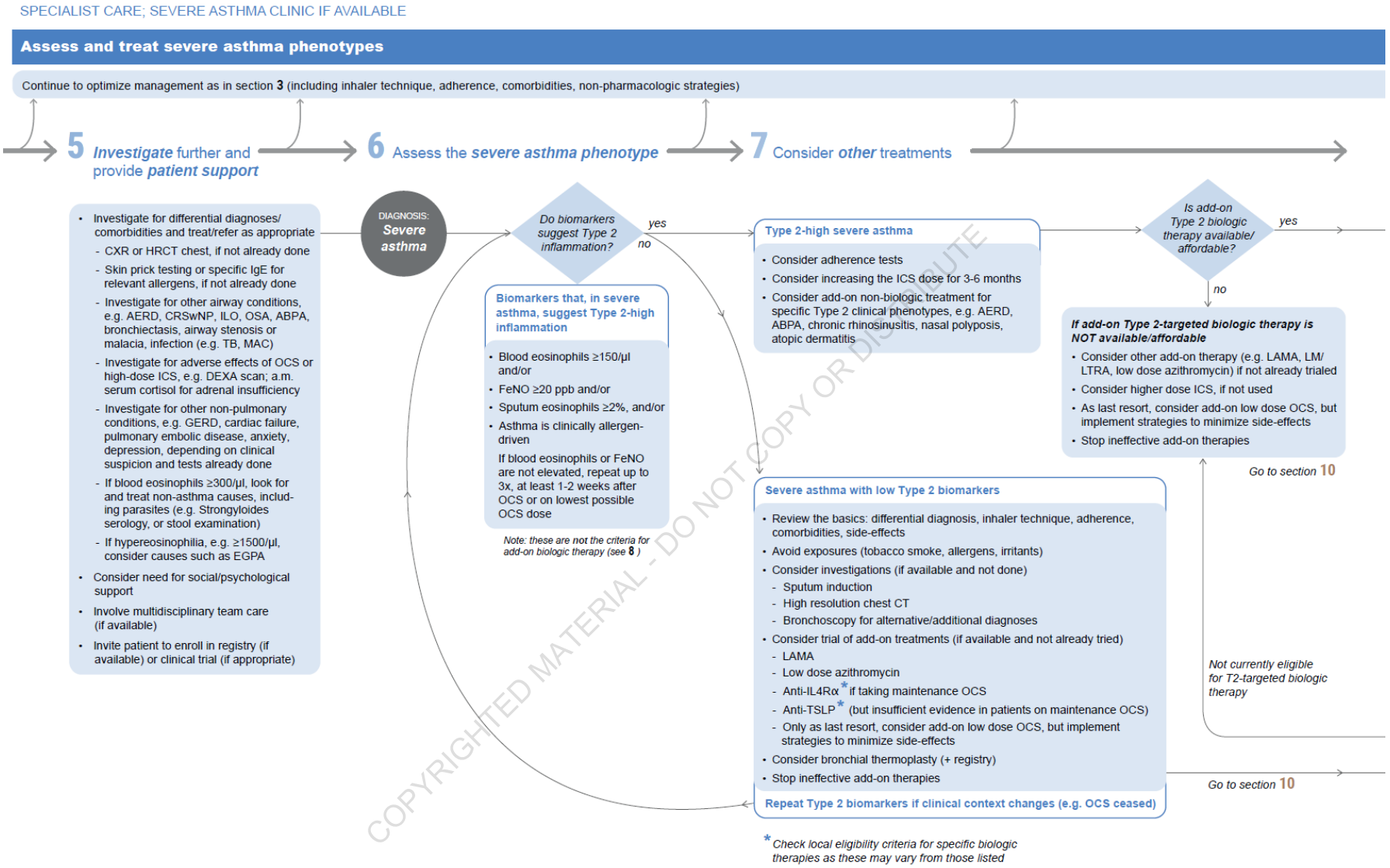
The decision tree is followed by more detailed information on each stage of assessment and management.

Box 8-2. Decision tree – investigate and manage difficult to treat asthma in adult and adolescent patients



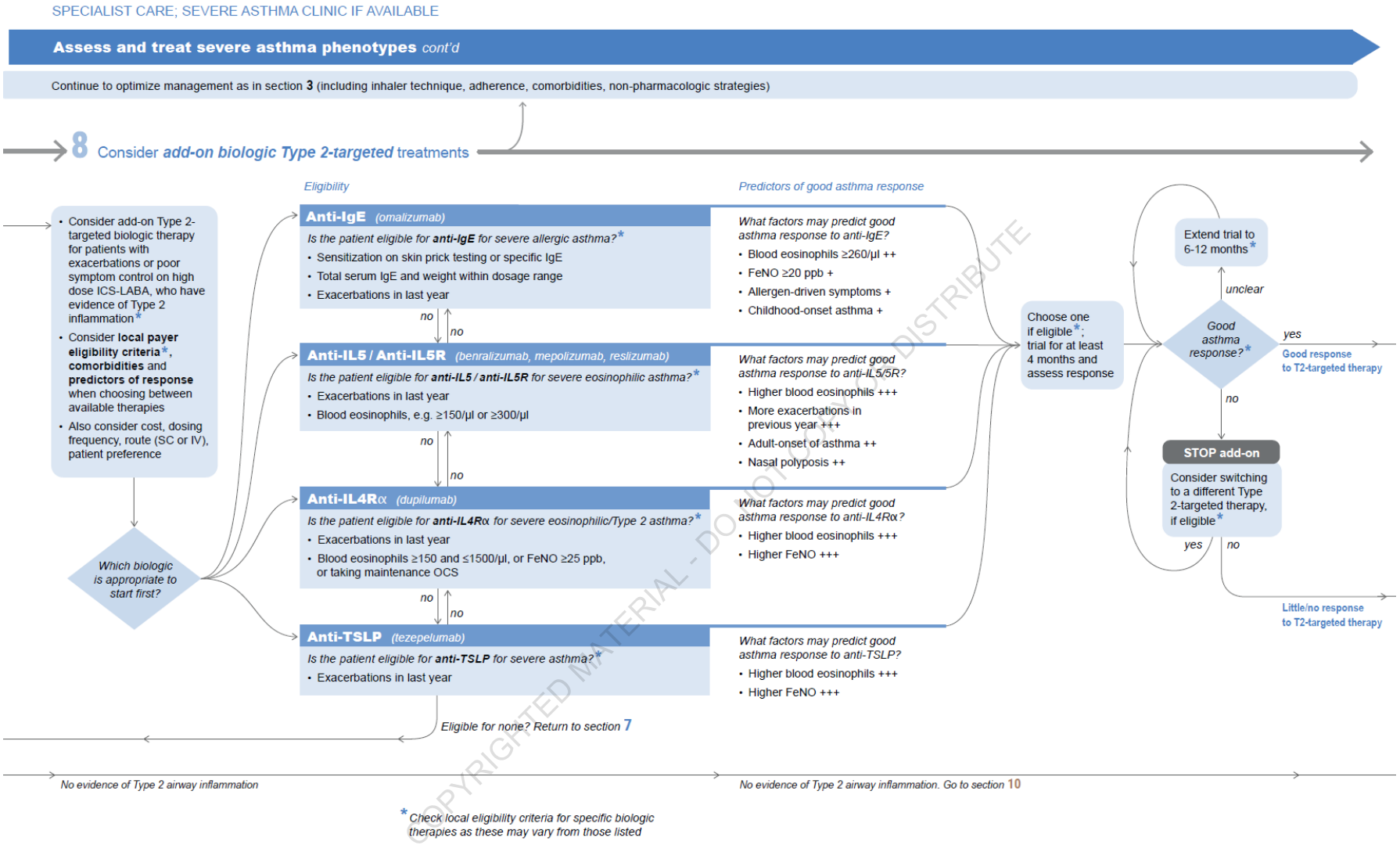
GERD: gastroesophageal reflux disease; ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonists; LM: leukotriene modifiers; LTRA: leukotriene receptor antagonists; MART: maintenance-and-reliever therapy with ICS-formoterol; NSAIDs: non-steroidal anti-inflammatory drugs; OCS: oral corticosteroids; OSA: obstructive sleep apnea; SABA: short-acting beta$_2$-agonist

Box 8-3. Decision tree – assess and treat severe asthma phenotypes



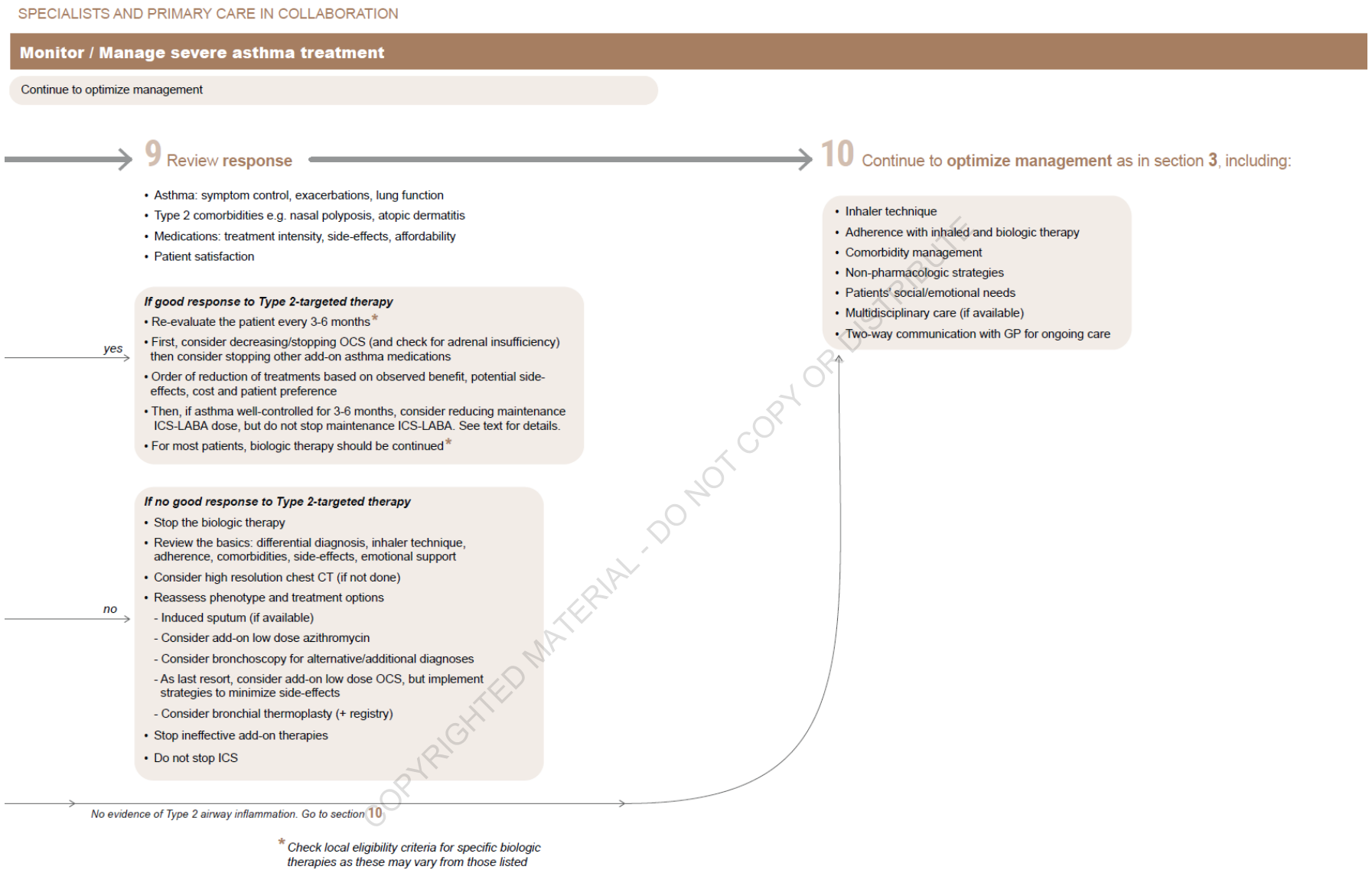
ABPA: allergic bronchopulmonary aspergillosis; AERD: aspirin-exacerbated respiratory disease; CRSwNP: chronic rhinosinusitis with nasal polyps; CXR: chest X-ray; DEXA: Dual-energy X-ray Absorptiometry; EGPA: eosinophilic granulomatosis with polyangiitis; FeNO: fractional exhaled nitric oxide; GERD: gastroesophageal reflux disease; HRCT: high resolution computed tomography; ICS: inhaled corticosteroids; Ig: immunoglobulin; IL: interleukin; ILO: inducible laryngeal obstruction; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonists; MAC: Mycobacterium avium complex; NSAIDs: non-steroidal anti-inflammatory drugs; OCS: oral corticosteroids; OSA: obstructive sleep apnea; SABA: short-acting beta$_2$-agonist; TB: tuberculosis; TSLP: thymic stromal lymphopoietin.

Box 8-4. Decision tree – consider add-on biologic Type 2-targeted treatments



FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroids; Ig: immunoglobulin; IL: interleukin; IV: intravenous; LABA: long-acting beta$_2$-agonist; OCS: oral corticosteroids; SC: subcutaneous; TSLP: thymic stromal lymphopoietin.

Box 8-5. Decision tree – monitor and manage severe asthma treatment



CT: computed tomography; GP: general practitioner/family physician; ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; OCS: oral corticosteroids.

INVESTIGATE AND MANAGE DIFFICULT-TO-TREAT ASTHMA IN ADULTS AND ADOLESCENTS

1. Confirm the diagnosis (asthma or differential diagnoses)

Stages 1–5 can be carried out in primary or specialist care. A patient is classified as having difficult-to-treat asthma if they have persistent asthma symptoms and/or exacerbations despite prescribing of medium- or high-dose ICS with another controller such as LABA, or maintenance OCS, or require high-dose ICS-LABA treatment to maintain good symptom control and prevent exacerbations. Difficult-to-treat asthma 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
- Patient has confirmed food allergy or a history of anaphylaxis, as this increases the risk of death
- Symptoms are suggestive of infective or cardiac cause
- Symptoms are suggestive of complications such as bronchiectasis
- Patient has multimorbidity.

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:

- **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, angiotensin-converting enzyme (ACE) inhibitors
- **Wheeze:** obesity, COPD, tracheobronchomalacia, VCD.

Investigate according to clinical suspicion and age (see Box 1-3, p.27).

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.[691] Perform spirometry, before and after bronchodilator, to assess baseline lung function and seek objective evidence of variable expiratory airflow. If initial bronchodilator responsiveness testing is negative (<200 mL or <12% increase in FEV_1), consider repeating after withholding bronchodilators or when symptomatic, or consider stepping controller treatment up or down before further investigations such as bronchial provocation testing (see Box 1-4, p.30). Check full flow-volume curve to assess for upper airway obstruction. If spirometry is not available, measure peak expiratory flow (PEF) before and after bronchodilator (highest of 3 PEF readings each time); an increase in PEF ≥20% supports the diagnosis of asthma. If spirometry is normal, provide the patient with a peak flow meter and diary for assessing variability; consider bronchial provocation testing if patient is able to withhold bronchodilators (short-acting $beta_2$-agonist [SABA] for at least 6 hours, LABA for up to 2 days depending on duration of action).[40] For more details, see Box 1-2. Strategies for confirming the diagnosis of asthma in patients already taking ICS-containing treatment are shown in Box 1-4 (p.30).

Airflow limitation may be persistent in patients with longstanding 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 5-3, p.112). 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. A FeNO suppression test, i.e., reduced FeNO during a week of high-dose ICS, added to usual maintenance ICS-LABA (p.111), can identify patients with poor adherence.{McNicholl, 2012 #671}[236] Electronic inhaler monitoring, if available, can be helpful in screening for poor adherence, in some cases avoiding the need for biologic therapy.[518]
- *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 (p.117), deconditioning, chronic rhinosinusitis (p.120), inducible laryngeal obstruction, GERD (p.118), COPD (p.133), 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, vaping, 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-steroidal anti-inflammatory drugs (NSAIDs). For allergens, check for sensitization using skin prick testing or specific immunoglobin (Ig) E.
- *Regular use and over-use of SABAs*: Regular SABA use causes beta-receptor down-regulation and reduction in response,[692] leading in turn to greater use. SABA over-use may also be habitual. Dispensing of ≥3 SABA canisters per year (corresponding to average use more than daily) is associated with increased risk of emergency department visit or hospitalization independent of severity,[92,93] and dispensing of ≥12 canisters per year (one a month) is associated with substantially increased risk of death.[93,95] Risks are higher with nebulized SABA.[693]
- *Anxiety, depression and social and economic problems*: These are very common in asthma, particularly in difficult asthma[687] 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 candidiasis 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 at Stage 2:

- *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 asthma 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.[694] Address suboptimal adherence, both intentional and unintentional.[525] Switch to ICS-formoterol maintenance-and-reliever therapy (MART) if available, to reduce the risk of exacerbations.[233] Electronic inhaler monitoring with feedback can improve adherence.[518]
- *Consider non-pharmacological add-on therapy*, e.g., smoking cessation, physical exercise,[243] healthy diet, weight loss, mucus clearance strategies, vaccinations including influenza and RSV (p.106), pulmonary rehabilitation (p.60), breathing exercises (p.63), and allergen avoidance, if feasible, for patients who are sensitized and exposed

(p.61, p.64). For details see text following Box 3-6, p.57. However, **do not delay referral** for specialist assessment if the person has made unsuccessful attempts at smoking cessation and weight loss. Consider exposure mitigation for respiratory viruses (physical distancing from contacts with respiratory infections, mask wearing).

- *Treat comorbidities and modifiable risk factors* identified in Stage 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.118). Avoid medications that make asthma worse (beta-blockers including eye-drops, aspirin and other NSAIDs in patients with aspirin-exacerbated respiratory disease, p.128). Refer for management of mental health problems, if relevant. For more details on multimorbidity, see Section 6 (p.117), including information about treatment of chronic rhinosinusitis with (CRSwNP) and without (CRSsNP) nasal polyps (p.120).
- *Consider trial of non-biologic medication* added to medium dose ICS, e.g., LABA, LAMA, LTRA if not already tried. Note concerns about neuropsychiatric adverse effects with montelukast.[309]
- *Consider short-term (3–6 months) trial of high-dose ICS-LABA* if not currently used.

4. Review response after approximately 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, SABA 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 is likely. 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), checking for adrenal insufficiency, then consider removing other add-on therapy, then decrease ICS dose, but do not stop ICS. See Box 4-13 (p.102) 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 is likely. 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.

INVESTIGATE THE SEVERE ASTHMA PHENOTYPE AND CONSIDER NON-BIOLOGIC THERAPIES

5. Investigate further and provide patient support

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

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:

- Chest X-ray or high resolution CT chest, if not already done
- Allergy testing for clinically relevant allergens: skin prick test or specific IgE, if not already done
- Investigate for other airway/lung conditions, e.g., AERD, CRSwNP, inducible laryngeal obstruction (ILO), obstructive sleep apnea (OSA), allergic bronchopulmonary aspergillosis (ABPA), bronchiectasis, tracheobronchomalacia, and infection (e.g., TB, mycobacterium avian complex (MAC), based on clinical suspicion and other findings
- Bone density scan, because of risk of osteoporosis with maintenance or frequent OCS or long-term high-dose ICS[410]
- Investigate for other adverse effects of OCS or high-dose ICS, e.g., morning serum cortisol for adrenal insufficiency
- Investigate for other non-pulmonary conditions that may be contributing to respiratory symptoms, exacerbations or poor quality of life, e.g., GERD, cardiac failure, pulmonary embolic disease, anxiety, depression, depending on clinical suspicion and tests already done.

If blood eosinophils are ≥300/μL, look for and treat non-asthma causes, including parasites (e.g., Strongyloides serology or stool examination), because parasitic infection may be the cause of the blood eosinophilia, and because OCS or biologic therapy in a patient with untreated parasitic infection could potentially lead to disseminated disease. Strongyloides infection is usually asymptomatic.[695]

If hypereosinophilia is found, e.g., blood eosinophils ≥1500/μL, consider causes such as eosinophilic granulomatosis with polyangiitis (EGPA).

If other causes of the patient's symptoms and exacerbations have been excluded, the diagnosis of severe asthma is confirmed.

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.[687] 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 identification of comorbidities and improves outcomes.[696]

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. Participants in randomized controlled trials designed for regulatory purposes may not necessarily be representative of patients seen in clinical practice. For example, a registry study found that over 80% of patients with severe asthma would have been excluded from key studies evaluating biologic therapy.[383]

6. Assess the severe asthma phenotype

The next stage is to assess the patient's inflammatory phenotype – is there evidence of Type 2 inflammation?

What is Type 2 inflammation?

Evidence of Type 2 inflammation is found in most people with severe asthma. It is often characterized by the presence of cytokines such as interleukin (IL)-4, IL-5 and IL-13, which are produced by the adaptive immune system on recognition of allergens. The adaptive immune system may also be activated by viruses, bacteria and irritants that stimulate it via production of IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) by epithelial cells. Type 2 inflammation is often characterized by elevated sputum and blood eosinophils or increased fractional exhaled nitric oxide (FeNO), and it may be accompanied by atopy and elevated IgE, whereas patients without evidence of Type 2 inflammation often have increased neutrophils.[697]

A single low blood eosinophil count does not rule out Type 2 asthma, and may reflect fluctuating levels. In one study, patients with fluctuating blood eosinophil counts had similar exacerbation rates as those with persistently high levels.[698]

In many patients with asthma, Type 2 inflammation rapidly improves when an ICS is taken regularly and correctly;[236,518] these patients do not have severe asthma. In severe asthma, Type 2 inflammation may be relatively refractory to high-dose ICS. It may respond to OCS, but this should be avoided because of their serious adverse effects.[234,408]

In adult patients with uncontrolled asthma despite medium- or high-dose ICS plus LABA or other controllers, a history of exacerbations in the previous year, higher blood eosinophil counts and higher FeNO levels are associated with a greater risk of severe exacerbations.[14,699] However, there are multiple sources of variation in blood eosinophils[53,700] and in FeNO,[50] which may impact on the ability to document a patient's eligibility for Type 2-directed biologic therapy. (See Appendix A, p.217).

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 ≥150/μL
- FeNO ≥20 ppb
- Sputum eosinophils ≥2%
- 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 at least 1–2 weeks after a course of OCS, or on the lowest possible OCS dose.

There are multiple causes of variation in blood eosinophil count and FeNO, summarized in Appendix A (p.217). These include time of day, with blood eosinophils higher in the morning and FeNO higher in the afternoon (p.217). One study of patients with uncontrolled asthma taking medium- to high-dose ICS-LABA found that 65% had a shift in their blood eosinophil category over 48–56 weeks.[701] Therefore, consider repeating blood eosinophils and FeNO up to 3 times (e.g., when asthma worsens, before giving OCS, or at least 1–2 weeks after a course of OCS, or on the lowest possible OCS dose), before assuming that the patient is not eligible for Type 2-targeted therapy. A pause of even two days in OCS dosing may allow the blood eosinophil count to reach the eligibility threshold.[702]

The above criteria are suggested for initial assessment; those for blood eosinophils and FeNO are based on the 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 stage 8 (p.152) and local regulatory and payer criteria.

Why is the inflammatory phenotype assessed on high-dose ICS?

- Most randomized controlled trial (RCT) evidence about Type 2 targeted biologics is in such patients.
- Modifiable ICS treatment problems such as poor adherence and incorrect inhaler technique are common causes of uncontrolled Type 2 inflammation.
- 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.

7.1. Consider other treatments if there is no evidence of Type 2 inflammation

If the patient has no evidence of persistent Type 2 inflammation (stage 6):

- Review the basics for factors that may be contributing to symptoms or exacerbations: differential diagnosis, inhaler technique, adherence, comorbidities, medication side-effects (stage 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 add-on treatment if available and not already tried (but check local eligibility and payer criteria for specific therapies as they may vary from those listed):
  - LAMA[366]
  - Low-dose azithromycin (adults),[388,389] but first check sputum for atypical mycobacteria, check ECG for long QTc (and re-check after a month on treatment), and consider potential for antibiotic resistance.
  - Anti-IL4Rα if taking maintenance OCS (see stage 8 for more details)
  - Anti-thymic stromal lymphopoietin (TSLP) (but insufficient evidence in patients taking maintenance OCS; see stage 8 for more details).
  - As a last resort, consider add-on low-dose OCS, but implement strategies with this such as alternate-day treatment to help reduce the dose further and minimize side-effects.
- Consider bronchial thermoplasty, with registry enrollment. However, the evidence for efficacy and long-term safety is limited.[157,477]
- Stop ineffective add-on therapies.
- Continue to optimize treatment, including inhaler technique, adherence, non-pharmacologic strategies and treating comorbidities (see stages 3 and 10).
- Repeat Type 2 biomarkers if the clinical context changes, e.g., cessation or reduction in OCS dose.

7.2. Consider non-biologic options if there is evidence of Type 2 inflammation

For patients with elevated Type 2 biomarkers despite high-dose ICS (see stage 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,[703] or electronic inhaler monitoring.[504] Suppression of high FeNO after 5 days of directly observed therapy is an indicator of past poor adherence,[236] and was found in almost two-thirds of patients with difficult-to-treat asthma.[506] In one study, electronic monitoring of adherence and inhaler technique, with feedback to patients, improved adherence and reduced the proportion of patients who needed escalation to biologic therapy.[518]
- *Consider increasing the ICS dose for 3–6 months*, and review again.
- *Consider add-on non-biologic treatment for specific Type 2 clinical phenotypes* (see Section 6, p.117). For example, for aspirin-exacerbated respiratory disease (AERD), consider add-on LTRA and possibly aspirin desensitization (p.128). For allergic bronchopulmonary aspergillosis (ABPA), consider add-on OCS ± anti-fungal agent (p.129). For chronic rhinosinusitis with or without nasal polyps, consider intensive intranasal corticosteroids; surgical advice may be needed (p.120). For patients with atopic dermatitis, topical steroidal or non-steroidal

therapy may be helpful. Allergen immunotherapy may sometimes be used in severe asthma, but only after asthma has been well controlled, to minimize the risk of severe adverse reactions. Allergen immunotherapy extracts for subcutaneous immunotherapy (SCIT) should only be prepared and administered by clinicians skilled in immunotherapy (see p.104).

7.3. Is Type 2-targeted biologic therapy available and affordable?

If NOT:

- Consider higher dose ICS-LABA, if not used.
- Consider other add-on therapy, e.g., LAMA, LTRA, low-dose azithromycin, if not already used.
- As last resort, consider add-on low-dose OCS, but implement strategies to minimize side-effects.
- Stop ineffective add-on therapies.
- Continue to optimize treatment, including inhaler technique, adherence, non-pharmacologic strategies and treating comorbidities (see stages 3 and 10).

CONSIDER TYPE 2-TARGETED BIOLOGIC THERAPIES

8. Consider add-on biologic Type 2-targeted treatments

If available and affordable, consider an add-on Type 2 targeted biologic for patients with exacerbations and/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 treatment (see stage 5).

Consider whether to start first with anti-IgE, anti-IL5/5Rα, anti-IL4Rα or anti-TSLP. When choosing between available therapies, consider the following:

- Does the patient satisfy local payer eligibility criteria?
- Type 2 comorbidities such as atopic dermatitis, nasal polyps
- Clinical history suggesting allergen-triggered symptoms
- Predictors of asthma response (see below)
- Cost
- Dosing frequency
- Delivery route (IV or SC; potential for self-administration)
- Patient preference.

Always check local payer eligibility criteria for biologic therapy, as they may vary substantially. However, GINA recommends the use of biologic therapy only for patients with severe asthma, and only after treatment has been optimized. 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. Omalizumab injections contain polysorbate, which may induce allergic reactions in some patients. GINA suggests that the **first** dose of asthma biologic therapy should not be given on the same day as a vaccine, so that adverse effects of either can be more easily distinguished.

Provide practical advice for patients, e.g., allow the refrigerated syringe or pen to come to room temperature before injecting the biologic, as this reduces pain.

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

Regulatory approvals may include: omalizumab for ages ≥6 years, given by SC injection every 2–4 weeks, with dose based on weight and serum IgE. May also be indicated for nasal polyps, chronic spontaneous (idiopathic) urticaria, and IgE-mediated food allergy. Self-administration may be an option. Check local payer criteria, as they may differ from these.

Mechanism: binds to Fc part of free IgE, preventing binding of IgE to FcƐR1 receptors, reducing free IgE and down-regulating receptor expression.

Eligibility criteria (in addition to criteria for severe asthma) may vary between payers or by age-group, but often 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.

Outcomes: Meta-analysis of RCTs in severe allergic asthma: anti-IgE led to 44% decrease in severe exacerbations, and improved quality of life; improvements in symptom control and lung function were statistically significant but less than clinically important differences.[391] No double-blind randomized controlled trials of OCS-sparing effect. In a meta-analysis of observational studies in patients with severe allergic asthma, there was a 59% reduction in exacerbation rate, a 41% reduction in the proportion of patients receiving maintenance OCS, and a significant improvement in symptom control.[704] In patients with nasal polyps, omalizumab improved subjective and objective nasal outcomes.[578] Additional details about treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) are found on p.120. A registry study of omalizumab in pregnancy found no increased risk of congenital malformations.[614]

Potential predictors of good asthma response to omalizumab:

- Baseline IgE level does not predict likelihood of response.[705]
- Type 2 biomarkers: In a post-hoc analysis of one clinical trial, a greater decrease in exacerbations was observed (compared with placebo) with blood eosinophils ≥260/µL[706,707] or FeNO ≥19.5 ppb[706] (these criteria representing their median value in that study) but in two large observational studies, exacerbations were reduced with both low or high blood eosinophils[708-710] or with both low or high FeNO.[710]
- Childhood-onset asthma
- Clinical history suggesting allergen-driven symptoms.

Adverse effects: injection site reactions, anaphylaxis in approximately 0.2% patients[711] In adults, long-term safety and efficacy of omalizumab have been reported for more than 5 years of treatment.[712]

Suggested initial trial: at least 4 months

Add-on anti-IL5 or anti-IL5Rα for severe eosinophilic asthma

Regulatory approvals may include:

- For ages ≥12 years: mepolizumab (anti-IL5), 100 mg by SC injection every 4 weeks, or benralizumab (anti-IL5 receptor α), 30 mg by SC injection every 4 weeks for 3 doses then every 8 weeks
- For ages ≥18 years: reslizumab (anti-IL5), 3 mg/kg by IV infusion every 4 weeks
- For ages 6–11 years, mepolizumab (anti-IL5), 40 mg by SC injection every 4 weeks.

Mepolizumab and benralizumab may also be indicated for EGPA, and mepolizumab also for hypereosinophilic syndrome and chronic rhinosinusitis with nasal polyps. Self-administration may be an option. Check local payer criteria, as they may differ from these.

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 (in addition to criteria for severe asthma): 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 locally specified level (e.g., ≥150 or ≥300/μL). There is sometimes a different eosinophil cut-point for patients taking OCS.

Outcomes: Meta-analysis of RCTs in severe asthma patients with exacerbations in the last year, with varying eosinophil criteria: anti-IL5 and anti-IL5Rα led to 47–54% reduction in severe exacerbations. Improvements in lung function and symptom control were statistically significant,[397] but less than clinically important differences. There was a clinically important improvement in quality of life with mepolizumab.[397] All anti-IL5/5Rα biologics reduced blood eosinophils; almost completely with benralizumab.[713] In post hoc analyses, clinical outcomes with mepolizumab or benralizumab were similar in patients with eosinophilic asthma with and without an allergic phenotype.[714,715] However, in patients with non-severe younger-onset allergic asthma, mepolizumab and benralizumab did not attenuate either the allergen-induced early or late asthmatic response, or airway hyperresponsiveness to methacholine.[716] In patients taking OCS, median OCS dose was able to be reduced by approximately 50% with mepolizumab[717] or benralizumab,[395] compared with placebo. In urban children aged 6 years and older with eosinophilic exacerbation-prone asthma, an RCT showed a reduction in the number of exacerbations with subcutaneous mepolizumab versus placebo.[396] No differences were seen in lung function, a composite asthma score (CASI), or physician–patient global assessment.[396] In patients with nasal polyps, mepolizumab improved subjective and objective outcomes and reduced the need for surgery,[579,580] and in patients with nasal polyps and severe eosinophilic asthma, benralizumab improved subjective outcomes for both conditions and improved quality of life.[718] See p.120 for more details about treatment of nasal polyps.

Potential predictors of good asthma response to anti-IL5 or anti-IL5Rα:

- Higher blood eosinophils (strongly predictive)[719]
- Higher number of severe exacerbations in previous year (strongly predictive)[719]
- Adult-onset asthma[720]
- Nasal polyps[715]
- Maintenance OCS at baseline[715]
- Low lung function (FEV_1 <65% predicted) in one study.[721]

Adverse effects: In adults, injection site reactions, anaphylaxis rare, adverse events generally similar between active and placebo. In children, more skin/subcutaneous tissue and nervous system disorders (e.g., headache, dizziness, syncope) were seen with mepolizumab than placebo.[396] In adults, long-term safety and efficacy of mepolizumab and benralizumab have been reported for more than 5 years of treatment.[722,723]

Suggested initial trial: at least 4 months

Add-on anti-IL4Rα for severe eosinophilic/Type 2 asthma or patients requiring maintenance OCS

Regulatory approvals may include: For ages ≥12 years: dupilumab (anti-IL4 receptor α), 200 mg or 300 mg by SC injection every 2 weeks for severe eosinophilic/Type 2 asthma; 300 mg by SC injection every 2 weeks for OCS-dependent severe asthma or if there is concomitant moderate/severe atopic dermatitis or CRSwNP. For children 6–11 years with severe eosinophilic/Type 2 asthma by SC injection, with dose and frequency depending on weight. May also be indicated for treatment of skin conditions including moderate-to-severe atopic dermatitis, and for chronic rhinosinusitis with nasal polyps, COPD with chronic bronchitis and elevated blood eosinophils, and eosinophilic esophagitis. Self-administration may be an option. Check local payer criteria, as they may differ from these.

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

Eligibility criteria (in addition to criteria for severe asthma): these may vary between payers or by age-group, but often 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 ≥150/μL and ≤1500/μL, or FeNO ≥25 ppb) OR requirement for maintenance OCS.

Outcomes: Meta-analysis of RCTs in patients with uncontrolled severe asthma (ACQ-5 ≥1.5) and at least one exacerbation in the last year: anti-IL4Rα led to 56% reduction in severe exacerbations; improvements in quality of life, symptom control and lung function were statistically significant,[400] but less than the clinically important differences. In a post hoc analysis, clinical outcomes were similar in patients with allergic and non-allergic phenotype at baseline.[724] In patients with OCS-dependent severe asthma, without minimum requirements for blood eosinophil count or FeNO, the median reduction in OCS dose with anti-IL4Rα versus placebo was 50%.[725] Changes were maintained through 2 years of follow-up.[726] In children 6–11 years with eosinophilic/Type 2 asthma, dupilumab reduced severe exacerbation rate and increased lung function; children taking maintenance OCS were excluded.[401] In patients with chronic rhinosinusitis with nasal polyps, dupilumab improved subjective and objective outcomes and reduced the need for OCS or for sinus surgery.[581,727] See p.120 for more details about nasal polyps.

Potential predictors of good asthma response to dupilumab:

- Higher blood eosinophils (strongly predictive)[398] including in children[728]
- Higher FeNO (strongly predictive).[398] including in children.[728]

Adverse effects: injection-site reactions; transient blood eosinophilia (occurs in 4–13% of patients); rare cases of EGPA may be unmasked following reduction/cessation of OCS treatment on dupilumab. Anti-IL4Rα is not suggested for patients with baseline or historic blood eosinophils >1,500 cells/μL because of limited evidence (such patients were excluded from Phase III trials). In adults, safety and efficacy of dupilumab have been reported for over 5 years of treatment, and in children, for up to 2 years.[729]

Suggested initial trial: at least 4 months

Add-on anti-TSLP for severe asthma

Regulatory approvals may include: For ages ≥12 years: tezepelumab (anti-TSLP), 210 mg by SC injection every 4 weeks. Self-administration may be an option. Check local payer criteria, as they may differ from these.

Mechanism: Tezepelumab binds circulating TSLP, a bronchial epithelial cell-derived alarmin implicated in multiple downstream processes involved in asthma pathophysiology.

Eligibility criteria (in addition to criteria for severe asthma): These vary between payers, but usually include severe exacerbations in the last year.

Anti-TSLP may also be considered in patients with no elevated Type 2 markers (Stage 7.1).

Outcomes: In two RCTs in severe asthma patients with severe exacerbations in the last year, anti-TSLP led to 30–70% reduction in severe exacerbations, and improved quality of life, lung function and symptom control, irrespective of allergic status.[402,403] There was a clear correlation between higher baseline blood eosinophils or FeNO and better clinical outcomes.[403] In patients taking maintenance OCS, anti-TSLP did not lead to a reduced OCS dose, compared with placebo.[404]

Potential predictors of good asthma response to anti-TSLP:

- Higher blood eosinophils (strongly predictive)
- Higher FeNO levels (strongly predictive).

Adverse effects: Injection site reactions, anaphylaxis is rare, adverse events generally similar between active and placebo groups. In adults, safety and efficacy of tezepelumab have been reported over up to 2 years of treatment.[730]

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, treatment intensity (including OCS dose), and patient satisfaction.
- If the response is unclear, consider extending the trial to a total of 6–12 months.
- Monitor for potential adverse events, including for infections
- 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. Also consider the patient's biomarkers (interval and during exacerbations, if available), and response of any comorbid Type 2 conditions (atopic dermatitis, nasal polyps etc). Review response as above.

ASSESS, MANAGE AND MONITOR ONGOING SEVERE ASTHMA TREATMENT

9. Review response and implications for treatment

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

- Asthma: symptom control, both recent e.g., with validated tools such as Asthma Control Test (4 weeks) and Asthma Control Questionnaire (ACQ-5, 1 week), and over the whole period since last review, frequency and severity of exacerbations (including whether OCS were needed); lung function
- Any change in relevant Type 2 comorbidities, e.g., nasal polyps, atopic dermatitis
- Medications: treatment intensity, including courses of OCS and dose of any maintenance OCS, side-effects, affordability
- Patient satisfaction.

The goals of management (Box 3-3, p.52) are to achieve the best possible outcomes for the individual, including long-term symptom control and long-term asthma risk minimization. For patients with a good response to treatment for severe asthma, this may include clinical remission on treatment (p.50).

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 emphasize to patients and their primary care physician that they should not completely stop ICS-containing therapy. Base the order of reduction or cessation of add-on treatments on potential adverse effects, the observed benefit when the medication was started, patient risk factors, cost, and patient satisfaction. Minimizing the use of OCS is a very high priority.

After reducing/ceasing any medication, confirm asthma stability before making any further treatment changes.

For oral treatments, gradually decrease or stop OCS first, because of their significant adverse effects. Tapering of OCS in severe asthma may be supported by internet-based monitoring of symptom control and FeNO.[731] Monitor patients for risk of adrenal insufficiency by measuring morning serum cortisol, and provide patient and primary care physician 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.[410]

If asthma remains well controlled, consider reducing or ceasing other therapies, based on the above considerations.

For inhaled treatments, consider ceasing add-on inhaled therapy such as LAMA before reducing ICS-LABA dose. Reduction in dose of ICS-containing therapy may be considered after asthma has been well controlled on biologic therapy for at least 3–6 months and stability has been confirmed after any other medication changes. However, do not completely stop ICS-containing therapy. Previous advice based on consensus was to continue at least medium-dose ICS-LABA. In an open-label study in patients with good symptom control on anti-IL5Rα, most of those randomized to MART with ICS-formoterol were able to have their maintenance ICS-formoterol dose gradually reduced (and in some cases stopped, continuing as-needed-only ICS-formoterol) without exacerbations.[385] However, patients who ceased maintenance ICS-formoterol treatment demonstrated evidence of under-dosing with ICS, with reduction in lung function and increase in FeNO, suggesting that in patients with severe asthma, maintenance ICS-containing therapy should not be stopped completely.[385] Any reduction in ICS dose should be considered as a treatment trial and the previous dose reinstated if deterioration occurs (Box 4-13, p.102). Remind patients it is important to continue their maintenance ICS-containing treatment.

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-containing therapy, and (for allergic asthma) there is no further exposure to a previous well-documented allergic trigger. There are few studies of cessation of biologic therapy,[732-734] in these studies, symptom control worsened and/or exacerbations recurred for many (but not all) patients after cessation of the biologic. For example, in a double-blind randomized controlled trial, significantly more patients who stopped mepolizumab experienced a severe exacerbation within 12 months than those who continued treatment. In this study, there was a small increase in ACQ-5 but no significant difference in symptom control between groups.[735]

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

Stop the biologic therapy.

Review the basics for factors contributing to symptoms, exacerbations and poor quality of life (see Section 2): diagnosis/differential 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 bronchoscopy for alternative or additional diagnoses, consider referral if available, including for diagnosis of alternative conditions.

Reassess treatment options (if not already done), such as:

- Add-on low-dose azithromycin[388,389] (adults only; first check sputum for atypical mycobacteria and check ECG for long QTc (and re-check after a month on treatment); consider potential for antibiotic resistance)
- As last resort, consider add-on low-dose maintenance OCS, but implement strategies such as alternate-day therapy; add bisphosphonate to minimize side-effects on bones,[410] 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.

10. Continue collaborative optimization of patient care

Ongoing management of a patient with severe asthma involves a collaboration between the patient, the primary care physician, specialist(s), and other healthcare providers, to optimize clinical outcomes and patient satisfaction. Continue pharmacologic and non-pharmacologic (p.59) management to achieve the goal of obtaining the best outcomes for the individual patient (p.50).

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

- Clinical asthma measures (symptom control, exacerbations, lung function)
- Comorbidities
- 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, and optimize comorbidity management and non-pharmacologic strategies)
- The patient's social and emotional needs.

The optimal frequency and location of review (primary care physician 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 with the family physician and other members of the health care team 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.

9. Management of worsening asthma and exacerbations in adults, adolescents and children 6–11 years

KEY POINTS

Terminology

- 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 terms "flare-up" and "severe flare-up" are suitable 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 (i.e., printed, digital or pictorial) asthma action plan appropriate for their age, their current treatment regimen and their reliever inhaler (combination inhaled corticosteroid [ICS]-formoterol, short-acting beta$_2$-agonist [SABA], or combination ICS-SABA), their level of asthma control, and their 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/or maintenance medications, use oral corticosteroids (OCS) if needed, 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 if their asthma starts to worsen.
- Base the action plan on changes in symptoms; in adults, peak expiratory flow (PEF) can also be included.

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 (usually PEF), while starting SABA and oxygen therapy. Oxygen saturation targets should be adjusted for altitude, where appropriate.
- 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 [pMDI] and spacer), early introduction of oral corticosteroids, and controlled flow oxygen if available and required. Review response of symptoms, oxygen saturation and lung function after 1 hour. Give ipratropium bromide and systemic corticosteroids for moderate or 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.

Discharge management

- Arrange ongoing treatment before the patient goes home, train the patient in how to use the inhaler(s), and provide a supply if possible. For all patients, start or continue ICS-containing treatment, and reduce reliever medication to as-needed use.
- For patients using SABA as reliever before the exacerbation, consider switching their treatment regimen to maintenance-and-reliever therapy with ICS-formoterol (MART, Track 1, p.77), to reduce the risk of future exacerbations. If MART is not available, start ICS-LABA at medium dose or increase the current ICS-LABA dose to medium for up to 2–4 weeks.
- Patients using an anti-inflammatory reliever (e.g., ICS-formoterol) before the exacerbation should resume or continue this instead of SABA reliever before or on discharge. If the patient was previously using maintenance-

and-reliever therapy (MART) with ICS-formoterol, they should resume MART. If the patient was previously using as-needed-only ICS-formoterol (AIR-only), they should be stepped up to MART, i.e., add maintenance ICS-formoterol. There is no need to prescribe or provide SABA for patients prescribed ICS-formoterol reliever.

Arrange early follow-up after any exacerbation, regardless of where it was managed.

At follow-up:

- Review the patient's symptom control and risk factors for further exacerbations.
- Prescribe ongoing ICS-containing therapy to reduce the risk of further exacerbations. If already taking ICS-containing therapy, continue increased doses for 2–4 weeks, but do not stop ICS-containing therapy.
- Provide a written asthma action plan and, where relevant, advice about avoiding exacerbation triggers, including e.g., relevant vaccinations
- Check inhaler technique and adherence.

For management of asthma exacerbations in children 5 years and younger, see Section 12 (p.201).

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.[37] 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[104] or pollution) and/or poor adherence to ICS-containing medication, but onset can be more acute and without known exposure to risk factors in some patients.[736,737] Severe exacerbations can occur in patients with mild or well-controlled asthma symptoms.[27,321] Box 2-2B (p.37) lists factors that increase a patient's risk of exacerbations, independent of their level of symptom control.

Common exacerbation triggers include:

- Viral respiratory infections,[738] e.g., rhinovirus, influenza, adenovirus, pertussis, respiratory syncytial virus
- Allergen exposure e.g., grass pollen and other pollens,[104,301] soybean dust,[302] fungal spores
- Food allergy[100]
- Outdoor air pollution[107,108,739]
- Seasonal changes and/or returning to school in fall (autumn)[740]
- Poor adherence to ICS[741]
- 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,[300] and with environmental exposure to soybean dust.[302]

Identifying patients at risk of asthma-related death

In addition to factors known to increase the risk of asthma exacerbations (Box 2-2, p.37), some features are specifically associated with an increase in the risk of asthma-related death (Box 9-1, p.161). 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 9-1. Factors associated with increased risk of asthma-related death

- A history of near-fatal asthma requiring intubation and mechanical ventilation[742]
- Hospitalization[742,743] or emergency care visit for asthma in the past year
- Currently using or having recently stopped using oral corticosteroids (a marker of event severity)[95,742]
- Not currently using inhaled corticosteroids[96,742]
- Over-use of short-acting beta$_2$-agonists (SABA), especially use of an average of more than one canister of salbutamol (or equivalent) per month,[93,117,744] or using nebulized SABA[745]
- Poor adherence to ICS-containing medications and/or poor adherence to (or lack of) a written asthma action plan[109]
- A history of psychiatric disease or psychosocial problems[109]
- Food allergy in a patient with asthma[564,746]
- Certain comorbidities, including pneumonia, diabetes and arrhythmias (independently associated with an increased risk of death after hospitalization for an asthma exacerbation)[743]

ICS: inhaled corticosteroids; SABA: short-acting beta$_2$-agonist

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.[747,748] 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 healthcare providers but with widely varying meanings, and it may not be perceived as including gradual worsening.[747,748] In pediatric literature, the term “episode” is commonly used, but understanding of this term by parent/caregivers is not known.

DIAGNOSIS OF EXACERBATIONS

Exacerbations represent a change in symptoms and lung function from the patient’s usual status.[37] The decrease in expiratory airflow can be quantified by lung function measurements such as PEF or forced expiratory volume in 1 second (FEV_1),[749] 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.[750] Consider the possibility of pertussis in a patient with an atypical exacerbation presentation in which cough is the predominant symptom.

A minority of patients perceive airflow limitation poorly and can experience a significant decline in lung function without a change in symptoms.[159,172,180] This especially affects patients with a history of near-fatal asthma and also appears to be more common in males. Regular PEF monitoring may be considered for such patients.

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 healthcare 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, and parents/caregivers of children with asthma, should be provided with guided self-management education as described in Section 5 (p.108). The definition of guided self-management education includes monitoring of symptoms and/or lung function, a written asthma action plan, and regular review by a healthcare provider.[535] (For children 5 years and younger, see Section 11, p.189).

A written (i.e., documented) asthma action plan may be printed, digital, or pictorial, to suit the patient’s needs and literacy.

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/or maintenance medications, when and how to use OCS if needed (Box 9-2, p.163) and when and how to access medical care.

Use an action plan template appropriate for the patient's reliever: ICS-formoterol, ICS-SABA, or SABA.

- For patients prescribed an anti-inflammatory reliever (as-needed combination ICS-formoterol or ICS-SABA), the patient should take extra doses of their reliever when needed for symptom relief, and continue their usual dose of maintenance ICS-containing treatment. The anti-inflammatory reliever provides extra ICS without delay as well as extra rapid-acting bronchodilator whenever the reliever is used. This significantly reduces the risk of progressing to a severe exacerbation and the need for OCS compared with using a SABA reliever (p.78). In the case of as-needed ICS-formoterol, both the ICS and the formoterol contribute to the reduction in severe exacerbations, compared with using a SABA reliever.[415] See Box 4-8 (p.84) for more details about as-needed ICS-formoterol, including medications and dosages.
- For patients prescribed ICS-containing treatment with a SABA reliever, the criteria for initiating an increase in maintenance medication will vary from patient to patient. In studies that evaluated an increase in maintenance ICS-containing treatment, this was usually initiated when there was a clinically important change from the patient's usual level of asthma control, for example, if asthma symptoms were interfering with normal activities, or PEF had fallen by >20% for more than 2 days.[540]

A specific action plan template is available for patients prescribed maintenance-and-reliever therapy with ICS-formoterol.[327] This template can also be adapted for patients prescribed as-needed-only ICS-formoterol.

Box 9-2. Medication options for written asthma action plans

Track & step	Usual asthma treatment	Short-term action plan change (1–4 weeks) for worsening asthma	Evidence level
GINA Track 1 with ICS-formoterol reliever*			
Steps 1–2	As-needed-only ICS-formoterol (AIR-only)	For symptom relief, use 1 inhalation of ICS-formoterol (e.g., budesonide-formoterol 200/6 [160/4.5] mcg or BDP-formoterol 100/6 mcg) whenever needed. Maximum 12 inhalations in any 24-hour period.	A
Steps 3–5	Maintenance and reliever therapy (MART) with ICS-formoterol	Continue usual maintenance dose of ICS-formoterol. For symptom relief, use 1 inhalation of ICS-formoterol whenever needed. Maximum total 12 inhalations in any 24-hour period (as-needed + maintenance doses).	A
GINA Track 2 with combination ICS-SABA reliever#			
Step 1	As-needed-only combination ICS-SABA	For symptom relief, take 2 inhalations of ICS-SABA as needed. Do not take more than 6 doses (12 inhalations) in any 24-hour period.	B
Step 2	Maintenance ICS	Continue usual maintenance ICS dose. For symptom relief, take 2 inhalations of ICS-SABA as needed. Do not take more than 6 doses (12 inhalations) of ICS-SABA in any 24-hour period.	A
Steps 3–4	Maintenance ICS-LABA	Continue usual maintenance ICS-LABA dose. For symptom relief, take 2 inhalations of ICS-SABA as needed. Do not take more than 6 doses (12 inhalations) of ICS-SABA in any 24-hour period.	B
GINA Track 2 with SABA reliever			
Step 1	As-needed SABA plus ICS (separate inhalers)	For symptom relief, use SABA as below, and take ICS whenever SABA is taken (e.g., 1 inhalation of BDP 40 mcg per inhalation of SABA).	B
Step 2	Maintenance ICS	Consider quadrupling maintenance dose of ICS for 1–2 weeks. For symptom relief with SABA, see below.	B
Steps 3–4	Maintenance ICS-formoterol	Consider quadrupling maintenance dose of ICS-formoterol for 1–2 weeks. For symptom relief with SABA, see below.	B
	Maintenance ICS-LABA (non-formoterol)	Consider stepping up to higher dose formulation of ICS-LABA, if available. In adults, consider adding a separate ICS inhaler to quadruple ICS dose. For symptom relief with SABA, see below.	D
Reliever	As-needed SABA	For symptom relief, take 2 inhalations of SABA every 4–6 hours if needed. More frequent use or more inhalations of SABA is not recommended.	-
Severe exacerbations – all regimens			
All steps	• For severe exacerbations, e.g., PEF or FEV1 <60% personal best or predicted), or if not responding to above treatment over 2–3 days, consider adding short-course of oral corticosteroids. After first dose, morning dosing is preferable to minimize insomnia. Advise patients about potential adverse effects. • Usual dose of prednisolone: adults/adolescents, 40–50 mg/day for 5–7 days; children, 0.5 mg/kg/day, maximum 40 mg/day, for 3–5 days. See text for other systemic corticosteroid options. • Tapering not needed if OCS taken for less than 2 weeks • After any exacerbation, review triggers and risk factors including adherence and inhaler technique, and review the patient's action plan. Switch to Track 1 if possible to reduce the risk of further exacerbations. See Box 9-5 (p.171) for more details about post-exacerbation review.	A B B B

AIR: anti-inflammatory reliever; BDP: beclometasone dipropionate; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; LABA: long-acting $beta_2$-agonist; MART: maintenance-and-reliever therapy with combination ICS-formoterol; OCS: oral corticosteroids; PEF: peak expiratory flow; SABA: short-acting $beta_2$-agonist.

*See Box 4-8 (p.84) for details of other medications for GINA Track 1 with ICS-formoterol.
Combination budesonide-salbutamol (albuterol) 2 puffs of 100/100 mcg (delivered dose 80/90 mcg).

See text for more details about action plan options in adults, adolescents and children.

Treatment options for written asthma action plans – relievers

Inhaled combination ICS-formoterol reliever

In adults and adolescents, use of as-needed combination low-dose ICS-formoterol for symptom relief (without maintenance treatment) reduces the risk of severe exacerbations requiring OCS or requiring emergency department visit or hospitalization by 65%, compared with SABA-only treatment.[191] It also reduces the risk of needing an emergency department visit or hospitalization by 37%, compared with daily ICS plus as-needed SABA.[191] In a large 12-month RCT, after a day of even small increased doses of as-needed ICS-formoterol, the risk of severe exacerbation in the following 3 weeks was reduced, compared with using the same doses of SABA alone.[134] Details of the evidence are found on p.79 and p.81.

In adults, adolescents and children 6–11 years, maintenance-and-reliever therapy (MART) with very low- or low-dose ICS-formoterol reduces the risk of severe exacerbations, compared with the same or higher dose of ICS or ICS-LABA, with similar symptom control.[233,235,423] Details about the evidence are found on p.98 and p.99.

Information about medications and doses for use of as-needed ICS-formoterol is summarized in Box 4-8 (p.84). For adults and adolescents, most of the evidence is with use of budesonide-formoterol 200/6 mcg metered dose (160/4.5 mcg delivered dose) by dry-powder inhaler and, for children aged 6–11 prescribed MART, one study with budesonide-formoterol 100/6 mcg metered dose (80/4.5 mcg delivered dose) by dry-powder inhaler.

Patients prescribed ICS-formoterol as their reliever (with or without maintenance ICS-formoterol) should take 1 inhalation of their ICS-formoterol reliever whenever needed for symptom relief; for formulations with 3 mcg [2.25 delivered dose] of formoterol per inhalation, 2 inhalations should be taken whenever needed for symptom relief. If necessary, an extra dose can be taken a few minutes later.

Additional doses are taken when symptoms recur, even if this is within 4 hours, but the maximum total recommended dose in any single day for adults and adolescents (as-needed plus maintenance doses, if used) is 12 inhalations for budesonide-formoterol (total 72 mcg formoterol [54 mcg delivered dose]). Based on extensive evidence for efficacy and safety of budesonide-formoterol up to this total maximum dose in any day, GINA suggests that the same maximum total dose in a single day should also apply to beclometasone-formoterol. For children, budesonide-formoterol can, if needed, be used up to a total (as-needed and maintenance doses, if used) of 8 inhalations in any day. This is the maximum total of as-needed doses and maintenance doses, if used. See Box 4-8 (p.84) for specific details.

If the patient is rapidly worsening, or has failed to respond to an increase in as-needed doses of ICS-formoterol over 2–3 days, they should contact their healthcare provider or seek medical assistance.

Inhaled combination ICS-SABA reliever

For adults prescribed as-needed combination ICS-SABA reliever with maintenance ICS-containing therapy, the recommended dose is 2 inhalations of budesonide-salbutamol (albuterol) 100/100 mcg metered dose (80/90 mcg delivered dose) as needed, a maximum of 6 times in a day. Overall, in patients on Step 3–5 therapy, this reduced the risk of severe exacerbations by 26%, compared with using a SABA reliever, with the greatest benefit seen in patients taking maintenance low-dose ICS-LABA or medium-dose ICS.[357] There is only one published study to date about use of as-needed combination ICS-SABA alone, i.e., without maintenance ICS or ICS-LABA (see p.98).[338]

If the patient's symptoms/signs are rapidly worsening, or they need repeated doses of as-needed ICS-SABA reliever over 1–2 days, they should contact their healthcare provider or seek medical assistance.

Inhaled SABA reliever

For patients prescribed a SABA bronchodilator reliever, repeated dosing provides temporary relief until the cause of the worsening symptoms passes or increased ICS-containing 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 with[233] or without[315,316] daily maintenance ICS-containing treatment, or than combination ICS-SABA reliever (see Section 4, p.67).

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

Treatment options for written asthma action plans – maintenance medications

Maintenance-and-reliever therapy (MART) with combination low-dose ICS-formoterol

In adults and adolescents, the combination of a rapid-onset LABA (formoterol) and low-dose ICS (budesonide or beclometasone) in a single inhaler as both the maintenance and the reliever medication is effective in improving asthma symptom control,[332] and it reduces exacerbations requiring OCS, and hospitalizations,[233,751-754] compared with the same or higher dose of ICS or ICS-LABA with as-needed SABA reliever (Evidence A). This regimen is also effective in reducing exacerbations in children aged 4–11 years (Evidence B).[423]

For adults and adolescents prescribed MART, the recommended maximum total dose of formoterol in 24 hours with budesonide-formoterol is 72 mcg (delivered dose 54 mcg), with extensive evidence from large studies of its safety and efficacy up to this frequency in a single day (as above). Based on this evidence, GINA suggests that the same maximum total dose in a single day should apply to beclometasone-formoterol (See Box 4-8, p.84). This approach should not be attempted with other combination ICS-LABA medications with a slower-onset LABA (e.g., ICS-salmeterol), or that lack the dose response and safety profile that is required for a maintenance-and-reliever regimen.

The benefit of the MART regimen in reducing the risk of severe exacerbations requiring OCS appears to be due to the increase in doses of both the ICS and the formoterol at a very early stage of worsening asthma.[132-134]

In an action plan for patients prescribed maintenance-and-reliever therapy with ICS-formoterol, the maintenance dose does not normally need to be increased. Instead, the patient increases their as-needed doses of ICS-formoterol. More details of medications and doses for different age-groups are available in Box 4-8, p.84. Examples of action plans customized for MART are available online.[327,328]

Other ICS and ICS-LABA maintenance treatment regimens plus as-needed SABA

In a systematic review, self-management studies in which the ICS dose was at least doubled were associated with improved asthma outcomes and reduced healthcare utilization (Evidence A).[540] In placebo-controlled trials, temporarily doubling the dose of ICS was not effective (Evidence A);[755] however, the delay before increasing the ICS dose (mean 5–7 days)[752,753] may have contributed. Some studies in adults[754] and young children[756] have reported that higher ICS doses might help prevent worsening asthma progressing to a severe exacerbation. In a randomized controlled trial in primary care with patients aged ≥16 years, those who quadrupled their ICS dose (to average of 2000 mcg/day beclometasone dipropionate [BDP] equivalent) after their PEF fell were significantly less likely to require OCS.[757] 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 3200 mcg/day BDP equivalent) was associated with a modest reduction in prescribing of OCS.[758] 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 1600 mcg BDP-equivalent) versus continuing maintenance low-dose therapy.[759] Given the shape of the ICS dose-response curve, increasing the maintenance ICS dose is unlikely to provide benefit in patients with good adherence.

In addition, in several of the studies evaluating ICS increases,[752,753,759] a pre-specified level of deterioration in symptoms (± lung function) had to be reached before the extra ICS could be started. This may help to explain the greater reduction in severe exacerbations seen with maintenance-and-reliever therapy with ICS-formoterol, where there is no lag before the doses of both ICS and formoterol are increased.

In adult with an acute deterioration, high-dose ICS for 7–14 days (500–1600 mcg BDP-HFA standard-particle equivalent) had an equivalent benefit to a short course of OCS (Evidence A).[754] For adults taking combination ICS-LABA with as-needed SABA, the ICS dose may be increased by adding a separate ICS inhaler (Evidence D).[754,758]

Leukotriene receptor antagonists

If patients are using a leukotriene receptor antagonist (LTRA) as their only controller, there are no specific studies about how to manage worsening asthma. Clinicians' judgment should be used (Evidence D). For ongoing treatment, the patient should be switched to an ICS-containing controller to reduce the risk of further exacerbations.[361]

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., for adults, 40–50 mg/day usually for 5–7 days, Evidence B)[754] for patients with:

- Symptoms that fail to respond to an increase in reliever and/or ICS-containing maintenance medication for 2–3 days
- Rapid clinical deterioration or PEF/FEV_1 <60% of their personal best or predicted value
- Worsening asthma in a patient with a history of sudden severe exacerbations.

For children 6–11 years, the recommended dose of prednisone 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.[760] Patients should contact their doctor if they start taking OCS (Evidence D).

Even occasional short courses of OCS are associated with significant short-term and cumulative long-term adverse effects,[234,592] with a pronounced dose response. For all patients, therefore, asthma management should be optimized to reduce the risk of further exacerbations requiring OCS. This includes optimizing ICS-containing therapy (with a switch for adults and adolescents to Track 1 with ICS-formoterol if available), treating modifiable risk factors and comorbidities, using relevant non-pharmacologic strategies, and providing education and skills training including a written asthma action plan (see Box 9-2 (p.163) and Section 5, p.108 for details).

Box 9-3. Optimizing asthma treatment to minimize need for OCS

Optimize asthma treatment to minimize cumulative adverse effects of OCS use

- OCS can be life-saving during severe asthma exacerbations, but there is increasing awareness of the risks of single and repeated courses.
- In adults, short-term adverse effects of OCS include sleep disturbance, increased appetite, reflux, mood changes,[760] sepsis, pneumonia, and thromboembolism.[592]
- In adults, even 4–5 lifetime courses of OCS are associated with a significantly increased dose-dependent risk of diabetes, cataract, heart failure, osteoporosis and several other conditions.[234]
- The need for OCS can be reduced by optimizing asthma therapy, including ICS-containing medications, treating modifiable risk factors, using relevant non-pharmacological strategies, and providing education and skills training, including inhaler technique and adherence. Refer patients for expert advice if needed (Box 3-8, p.66).
- Make sure that all patients are receiving ICS-containing therapy. For adults and adolescents, GINA Track 1 with ICS-formoterol as anti-inflammatory reliever reduces the risk of severe exacerbations requiring OCS, compared with using a SABA reliever (see Box 4-6, p.77).
- All patients should have a written asthma action plan, showing them how to increase their inhaled medications and when to contact medical care.

ICS: inhaled corticosteroid; OCS: oral corticosteroids; SABA: short-acting $beta_2$-agonist.

Reviewing response

Patients should see their doctor immediately or go 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 healthcare provider for a semi-urgent review (e.g., within 1–2 weeks, but preferably before ceasing oral corticosteroids if prescribed), for assessment of symptom control and additional risk factors for exacerbations (Box 2-2, p.37), 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. This visit provides

an opportunity for providing or arranging additional asthma education by a trained asthma educator or trained lay healthcare worker.

Make sure that patients are using their reliever inhaler as-needed, rather than regularly. For patients prescribed a GINA Track 2 regimen with as-needed SABA, maintenance asthma treatment can generally be reduced to 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, after checking inhaler technique and adherence, a step-up in treatment may be indicated (Box 4-6, p.77).

Patients with more than 1–2 exacerbations per year despite Step 4–5 therapy (or Step 4 therapy in children 6–11 years), or with several emergency department visits, should be referred to a specialist center, if available, for assessment and strategies to reduce their risk of future exacerbations and their risk of exposure to OCS. See decision tree for difficult-to-treat and severe asthma in Section 8 (p.139).

PRIMARY CARE MANAGEMENT OF ASTHMA EXACERBATIONS (ADULTS, ADOLESCENTS, CHILDREN 6–11 YEARS)

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 or history of anaphylaxis
- Any risk factors for asthma-related death (Box 9-1, p.161)
- All current reliever and maintenance medications, including doses and devices prescribed, adherence pattern, any recent dose changes, and response to current therapy.

Physical examination

The physical examination should assess:

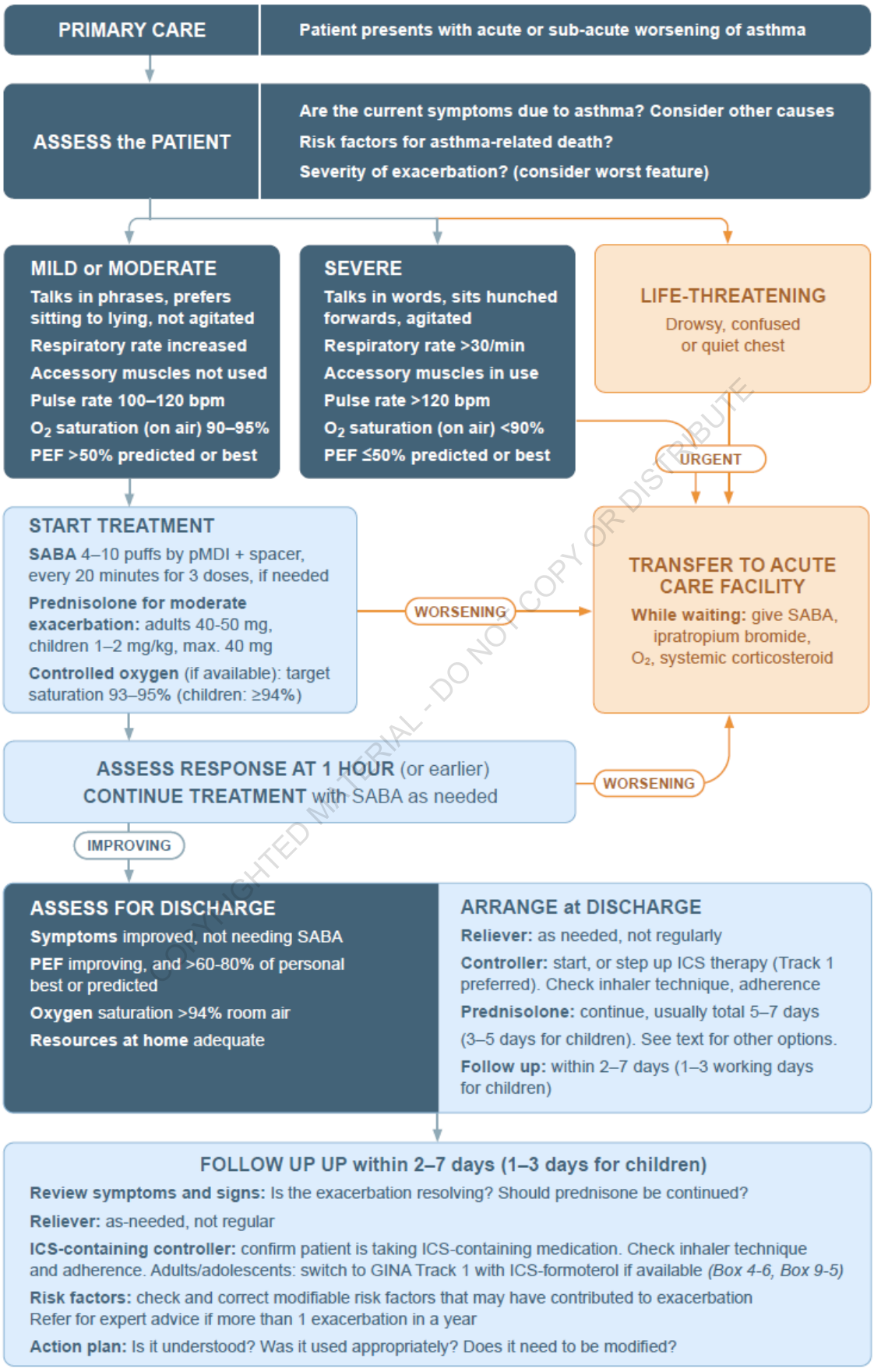
- Signs of exacerbation severity (Box 9-4, p.168) and vital signs (e.g., level of consciousness, temperature, pulse rate, respiratory rate, blood pressure, ability to complete sentences, use of accessory muscles, wheeze).
- Complicating factors (e.g., anaphylaxis, pneumonia, pneumothorax)
- Signs of 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. Under conditions of hypoxemia, oxygen saturation may be over-estimated by pulse oximetry in people with dark skin color.[761] Oxygen saturation targets should be adjusted for altitude, where appropriate.[762]

PEF in patients older than 5 years (Box 9-4, p.168)

Box 9-4. Management of asthma exacerbations in primary care (adults, adolescents, children 6–11 years)



ICS: inhaled corticosteroid; PEF: peak expiratory flow; SABA: short-acting beta$_2$-agonist (doses are for salbutamol [albuterol] 100 mcg/actuation).

Treating exacerbations in primary care

The main initial therapies (Box 9-4, p.168) include repeated administration of rapid-acting inhaled bronchodilators, early introduction of systemic corticosteroids for moderate or severe exacerbations, and controlled flow oxygen supplementation.[749] The aim is to rapidly relieve airflow obstruction and hypoxemia, address the underlying inflammatory pathophysiology, and prevent relapse. Infection control procedures should be followed if the patient has symptoms of respiratory viral infection.

Inhaled short-acting beta$_2$-agonists

Currently, inhaled salbutamol (albuterol) is the usual bronchodilator for acute asthma management. For mild-to-moderate exacerbations, repeated administration of inhaled SABA (up to 4–10 puffs every 20 minutes for a total of 3 doses **if needed**) is an effective and efficient way to achieve rapid reversal of airflow limitation (Evidence A).[763] After the first hour, 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). If symptoms persist or return, 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.

Delivery of SABA via a pMDI and spacer or a DPI leads to a similar improvement in lung function as delivery via nebulizer (Evidence A); [763,764] however, patients with severe acute asthma were not included in these studies. The most cost-effective route of delivery is pMDI and spacer,[765] provided the patient can use this device. This also avoids the potential for transmission of infection from use of a nebulizer. Because of static charge, some spacers require pre-washing with detergent before use. The manufacturer's advice should be followed.

Combination ICS-formoterol in management of acute asthma exacerbations

Combination ICS-formoterol (budesonide-formoterol or beclometasone-formoterol) is now widely used as an anti-inflammatory reliever as part of routine asthma management in adults and adolescents, because it reduces the risk of severe exacerbations and exposure to OCS, compared with use of a SABA reliever (GINA Track 1, p.78). Up to a maximum total of 12 inhalations of budesonide-formoterol 200/6 mcg (160/4.5 mcg delivered dose) can be taken in a single 24-hour period if needed (total of as-needed and maintenance doses, if used), based on evidence from large studies of its efficacy and safety up to this level of use.[233,235] Given this extensive evidence, GINA suggests that the same maximum total use in a 24-hour period should apply to beclometasone-formoterol (see Box 4-8, p.84 for details of medications and doses).

In emergency departments, a randomized controlled trial in adult and adolescent patients with average FEV_1 42–45% predicted compared the effect of 2 doses of budesonide-formoterol 400/12 mcg (delivered dose 320/9 mcg) versus 8 doses of salbutamol (albuterol) 100 mcg (delivered dose 90 mcg), with these doses repeated again after 5 minutes; all patients received OCS. Lung function was similar over 3 hours, but pulse rate was higher in the SABA group.[766] A meta-analysis of earlier RCTs found that the efficacy and safety of formoterol itself was similar to that of salbutamol (albuterol) in management of acute asthma.[767] Formoterol is no longer used for this purpose, but there is no evidence that budesonide-formoterol would be less effective in management of asthma exacerbations.[767] More studies are needed. There are no published data on use of combination ICS-SABA in an emergency department setting.

Controlled oxygen therapy (if available and required)

Oxygen therapy should be titrated against pulse oximetry (if available) to maintain oxygen saturation at 93–95% (≥94% for children 6–11 years). Note the potential for overestimation of oxygen saturation in people with dark skin color.[761] Oxygen saturation targets should be adjusted for altitude, where appropriate.[762] In hospitalized asthma patients, controlled or titrated oxygen therapy is associated with lower mortality and better outcomes than high concentration (100%) oxygen therapy (Evidence A).[768-771] Oxygen should not be withheld if oximetry is not available, but the patient should be monitored for deterioration, somnolence or fatigue because of the risk of hypercapnia and respiratory failure.[768-771] If supplemental oxygen is administered, oxygen saturation should be maintained no higher than 96% in adults.[772]

Systemic corticosteroids

OCS should be given promptly for moderate or severe exacerbations, especially if the patient is deteriorating, and should be considered if the patient has not responded to increased reliever and/or maintenance ICS-containing medications before presenting (Evidence B). The recommended dose of prednisolone for adults is 1 mg/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 in adults[773,774] and 3–5 days in children (Evidence B).[775] Patients should be advised about common short-term side-effects, including sleep disturbance, increased appetite, reflux and mood changes.[760] In adults, the risk of sepsis and thromboembolism is also increased after a short course of OCS.[592]

While OCS is life-saving in severe acute asthma, use of 4–5 lifetime courses in adults is associated with a dose-dependent increased risk of long-term adverse effects such as osteoporosis, fractures, diabetes, heart failure and cataract.[234] This emphasizes the importance of optimizing asthma management after any severe exacerbation to reduce the risk of further exacerbations (see Box 9-3, p.166 and Section 4, p.67).

Maintenance ICS-containing medication

Patients taking maintenance ICS-containing medication with as-needed SABA (GINA Track 2) should be advised to increase the maintenance dose of ICS or ICS-LABA for the next 2–4 weeks, as summarized in Box 9-2 (p.163). For patients not currently taking controller medication, ICS-containing therapy should be commenced to reduce the risk of further exacerbations; SABA-only treatment of asthma is no longer recommended. Initiation of ICS-containing therapy during/after an exacerbation should usually be at Step 4, and preferably with MART (Box 4-5, p.76). An exacerbation requiring medical care indicates that the patient is at increased risk of future exacerbations (Box 2-2, p.37).

Antibiotics (not recommended)

Evidence does not support routine use of antibiotics in the treatment of acute asthma exacerbations unless there is strong evidence of lung infection (e.g., fever and purulent sputum or radiographic evidence of pneumonia).[776]

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 9-4, p.168), 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 FEV_1 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 regular maintenance ICS-containing treatment (see Box 4-8, p.84 and Box 9-5, p.171), as-needed reliever medication (low-dose ICS-formoterol, ICS-SABA or SABA) and a short course of OCS. 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 healthcare 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). For patients prescribed MART, remind them to use their ICS-formoterol for symptom relief, to reduce the risk of another exacerbation; SABA is not needed. Maintenance ICS-containing treatment can generally be stepped back to pre-exacerbation levels 2–4 weeks after the exacerbation. However, if the exacerbation was preceded by symptoms suggestive of chronically poorly controlled asthma, and inhaler technique and adherence are good, a step-up in treatment (Box 4-6, p.77) may be indicated.

Box 9-5. Discharge management after acute care for asthma (ED or hospital)

Medications

Inhaled corticosteroids (ICS): Initiate ICS-containing therapy before discharge, if not already prescribed. The preferred regimen is maintenance-and-reliever therapy with ICS-formoterol (MART) for adults/adolescents, starting at Step 4, as this will reduce risk of future exacerbations compared with using a SABA reliever. If prescribing ICS/ICS-LABA with SABA reliever, increase the ICS dose for 2–4 weeks. Emphasize adherence and correct inhaler technique.

Oral corticosteroids (OCS): Prescribe prednisolone 40–50 mg/day for 5–7 days for adults and 1–2 mg/kg/day to a maximum of 40 mg/day for 3–5 days for children. Review progress before stopping. If using dexamethasone, limit treatment to 1–2 days, switching to prednisolone if relapse occurs.

Reliever medication: Switch patients to as-needed rather than regular reliever use, as regular SABA use for even 1–2 weeks can worsen asthma or mask deterioration and can encourage over-use. Ipratropium bromide can be discontinued after hospital use. Patients using ICS–formoterol as their reliever should return to this on/before discharge if SABA was substituted in ED or hospital.

Risk factors and triggers that contributed to the exacerbation

Identify factors that may have contributed to the exacerbation, and implement strategies to reduce modifiable risk factors. For example:

- Irritant or allergen exposure
- Viral respiratory infections
- Inadequate long-term ICS treatment, including problems with adherence
- Lack of a written asthma action plan.

Hygiene strategies like handwashing, masks and distancing can help prevent viral infections.

Self-management skills and written asthma action plan

- Review and correct inhaler technique
- Provide or review a written asthma action plan.
- Evaluate how the exacerbation developed, and if patient response was adequate.
- Review the patient's use of medications before and during the exacerbation.

Follow up communication and appointment

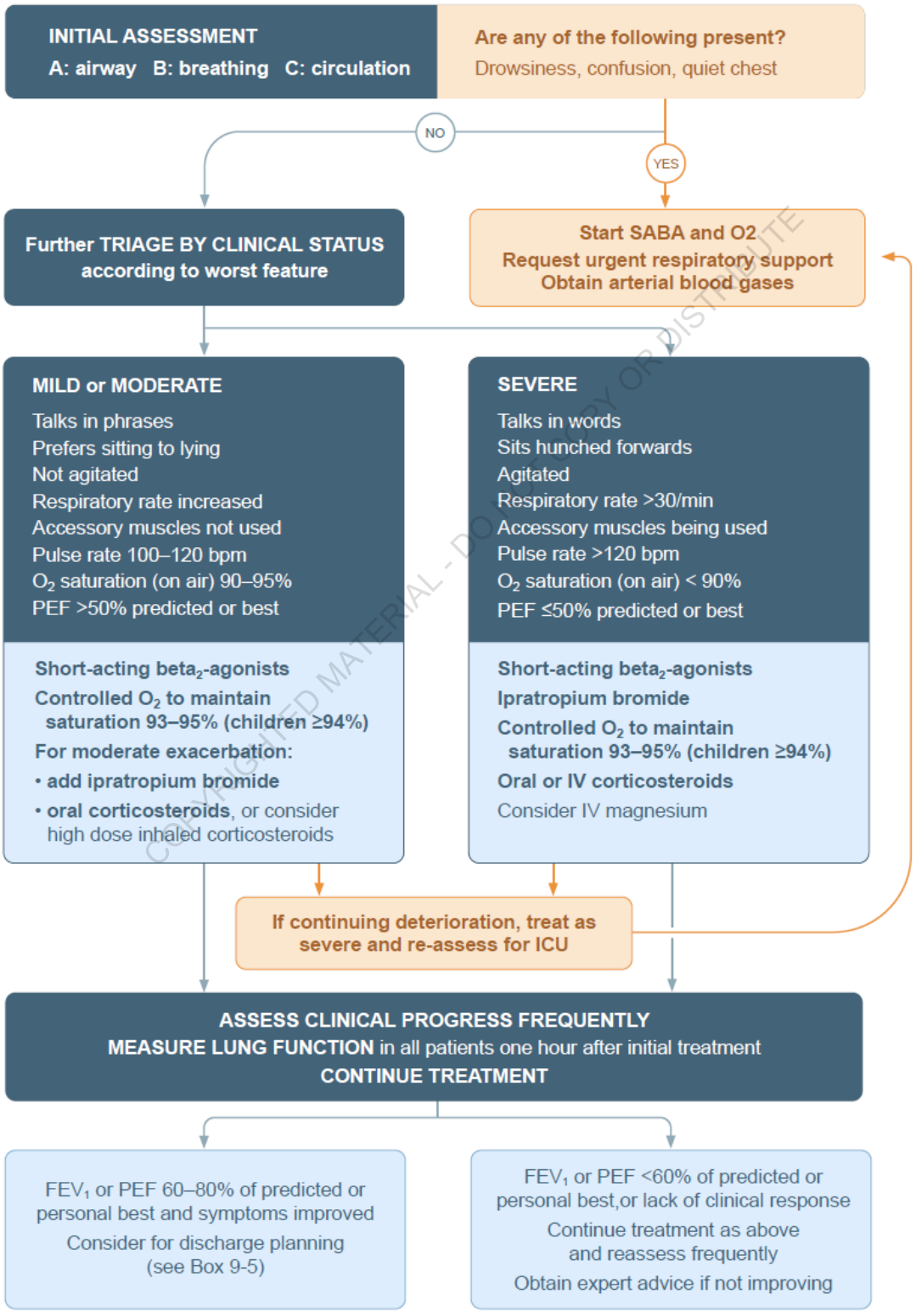
- Inform the patient's healthcare provider about their ED presentation or admission and discharge instructions.
- Schedule a follow-up appointment within 2–7 days of discharge (1–3 days for children) to assess progress and adherence.
- Refer for expert advice if ICU was required, or if the patient already had one or more exacerbations in the last 12 months.

ED: emergency department; ICS: inhaled corticosteroids; ICU: intensive care unit; LABA: long-acting beta$_2$-agonist; MART: maintenance-and-reliever therapy with ICS-formoterol; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist

EMERGENCY DEPARTMENT MANAGEMENT OF EXACERBATIONS (ADULTS, ADOLESCENTS, CHILDREN 6–11 YEARS)

Severe exacerbations of asthma are life-threatening medical emergencies, which are most safely managed in an acute care setting e.g., emergency department (Box 9-6, p.172). Management of asthma in the intensive care unit is beyond the scope of this report and readers are referred to a comprehensive review.[777]

Box 9-6. Management of asthma exacerbations in acute care facility (e.g., emergency department)



See list of abbreviations (p.11).

Assessment

History

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

- 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 9-1, p.161)
- All current reliever and maintenance 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 9-6, p.172), 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.[778,779] 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 FEV_1 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. In children, oxygen saturation is normally ≥95% when breathing room air at sea level, and saturation <92% is a predictor of the need for hospitalization (Evidence C).[780] 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. Of concern, under conditions of hypoxemia, oxygen saturation may be over-estimated by pulse oximeters in people with dark skin color.[761] Oxygen saturation targets should be adjusted for altitude, where appropriate.[762]

Arterial blood gas measurements are not routinely required:[781] They should be considered for patients with PEF or FEV_1 <50% predicted,[782] 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 pCO_2 may be increasing and airway intervention may be needed. PaO_2<60 mmHg (8 kPa) and normal or increased $PaCO_2$ (especially >45 mmHg, 6 kPa) indicate respiratory failure.

Chest X-ray is not routinely recommended: In adults, chest X-ray 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.[783] Similarly, in children, routine check X-ray is not recommended unless there are physical signs suggestive of pneumothorax, parenchymal disease or an inhaled foreign body. Features associated with positive chest X-ray findings in children include fever, no family history of asthma, and localized lung examination findings.[784]

Treatment in acute care settings such as the emergency department

The following treatments are usually administered concurrently to achieve rapid improvement.[785]

Oxygen

To achieve arterial oxygen saturation of 93–95% (≥94% for children 6–11 years), oxygen should be administered by nasal cannulae or mask. Note the potential for overestimation of saturation in people with dark skin color.[761] In adults with 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 concentration (100%) oxygen therapy (Evidence B).[768-770] 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. Oxygen saturation targets should be adjusted for altitude, where appropriate.[762]

Inhaled short-acting beta$_2$-agonists

Currently, inhaled salbutamol (albuterol) is the usual bronchodilator in acute asthma management. The most cost-effective and efficient delivery is by pMDI with a spacer (Evidence A).[763,765] Evidence for pMDI and spacer is less robust in severe and near-fatal asthma. Systematic reviews of intermittent versus continuous SABA in acute asthma, which mostly used nebulized SABA, provide conflicting results. Use of nebulizers can disseminate aerosols and potentially contribute to spread of respiratory viral infections.[586]

Current evidence does not support the routine use of intravenous beta$_2$-agonist in most patients with severe asthma exacerbations (Evidence A).[786]

Combination ICS-formoterol as an alternative to high dose SABA

Compared with SABA, similar efficacy and safety have been reported from emergency department studies with formoterol,[767] and in one study with budesonide-formoterol.[766] The later study showed that high-dose budesonide-formoterol had similar efficacy and safety profile to high dose SABA.[766] In this study, patients received 2 doses of budesonide-formoterol 400/12 mcg (delivered dose 320/9 mcg) or 8 doses of salbutamol (albuterol) 100 mcg (delivered dose 90 mcg), repeated once after 5 minutes; all patients received OCS.[766] While more studies are needed, meta-analysis of data from earlier studies comparing high-dose formoterol with high dose salbutamol (albuterol) for treatment of acute asthma in the ED setting suggest that budesonide-formoterol would also be effective.[767] Formoterol alone is no longer used for this purpose.

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.

Systemic corticosteroids

Systemic corticosteroids speed resolution of exacerbations and prevent relapse, and in acute care settings should be utilized in all but the mildest exacerbations in adults, adolescents and children 6–11 years.[787,788] (Evidence A). Where possible, systemic corticosteroids should be administered to the patient within 1 hour of presentation;[787] some studies showed similar benefit with high-dose ICS.[789]

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.[790,791] 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. RCT evidence does not demonstrate a benefit of intramuscular corticosteroids over oral corticosteroids.[788]

Dosage: daily doses of OCS equivalent to 50 mg prednisolone as a single morning dose, or 200 mg hydrocortisone in divided doses, are typically used for adults. For children, a prednisolone dose of 1–2 mg/kg up to a maximum of 40 mg/day is suggested.[792]

Duration: 5- and 7-day courses of prednisone or prednisolone in adults have been found to be as effective as 10- and 14-day courses respectively (Evidence B),[773,774] and in most children, a 3–5-day course is usually considered sufficient. 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 term[793] or over several weeks[794] (Evidence B). In adults, a small number of studies examined oral dexamethasone 12–16 mg given once daily for 1–2 days in children and adults; the relapse rate was similar to that with prednisolone for 3–5 days, and adverse events rates were similar.[795-797] In children, a systematic review found no difference in relapse rate with oral dexamethasone 0.3 mg/kg or 0.6 mg/kg once daily for 1–2 days versus oral prednisone/prednisolone for 3–5 days; adherence was better, and there was a substantially lower risk of vomiting with dexamethasone.[798] Oral dexamethasone should not be continued beyond 2 days because of concerns about metabolic side-effects. If there is a failure of resolution, or relapse of symptoms, consideration should be given to switching to prednisolone.

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 corticosteroids (Evidence A).[789] When added to systemic corticosteroids, evidence is conflicting in adults.[799] In children, administration of ICS with or without concomitant systemic corticosteroids within the first hours of attendance to the emergency department might reduce the risk of hospital admission and need for systemic corticosteroids (Evidence B).[800] Overall, add-on ICS is well tolerated. However, cost may be a significant factor, and the agent, dose and duration of treatment with ICS in the management of asthma in the emergency department remain unclear. Patients admitted to hospital for an asthma exacerbation should continue, or be prescribed, ICS-containing therapy.

On discharge home: patients should be prescribed ongoing ICS-containing treatment, since the occurrence of a severe exacerbation is a risk factor for future exacerbations (Evidence B) (Box 2-2, p.37), and ICS-containing medications significantly reduce the risk of asthma-related death or hospitalization (Evidence A).[343] 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.[801] There was some evidence, however, that post-discharge ICS were as effective as systemic corticosteroids for milder exacerbations, but the confidence limits were wide (Evidence B).[801] Cost may be a significant factor for patients in the use of high-dose ICS, and further studies are required to establish their role.[801]

After an ED presentation or hospitalization, the preferred ongoing treatment is maintenance-and-reliver therapy (MART) with ICS-formoterol. In patients with a history of ≥1 severe exacerbations, MART reduces the risk of another severe exacerbation in the next 12 months by 32%, compared with same dose ICS or ICS-LABA plus as-needed SABA, and by 23% when compared with higher dose ICS-LABA plus as-needed SABA.[233] MART also reduces the risk of severe exacerbations in broader populations compared with conventional best practice with a SABA reliever.[235] See Box 4-8 (p.84) for medications and doses.

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 (Evidence A for adults;[802] Evidence B for adolescents/children[803]) and greater improvement in PEF and FEV_1, compared with SABA alone (Evidence A, adults/adolescents).[802-804] For children hospitalized for acute asthma, no benefits were seen from adding ipratropium to SABA, including no reduction in length of stay, but the risk of nausea and tremor was reduced.[803]

Aminophylline and theophylline (not recommended)

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.[805] Nausea and/or vomiting are more common with aminophylline.[803,805] 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.[805]

Magnesium

Intravenous magnesium sulfate is not recommended for routine use in asthma exacerbations. However, in adults and children who fail to respond to initial treatment and have persistent hypoxemia, and in children whose FEV_1 fails to reach 60% predicted after 1 hour of care, intravenous magnesium (as a single 2 g infusion over 20 minutes) reduces hospital admissions, including in adults with FEV_1 <25–30% predicted at presentation (Evidence A).[806] There is no significant benefit with nebulized magnesium sulfate in adults and adolescents[807-809] or children[808,810,811] (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),[812] but it may be considered for patients who do not respond to standard therapy. However, availability, cost and technical issues should be considered.

Leukotriene receptor antagonists (LTRAs)

There is limited evidence to support the use of oral or intravenous LTRAs in acute asthma. Small studies have demonstrated improvement in lung function,[813,814] but the clinical role and safety of these agents requires more study.

Antibiotics (not recommended)

RCT evidence does not support the routine use of antibiotics in the treatment of acute asthma exacerbations unless there is strong evidence of lung infection (e.g., fever or purulent sputum or radiographic evidence of pneumonia).[776]

Non-invasive ventilation (NIV)

The evidence regarding the role of NIV in asthma is weak. A systematic review identified five studies in adults involving 206 patients with severe acute asthma treated with NIV or placebo.[815] 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 to receive NIV (Evidence D).

Sedatives (MUST BE AVOIDED)

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.[816,817]

Reviewing response

Clinical status and oxygen saturation should be re-assessed frequently, with further treatment titrated according to the patient's response (Box 9-6, p.172). 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.[818,819]

Spirometric criteria that have been proposed for hospital admission or discharge from the emergency department:[820]

- If pre-treatment FEV_1 or PEF is <25% predicted or personal best, or post-treatment FEV_1 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 9-1, p.161) 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:[821-823]

- Female sex, older age and non-white race
- Use of more than eight beta$_2$-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 AND FOLLOW-UP

Prior to discharge from the emergency department or hospital to home, arrangements should be made for a follow-up appointment within 2–7 days (1–2 days for children), and strategies to improve asthma management including medications, inhaler skills and written asthma action plan, should be addressed (Box 9-5, p.171).[431]

All patients should be prescribed ongoing ICS-containing treatment to reduce the risk of further exacerbations. For adults and adolescents, the preferred regimen after discharge is maintenance-and-reliever therapy (MART) with the anti-inflammatory reliever ICS-formoterol, because this will reduce the risk of future severe exacerbations and reduce the need for OCS, compared with a regimen with a SABA reliever. In the context of a recent ED visit or hospitalization, it would be appropriate to commence treatment with ICS-formoterol in adults and adolescents at Step 4 (Box 4-5, p.76). For medications and doses, see Box 4-8 (p.84), The maintenance dose can be stepped down later, once the patient has fully recovered and asthma has remained stable for 2–3 months (see Box 4-13, p.102).

Follow up after emergency department presentation or hospitalization for asthma

Following discharge, the patient should be reviewed by their healthcare 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.[431]

At follow-up, again ensure that the patient's treatment has been optimized to reduce the risk of future exacerbations. Consider switching to GINA Track 1 with the anti-inflammatory reliever ICS-formoterol, if not already prescribed. See Box 4-8 (p.84) for medications and doses. Check and correct inhaler technique and adherence.

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.

Healthcare 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 3-5, p.56)
- The patient's understanding of the purposes and correct uses of medications, including ICS-containing maintenance treatment and anti-inflammatory reliever, if prescribed
- The actions the patient needs to take to respond to worsening symptoms or PEF.

After an emergency department presentation, comprehensive intervention programs that include optimization of asthma treatment, inhaler technique, and elements of self-management education (self-monitoring, written action plan and regular review)[201] are cost effective and have shown significant improvement in asthma outcomes (Evidence B).[431]

Referral for expert advice should be considered for patients who have been hospitalized for asthma, or who have had several presentations to an acute care setting despite having a primary care provider. Follow-up by a specialist is associated with fewer subsequent emergency department visits or hospitalizations and better asthma control.[431]

Optimize asthma treatment to minimize the use of OCS

OCS can be life-saving during severe asthma exacerbations, but there is increasing awareness of the risks of repeated courses.

In adults, short-term adverse effects of OCS include sleep disturbance, increased appetite, reflux, mood changes,[760] sepsis, pneumonia, and thromboembolism.[592]

In adults, even 4–5 lifetime courses of OCS are associated with a significantly increased dose-dependent risk of diabetes, cataract, heart failure, osteoporosis and several other conditions.[234]

The need for OCS can be reduced by optimizing inhaled therapy, including attention to inhaler technique and adherence.

For adults and adolescents, GINA Track 1 with ICS-formoterol as anti-inflammatory reliever reduces the risk of severe exacerbations requiring OCS, compared with using a SABA reliever (see Box 4-6, p.77).

ICS: inhaled corticosteroids; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist.

10. Diagnosis of asthma in children 5 years and younger

KEY POINTS

The diagnosis of asthma can be made in children aged 5 years or younger, though it may be challenging.

Diagnostic assessment in this age-group involves a thorough medical history and physical examination to identify signs and symptoms consistent with asthma and to exclude other respiratory conditions (e.g., viral bronchiolitis, tuberculosis, protracted bacterial bronchitis, and congenital lung anomalies).

The diagnosis of asthma is primarily clinical. All three of the following criteria should be met:

1. Recurrent acute wheezing episode(s):

A history of at least two reported acute wheezing episodes in the past 12 months

OR

At least one acute wheezing episode **AND** asthma-like symptoms between episodes: e.g., dry cough, coughing spells, symptoms worse during sleep, or after laughing, crying or activity.

Acute wheezing episodes are defined as asthma-like symptoms such as wheezing on expiration, accessory muscle use, breathlessness, or difficult, fast or heavy breathing, each episode lasting for more than 24 hours. For at least one episode, the presence of wheezing (as distinct from other respiratory noises) must be confirmed by a trained healthcare provider (preferred) or convincingly reported by a parent/caregiver (alternative).

2. No likely alternative cause for the respiratory symptoms (except for a concurrent viral respiratory infection) is unlikely to explain the signs/symptoms.

3. A timely clinical response to asthma treatment: clinical improvement after administration of short-acting beta$_2$-agonist (SABA) with or without oral corticosteroids during an acute episode, or after administration of SABA at home, or during a trial of inhaled corticosteroids for 2–3 months, documented by a trained healthcare provider (preferred) or convincingly reported by parent/caregiver (alternative).

Additional factors that may strengthen the diagnosis of asthma include a history of allergic disease (e.g., allergic rhinitis, atopic dermatitis, allergic sensitization) in the child, or a family history of asthma or allergic disease in a parent, sibling, or other first-degree relative. These features are not required for the diagnosis of asthma, and are not specific for asthma.

Suspected asthma: A definitive diagnosis may not always be possible in young children. If one or more of the above criteria has not yet been fulfilled, a provisional diagnosis of "suspected asthma" should be given and treatment considered, with periodic reassessment to document the response to asthma medication and/or change in symptoms over time.

Asthma is less likely if:

- The child is experiencing their first episode of wheezing before 12 months; this is usually due to bronchiolitis, not asthma. The younger the child, the higher the likelihood of an alternative diagnosis.
- Lack of response to a SABA and/or inhaled corticosteroid (ICS) has been documented.
- The respiratory signs and symptoms are atypical.

When feasible and accessible, oscillometry can be used to document responsiveness of airflow limitation or airway hyperreactivity, but there is a lack of standardized reference values.

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.[824] Asthma often begins in early childhood; in up to half of people with asthma, symptoms commence during childhood.[825] Onset of asthma is earlier in males than females.[216,826-828]

No intervention has yet been shown to prevent the development of asthma or modify its long-term 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.[829]

Recurrent wheezing occurs in a large proportion of children aged 5 years or younger. In the past, various wheezing phenotypes have been described. However, these have limited clinical value as they may include a variety of conditions other than asthma, they have poor predictive value,[830] and/or some can only be applied retrospectively (e.g., time trend classifications), as below.

Viral-induced wheezing

This classification originally emerged because recurrent wheezing is typically associated with upper respiratory tract infections (URTI), which occur in this age group around 6–8 times per year.[831] Some viral infections, including respiratory syncytial virus (RSV) and rhinovirus, are associated with recurrent wheeze and asthma throughout childhood.[832] Wheezing in this age group is nonspecific and is not always due to asthma, particularly in very young children. In infants younger than 12 months, bronchiolitis may present with wheeze, but is usually accompanied by other signs that do not suggest asthma, such as crackles on chest auscultation. As viral triggers are not unique to asthma, careful observation is needed to judge whether wheezing with a respiratory infection represents a recurrent clinical presentation of childhood asthma or not.

Wheezing phenotypes

In the past, two main classifications of wheezing (called “wheezing phenotypes”) were proposed:

- **Symptom-based classification**:[833] 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[216]. 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.[834,835]

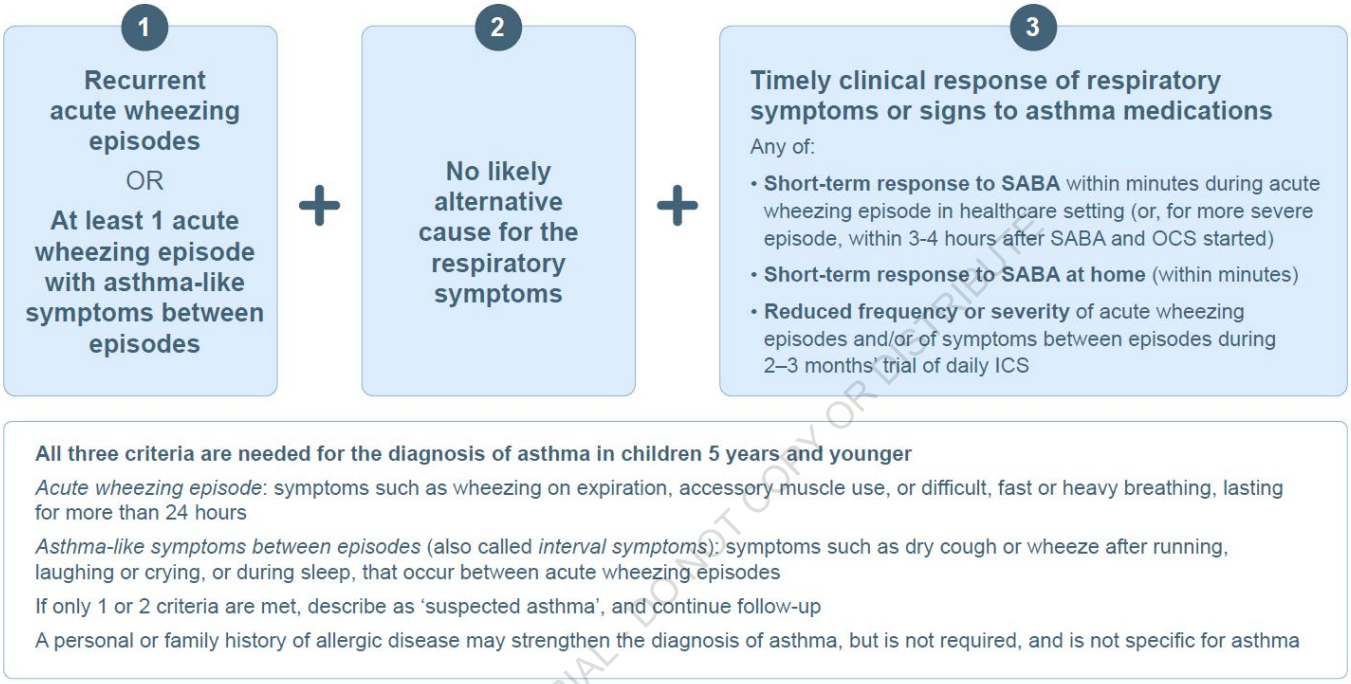
In clinical practice it has been difficult to apply these classifications to an individual patient. Research is still underway to assess the clinical utility of these classification systems, previous wheezing phenotype classifications, and systems for predicting asthma diagnosis at a later age.

The immediate clinical objective is to make a diagnosis in an individual child with respiratory signs/symptoms. The diagnostic approach below is aligned with the concepts of variable respiratory symptoms and variable expiratory airflow on which the diagnosis of asthma in older children and adults is based (Section1, p.22).

CLINICAL DIAGNOSIS OF ASTHMA

The diagnosis of asthma in young children is made by confirming a pattern of recurrent asthma-like symptoms, with careful consideration of the differential diagnosis, and confirming treatment response. A structured, criterion-based approach is recommended. All three criteria must be met to confirm the diagnosis of asthma. If only 1 or 2 criteria are met, consider describing the child's condition as "suspected asthma". Box 10-1 shows the overall approach, with more details in Boxes 10-2 (p.182) and 10-3 (p.185) and following text.

Box 10-1. Diagnostic criteria for asthma in children aged 5 years or younger



ICS: inhaled corticosteroid; SABA: short-acting beta$_2$-agonist; OCS: oral; corticosteroid

Box 10-2. Diagnostic criteria for asthma in children aged 5 years or younger

Criteria for diagnosis of asthma in a child aged 5 years or younger
All three criteria listed below must be fulfilled for diagnosis of asthma in this age-group. If only 1 or 2 criteria are fulfilled, record as suspected asthma. In these criteria, "confirmed" means that wheezing, or a response to treatment, has been documented by a trained healthcare provider (*preferred*), or convincingly described or imitated by a parent/caregiver (*alternative*), to distinguish it from other respiratory noises.
1. Recurrent acute wheezing episodes* with/without asthma-like symptoms between episodes
At least two acute episodes (lasting >24 hours) of asthma-like signs/symptoms (e.g., wheezing on expiration, accessory muscle use, difficult and/or heavy breathing), with wheezing confirmed during at least one episode **OR** At least one acute wheezing episode (lasting >24 hours) with wheezing confirmed AND with asthma-like symptoms between wheezing episodes ("interval symptoms").
2. No likely alternative cause for the respiratory symptoms
Based on a thorough medical history and examination, no other condition (except for a concurrent viral respiratory infection) is likely to explain the asthma-like signs/symptoms. For differential diagnosis, see Box 10-4, p.185. Imaging or laboratory tests are not usually required.
3. Timely clinical response to acute or longer-term asthma treatment
During an acute wheezing episode in a healthcare setting, there is confirmed improvement of respiratory symptoms and signs within 20–60 mins after administration of SABA or, for more severe episodes, within 3–4 hours after SABA and OCS are commenced. **OR** At home, the parent/caregiver reports that the child's wheezing or difficulty breathing improves within 20–60 mins after being given SABA **OR** During a 2- to 3-month trial of daily ICS (e.g., 100–250 mcg/day fluticasone-propionate equivalent by pMDI via spacer) plus as-needed SABA, the parent/caregiver reports a decrease in the severity and/or frequency of the child's acute wheezing episodes or asthma-like symptoms between acute wheezing episodes.

ICS: inhaled corticosteroid; OCS: oral corticosteroid; pMDI: pressurized metered-dose inhaler; SABA: short-acting beta$_2$-agonist

*Audible wheezing, heard without a stethoscope, means a high-pitched sound associated with turbulent expiratory airflow, including due to bronchoconstriction. However, parents/caregivers may use the word "wheeze" to describe any noisy or difficult breathing, including noises that may originate from the upper airway (e.g., congested nose, throat clearing, stridor) or lower airway (e.g., bronchial secretions) rather than from bronchoconstriction. The occurrence of expiratory wheezing consistent with asthma (compared with other conditions) should be confirmed by observation by a trained healthcare provider, or from a recording, or by asking the parent/caregiver to describe or imitate the child's respiratory sounds.

Box 10-3. Obtaining clinical features suggestive of asthma from the parent/caregiver or medical record

A. Questions for the parent/caregiver

1. Ask how a typical episode of respiratory symptoms starts and evolves

During times of difficult breathing, does your child have any of these?:

- Wheezing* (a high-pitched noise/squeaking sound when breathing out)? (To distinguish wheeze from other breathing sounds, play a video/audio recording or ask parent/caregiver to record or imitate the sound.)
- Dry cough, coughing spells, difficult or heavy breathing, or rapid breathing?

When are your child's breathing problems or coughing worse?

- After laughing, crying or when they are active (playing, running, excited)
- Are they worse during sleep? Does your child wake up because of breathing problems or coughing?

Do you see any of these when your child has breathing problems?:

- With each breath, does the skin in their neck or throat, or between the ribs, suck in, or the belly push out?
- Fast breathing or heavy/loud breathing, or gasping for air?
- A blue or gray color around the lips?

What triggers your child's episodes of difficult breathing?

- Having a cold?
- In cold air?
- When they are with animals, or things they are allergic to?
- When running fast or playing?

2. Ask about symptoms between episodes

When your child does <u>not</u> have a cold, do they:

- Have a dry cough or wheeze after running, laughing or crying, or during sleep (daytime nap or at night)?
- Wake up because of coughing, wheezing or difficult or heavy breathing, or shortness of breath?
- Stop running, because of coughing, wheezing or difficult or heavy breathing, or shortness of breath?
- Stop physical activity earlier than other children their age because of cough or shortness of breath?

3. Has your child had any of these treatments for the symptoms? (see Box 10.2)

A reliever inhaler? (check name, dose and whether spacer was used) Did it help to relieve symptoms? How long did it take for the symptoms to improve? (within 20–60 minutes is typical of asthma)

Corticosteroid by syrup or crushed pill? (check name, dose) Did it help to relieve symptoms? How long did it take for the symptoms to improve?

Daily inhaled or nebulized corticosteroid? (check name, dose, duration and frequency of use). Did it help to prevent symptoms? How long did it take for the symptoms to improve?

Ask about other features that support the diagnosis of Type 2 asthma (allergic and/or eosinophilic):

Has your child ever had eczema, or been diagnosed with food allergy, hay fever, or other allergies?

Does the child have a close relative (sibling, biological parent) with asthma, *hay fever, food allergy or eczema?*

B. Clinical findings including from the medical record

1. During an acute respiratory episode, has a trained healthcare provider observed any of the following?:

- Signs consistent with lower airway obstruction: wheezing (rhonchi), accessory muscle use, decreased air entry, prolonged expiration, decreased air exchange (low oxygen saturation, cyanosis, increased CO_2)
- Timely clinical improvement in response to asthma medications (See Box 10-2).

2. Does the child's medical record include a diagnosis of asthma or terms suggesting variable lower airway obstruction? (e.g., bronchospasm, reactive airway disease, airway hyperreactivity)

CRITERION 1: RECURRENT ACUTE WHEEZING EPISODES WITH/WITHOUT ASTHMA-LIKE SYMPTOMS BETWEEN EPISODES

Summary of criterion

At least 2 acute wheezing episodes in the last 12 months **OR** at least one acute wheezing episode plus interval symptoms/signs at another time.

Acute wheezing episodes are asthma-like symptoms (wheezing on expiration, accessory muscle use, breathlessness, difficult and/or heavy breathing), each lasting more than 24 hours. Episodes may occur with or without URTIs and/or in response to other triggers, such as exposure to allergens or irritants.

Confirmation of wheezing at least once is necessary, preferably by observation by a healthcare provider or from video/audio recording or convincingly reported by parents who have demonstrated the ability to distinguish wheezing from other sources of noisy breathing.

Interval symptoms/signs are asthma-like symptoms/signs that occur between acute episodes (e.g., dry cough and/or coughing spells with/without wheezing, difficult or heavy breathing, or breathlessness worsening during sleep or after laughing, crying or activity) lasting few minutes or hours. Interval symptoms typically occur during sleep (nocturnal symptoms or awakenings), after laughing or crying, with physical activity (e.g., limiting the child's activity), and/or exposure to various irritants or allergens (Box 10.3, p.185).

Description of signs and symptoms

Wheeze

Wheeze that is audible without a stethoscope is the most common and specific sign associated with asthma in children 5 years and younger. A wheeze that occurs recurrently, during sleep, or with triggers such as activity, laughing, or crying, is consistent with asthma.[836]

Wheezing is defined as a high-pitched sound associated with turbulent expiratory airflow due to bronchoconstriction. However, parents/caregivers may use the word "wheeze" to describe any noisy or difficult breathing, including noises that may originate from the upper airway (e.g., congested nose, throat clearing, stridor) or lower airway (e.g., bronchial secretions) rather than from bronchoconstriction.[837] Some cultures do not have a word for wheeze.

The clinical interpretation and significance of reported wheeze depends on:

- Who observed it (e.g., parent/caregiver versus a healthcare provider)
- The environmental context (e.g., high-income countries where prevalence of asthma is high versus geographical regions with a high prevalence of parasites that involve the lung)
- The cultural context (The relative importance of certain symptoms can differ between cultures, as can the diagnosis and treatment of respiratory tract diseases in general).

Therefore, wheezing consistent with asthma should be confirmed by direct observation by a trained healthcare provider, or from a recording, or by verifying that the parent/caregiver's description of the child's respiratory sounds is a convincing report of wheeze. Clinicians can guide parents/caregivers to distinguish wheezing from other types of noisy breathing, either by discussion or using video or audio recordings.[838]

Cough

Cough due to asthma is generally dry (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 after exercise, laughing or crying, in the absence of an apparent URTI, supports a diagnosis of asthma. The common cold and other respiratory illnesses, including pertussis infection, are also associated with coughing.

Breathlessness

Parents/caregivers may also use terms such as "difficult breathing", "heavy breathing", or "shortness of breath". Recurrent breathlessness during exercise is consistent with asthma. In infants and toddlers, crying and laughing represent physical exertion 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 parents/caregivers may be unaware of this behavior change. 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.

CRITERION 2: EXCLUSION OF OTHER DIAGNOSES

Summary of criterion

Clinical assessment that the signs and symptoms are unlikely to be explained by an alternative diagnosis.

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 10-4).[839] The exclusion of alternative diagnoses should be based on a thorough medical history and examination. Imaging or laboratory tests are not required for the diagnosis of asthma.

Considerations

Infants under 12 months: The younger the child, the greater the likelihood of an alternative diagnosis (see Box 10-4). A first episode of wheezing before age 12 months is usually due to bronchiolitis, not asthma.

Allergies: A personal or family history of allergic disease, e.g., atopic dermatitis, allergic rhinitis, may strengthen the support for confirming the diagnosis of asthma, but it is not necessary or sufficient for the diagnosis to be made.

Respiratory viral infections: The presence of URTI symptoms during episodes of wheezing, cough and breathlessness does not rule out a diagnosis of asthma; respiratory viral infections are a common trigger for asthma exacerbations.

Referral: Consider referral to a pediatrician or pediatric respiratory specialist for infants younger than 12 months with recurrent (≥ 2) episodes of wheezing. Expert assessment is strongly recommended if there is any suspicion of an alternative diagnosis, or if symptoms fail to respond to asthma therapy or the child's condition deteriorates during an appropriately conducted treatment trial of 2–3 months' duration.

Box 10-4. Common differential diagnoses of asthma in children 5 years and younger

If the symptoms or signs below are present, consider…	Condition
Mainly cough and runny congested nose for <10 days, *without* wheezing or difficulty breathing	Viral upper respiratory tract infection
Cough when feeding, recurrent chest infections	Gastroesophageal reflux +/- pharyngeal dysphagia
Sudden onset of symptoms, unilateral wheeze	Inhaled foreign body Other conditions including tuberculosis
Protracted paroxysms of coughing, often with stridor and vomiting	Pertussis
Persistent wet cough	Protracted bacterial bronchitis Tuberculosis
Noisy breathing when crying or eating; harsh cough	Tracheomalacia
Cardiac murmurs, failure to thrive	Congenital heart disease
Pre-term delivery, symptoms since birth	Bronchopulmonary dysplasia
Excessive cough and mucus production, gastrointestinal symptoms, failure to thrive	Cystic fibrosis
Cough and recurrent chest infections; neonatal respiratory distress, chronic ear infections and persistent nasal discharge from birth	Primary ciliary dyskinesia
Noisy breathing, feeding difficulties	Vascular ring

Recurrent fever and infections (including non-respiratory)	Primary immunodeficiency

Box 10-5. Key indications for referral from primary care of a child 5 years or younger for expert advice about diagnosis

Any of the following features in a child 5 years or younger 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, recurrent stridor or seal-like barking cough (airway malacia)
- 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 (<95%).

Indications for urgent referral for children experiencing an exacerbation are found in Box 12-3.

CRITERION 3: ASSESSING RESPONSE TO ASTHMA TREATMENT

Summary of criterion

Timely treatment response to asthma medication: either during an episode of acute wheezing, or during a treatment trial for 2–3 months with SABA as needed for symptom relief, or with maintenance ICS plus SABA as needed.

Response to treatment during an acute respiratory episode

During an acute care visit with asthma-like symptoms, if wheezing is confirmed by a healthcare provider and other diagnoses are unlikely, the diagnosis of asthma can be confirmed by a timely clinical response to treatment, documented by a trained healthcare provider.

A timely response to SABA means that symptoms/signs improve within 20–60 minutes after SABA is given. For a child with a moderate or severe exacerbation requiring SABA and oral corticosteroids (OCS), a timely response to treatment means that symptoms/signs improve within 3–4 hours after treatment is commenced. See Section 12 for management of acute exacerbations.

Response to as-needed SABA for mild acute wheezing episodes or infrequent interval symptoms

For a child with no or infrequent mild acute wheezing episodes that do not require unscheduled medical care, with or without mild intermittent asthma-like symptoms (e.g., twice/week or less), consider a trial for 2–3 months of as-needed SABA by pressurized metered-dose inhaler (pMDI) and spacer (with facemask if needed), given by parents or caregivers when asthma-like symptoms occur (Box 10-2).

Ask the parent/caregiver to monitor whether the child's symptoms improve after administration of SABA, and how quickly, and arrange a follow-up visit after 2–3 months. A clinical response to as-needed SABA means an improvement in symptoms/signs within 20–60 minutes of administration.

If the clinical response to SABA during respiratory symptoms is absent or incomplete, review inhalation technique and consider alternative diagnoses. If acute episodes and interval symptoms occur during adequately conducted treatment, or if an acute episode requires urgent medical treatment, consider switching to a trial of daily low-dose ICS plus as-needed SABA.

Treatment trial with inhaled corticosteroid

A 2- to 3-month trial of maintenance ICS, plus SABA as needed, should be considered for:

- children with a history of one or more acute asthma-like episodes requiring an acute care visit, oral corticosteroids or hospital admission in the past year
- children with asthma-like symptoms occurring more than twice a week.

For example, give fluticasone propionate 100–250 mcg/day or equivalent (see note below) by pMDI via spacer, with mouthpiece or facemask as appropriate).

Due to the variable nature of asthma, a treatment trial is most informative if conducted during seasons in which the child is most symptomatic. Response to treatment should be reviewed before deciding whether to continue or adjust therapy.

The purpose is to gain evidence of response to ICS treatment, corresponding to the effect on symptoms and airflow limitation on which the diagnosis of asthma is based in older children and in adults. Clinical response to ICS should be evaluated by the frequency and severity of interval (daytime and night-time) symptoms, and asthma-like episodes.

Marked clinical improvement during ICS treatment supports the diagnosis of asthma. If the clinical response is convincing, and the first two criteria for diagnosis have been met, the diagnosis of asthma can be made. Immediately after trial is completed, reduce the ICS dose to the minimum effective dose.

If the clinical response is absent or suboptimal, review adherence to medication and check inhalation technique. If both are adequate reconsider alternative diagnoses, as lack of response to ICS may indicate another condition, or severe asthma for which specialist referral should be considered. If acute episodes recur or interval symptoms recur or worsen after stopping the treatment trial, this further supports a diagnosis of asthma.

Note on ICS dose: Systematic reviews of randomized controlled trials testing the efficacy of daily ICS vs placebo in children younger than 6 years with repeated wheezing or asthma showed a significant reduction by 40% in the risk of exacerbations[840] and by 30% in the risk of exacerbations requiring rescue oral corticosteroids[841] (Evidence A). The median ICS dose used in the included studies was 200 mcg/day fluticasone propionate or equivalent (interquartile range 150, 250 mcg), with the doses used in these studies often determined by regulatory approvals. These ICS doses are higher than the low doses recommended for treatment of asthma in children aged 5 years and younger in clinical practice (Box 11-3). A dose–response analysis is needed to ascertain whether lower doses are effective in diagnostic treatment trials in children aged 5 years and younger. Until this evidence is available, it is suggested that clinicians should use the doses recommended above, but reduce the dose as soon as a clinical response indicates that the diagnosis of asthma has been confirmed.

TESTS TO ASSIST IN DIAGNOSIS

While no test can specifically and definitively diagnose asthma with certainty in children aged 5 years or younger, the following are useful adjuncts.

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 aged 3 years or older.[842] However, absence of sensitization to common aeroallergens does not rule out a diagnosis of asthma.

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 age 5 or 6 years many children can perform reproducible spirometry if coached by an experienced technician and with visual incentives.

Alternative measures for lung function testing, including oscillometry and bronchial provocation (challenge) testing, are available for children as young as 3 years old. Oscillometry is a non-invasive effort-independent lung function test obtained during quiet tidal breathing, which can be performed in children as young as 3 years, and can be used to assess bronchodilator responsiveness.[843] Oscillometry measurements differ between devices, so device-specific reference values should be used. Challenge testing should only be performed by trained personnel, using standardized protocols, in a setting where severe bronchoconstriction can be managed if it occurs.

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 offline in young children with tidal breathing, and normal reference values have been published for children aged 1–5 years, from morning measurements.[844] In preschool children with recurrent coughing and wheezing, an elevated FeNO recorded 4 weeks from any URTI predicted physician-diagnosed asthma at school age,[845] and increased the odds for wheezing, asthma and ICS use by school age, independent of clinical history and presence of specific IgE.[846]

11. Assessment and management of asthma in children 5 years and younger

KEY POINTS

The following principles apply to children aged 5 years and younger with a diagnosis of asthma (see Section 10).

- The goals of asthma management in young children are similar to those in older patients:
  - To achieve best possible control of symptoms and maintain normal activity levels
  - To minimize the risk of asthma flare-ups, impaired lung development and medication side-effects.
- Day-to-day asthma symptoms should be treated with inhaled short-acting beta$_2$-agonist (SABA) as reliever.
- Daily controller therapy should be initiated in children with asthma symptoms more than twice a week, or with one or more severe exacerbations requiring unscheduled medical care in the previous year. The preferred controller option is daily treatment with inhaled corticosteroids (ICS).
- Response to treatment should be reviewed before deciding whether to continue it or change it. If a clinical response is absent or incomplete, reconsider inhaler technique, adherence, modifiable risk factors, alternative diagnoses and comorbidities that may be contributing to exacerbations or respiratory symptoms.
- If there is a good response to ICS for 2–3 months, a dose reduction should be considered.
- The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered-dose inhaler (pMDI) via spacer, with face mask for children <3 years and mouthpiece for most children aged 3–5 years. Children should be switched from a face mask to mouthpiece as soon as they can demonstrate good technique. Inhaler technique should be repeatedly assessed and corrected when necessary.
- Education and an individualized written action plan should be provided to parents/caregivers.
- The need for asthma treatment should be reassessed periodically, since symptoms may fluctuate and asthma-like symptoms remit in many young children. If remission occurs, advise parents/caregivers that asthma symptoms will often return later in life.

GOAL OF ASTHMA MANAGEMENT

As with other age groups, the goal of asthma management in young children is to achieve the best possible long-term asthma outcomes for the child:

- To achieve and maintain good long-term control of symptoms and maintain normal activity levels
- To minimize future risk; that is to reduce the risk of exacerbations (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 for young children because engaging in play is important for their normal social and physical development. Avoiding flare-ups is important not only because of the health concerns, but also because of the disruption they cause to social and educational progress. It is important to also elicit the goals of the parent/caregiver, as these may differ from conventional medical goals.

The long-term goals of asthma management are achieved through a partnership between the parent/caregiver and the healthcare provider team, as a continual cycle:

- **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, side-effects, and parent satisfaction.

This cycle is conducted in combination with education of parent/caregiver, 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/caregiver
- 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.[37,88] Asthma control has two components (Box 11-1, p.191): symptom control, and future risk of exacerbations, poor lung function or treatment side-effects. The rationale for this is described on p.41. In young children, as in older patients, both symptom control and future risk should be monitored (Evidence D). Details follow below.

Assessing asthma symptom control

Assessment of whether asthma symptom control is satisfactory in children 5 years and younger depends on information about frequency and severity obtained from family members and carers, but they may be unaware either of how often the child has experienced asthma symptoms, or that their respiratory symptoms represent uncontrolled asthma. Parents/caregivers may report irritability, tiredness and mood changes in their child as the main problems when asthma is not well controlled.

Few objective measures to assess symptom control have been validated for children <4 years. The Childhood Asthma Control Test can be used for children aged 4–11 years.[149] The Test for Respiratory and Asthma Control in Kids (TRACK) is a validated questionnaire for parent/caregiver completion for preschool-aged children with symptoms consistent with asthma; it includes symptom control in the previous 4 weeks, reliever use in the previous 3 months, and courses of systemic corticosteroids in the previous year.[153] However, children with asthma who have no symptoms between acute wheezing episodes (interval symptoms) are still at risk of exacerbations, particularly with respiratory viral infections.

Box 11-1 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). There are no validated tools for assessing symptom control over longer periods than 1–4 weeks, but ask the parent/caregiver whether the child's recent symptoms and activity level are usual for the individual.

Assessing future risk of adverse outcomes

The relationship between symptom control and future risk of adverse outcomes, such as exacerbations (Box 11-1, p.191), has not been sufficiently studied in young children. Although exacerbations may occur in children after months of good symptom control (e.g., triggered by viral respiratory infections), the risk of exacerbations is greater if current symptom control is poor. In a randomized controlled trial in children aged 2–3 years assessed to be at high risk of asthma (based on modified API), those who were treated with daily low-dose ICS for 2 years experienced fewer days with asthma symptoms and a reduced risk of exacerbations than those receiving placebo.[847]

The risk of future 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,[147] and poorly controlled asthma can affect growth.[146] 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 (OCS), 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 to avoid local side-effects such as steroid rash (reddening and atrophy).

Box 11-1. GINA assessment of asthma control in children 5 years and younger

A. Recent symptom control (also ask about whole period since last visit)		**Level of asthma symptom control**		
In the past 4 weeks, has the child had:		**Well controlled**	**Partly controlled**	**Uncontrolled**
Daytime asthma symptoms more than twice a week?	Yes☐ No☐	None of these	1–2 of these	3–4 of these
Any night waking or night coughing due to asthma?	Yes☐ No☐			
SABA reliever medication needed* more than twice a week?	Yes☐ No☐			
Any activity limitation due to asthma? (Runs/plays less than other children, tires easily during walks/playing?)	Yes☐ No☐			

B. Future risk for poor asthma outcomes

Risk factors for asthma exacerbations within the next few months

- One or more severe acute episodes (ED attendance, hospitalization, or course of OCS) in previous year
- Uncontrolled asthma symptoms (as above)
- 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 infection[848]
- Major psychological or socio-economic problems for child or family
- Poor adherence to ICS medication, or incorrect inhaler technique
- Outdoor pollution (including NO_2 and particles)[107]

Risk factors for persistent airflow limitation

- Severe asthma with several hospitalizations
- History of bronchiolitis

Risk factors for medication side-effects

- Systemic: Frequent courses of OCS, high-dose and/or potent ICS (for low ICS doses, see Box 11-3, p.195)
- Local: moderate-to high-dose or potent ICS; incorrect inhaler technique; failure to protect skin or eyes when using ICS by nebulizer or spacer with face mask

ED: emergency department; ICS: inhaled corticosteroid; OCS: oral corticosteroid

* Excludes reliever taken before exercise. Before considering a change in 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.

REMISSION OF ASTHMA

Remission of asthma has been investigated extensively in the past, most commonly spontaneous remission of childhood asthma (long-term absence of symptoms/signs without treatment). Definitions and criteria vary, but they commonly refer to either *clinical remission* (e.g., no asthma symptoms or exacerbations for a specific period) or *complete (or pathophysiological) remission* (e.g., also including normal lung function, airway responsiveness and/or inflammatory markers). There has been interest in *remission off treatment*, and *remission on treatment*, for example with biologic therapy for severe asthma.[213-215]

The concept of clinical remission on treatment is consistent with the *long-term goal of asthma management* promoted by GINA (p.50), to achieve the best possible asthma outcomes for each patient. This includes control of symptoms (long-term, not just in recent days/weeks), unimpaired physical activity, improved or stable optimized lung function, prevention of exacerbations (particularly those requiring OCS), avoidance of maintenance OCS, prevention of asthma deaths, and avoidance of adverse effects of asthma medications.

Reported rates of *spontaneous remission (off treatment)* from studies in children with wheezing or asthma vary depending on the populations, definitions, and length of follow-up. For example, in one study, 59% of wheezing preschool children had no wheezing at 6 years,[216] whereas in another study, only 15% of children with persistent wheezing at/after 9 years had no wheezing at 26 years.[217] Clinical remission is more frequent than pathophysiological remission at all ages.[218,219]

The most important predictors of asthma remission during school years in children with childhood wheezing are fewer, milder or decreasing frequency of symptomatic episodes,[220-223] good or improving lung function, and less airway hyperresponsiveness.[219] Risk factors for persistence of childhood asthma include atopy, parental asthma/allergy, later onset of symptoms, wheezing without colds, and maternal smoking or tobacco smoke exposure.

Remission is not cure: asthma often recurs later in life, and children whose asthma has remitted have an increased risk of accelerated lung decline in adulthood, independent from, but synergistic with, tobacco smoking; and they may develop persistent airflow limitation, although this is less likely than for those whose asthma has persisted.[224] This suggests the importance of monitoring lung function in people with remission of asthma symptoms.

To date, there is no evidence that interventions in childhood increase the likelihood of remission of asthma or reduce the risk of recurrence. However, treatment of asthma in childhood with ICS substantially reduces the burden of asthma on the child and family, reduces absence from school and social events, reduces the risk of exacerbations and hospitalizations, and allows the child to participate in normal physical activity.

Parents/caregivers often ask if their child will grow out of their asthma, and will not need treatment in the future. Current consensus advice for discussions like these includes the following:

- If the child has no reported symptoms, check for evidence of ongoing disease activity, e.g., wheezing; child avoiding physical activity; lung function if available.
- Use a description like "*asthma has gone quiet for now*" to help avoid misunderstandings. If you use the term "remission" with parents/caregivers, explain the medical meaning, because it is often interpreted as meaning a permanent cure.
- Advise parents/caregivers that even if the child's symptoms resolve completely, their asthma may recur later.
- Emphasize the benefits of taking controller treatment for the child's current health, their risk of asthma attacks, and their ability to participate in school and sporting activities, avoiding claims about effect of therapy on future asthma outcomes.

Research needs: clinical questions about remission *off* treatment in children focus on risk factors for asthma persistence and recurrence (including clinical, pathological ,and genetic factors), the effect of risk reduction strategies on the likelihood of remission, whether monitoring after remission to allow early identification of asthma recurrence improves outcomes, and whether progression to persistent airflow limitation can be prevented. Clinical questions about remission *on* treatment (e.g., in children with severe asthma treated with biologic therapy) include whether inhaled anti-inflammatory therapy can be down-titrated.

Risk profiles for prediction of persistent asthma

Several risk profile tools have been developed with the aim of identifying which wheezing children aged 5 years and younger are at high risk of having asthma symptoms that persist after the preschool years. However, these tools have shown limited utility when evaluated in clinical practice. Each tool demonstrates different performance characteristics with varying criteria used to identify risk.[849]

Only three prediction tools have been externally validated (Asthma Predictive Index[850] from Tucson, USA, Prevention and Incidence of Asthma and Mite Allergy (PIAMA) index[851] from the Netherlands, and Leicester tool[852] from the UK). A systematic review has shown that these tools have poor predictive accuracy, with variation in sensitivity and positive predictive value.[853] Larger predictive studies using more advanced statistical methods, and with objective measurements for asthma diagnosis, are probably needed to propose a practical tool in clinical care to predict persistent asthma in recurrent wheezers in infancy and preschool age.

MEDICATIONS FOR SYMPTOM CONTROL AND RISK REDUCTION

Choosing medications for children 5 years and younger

Good control of asthma can be achieved in almost all young children with medication.[854] The treatment plan should be developed in a partnership between the family/carer and the healthcare provider. As with older children and adults, medications comprise only one component of asthma management in young children; other key components include education (p.113), skills training for inhaler devices (p.108) and adherence (p.111), non-pharmacological strategies (p.57) including environmental control, where appropriate, regular monitoring, and clinical review (p.116).

When recommending treatment for a young child, both general and individual questions apply (Box 3-4, p.54):

- *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 high quality observational data.
- *How does this individual child differ from other children with asthma*, in terms of:
  - Response to previous treatment
  - Patient characteristics that contribute to symptoms or risk of flare-ups: e.g., clinical phenotype, risk factors for flare-ups, comorbidities including allergic rhinitis, environmental exposures
  - Preferences of the parent/caregiver (goals, beliefs and concerns about medications)
  - Practical issues (cost, inhaler technique and adherence)?

Studies in preschool children 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.[855] In an analysis of several studies involving preschool children with recurrent wheezing, daily ICS treatment reduced the annualized exacerbation rate in the subset of children who had clinical features of allergy.[856] 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.

The following treatment recommendations for children aged 5 years or younger are based on the available evidence and on expert opinion. Evidence is expanding but is still rather limited, as clinical trials in this age group have differed in the populations included, definition of asthma, baseline characteristics recorded, and outcome measures including definitions of exacerbations.

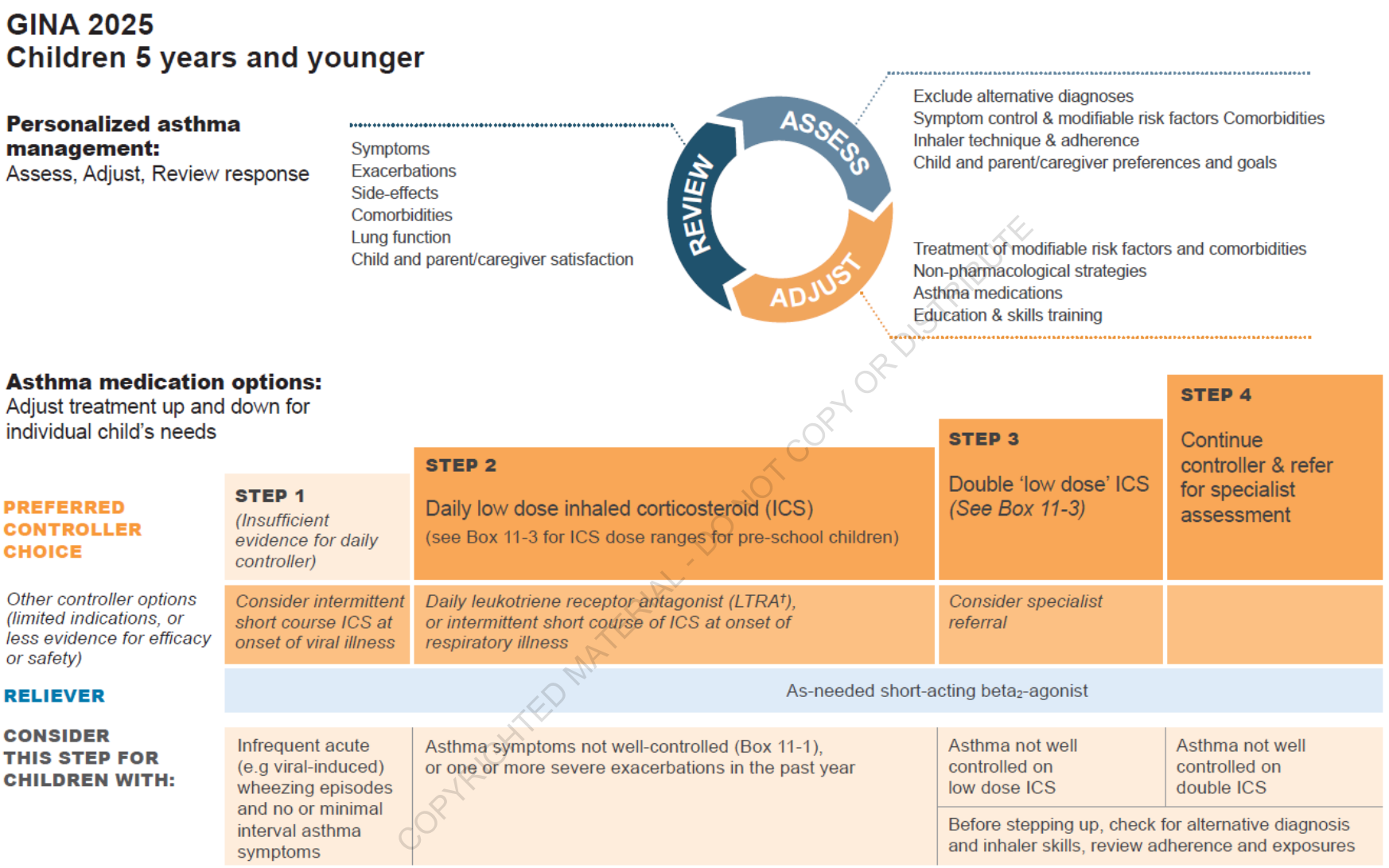
A stepwise treatment approach is recommended (Box 11-2, p.194), based on symptom control, risk of exacerbations and side-effects, and response to initial treatment. Generally, treatment includes the long-term, daily, use of low-dose ICS treatment to keep asthma well controlled (see Box 11-3 for doses), with reliever medications for as-needed symptom relief. The choice of inhaler device is also an important consideration (Box 11-4, p.195).

Rapid-acting bronchodilator (reliever) treatment

The recommended asthma reliever for preschoolers is SABA given as needed when symptoms occur, by pMDI with mouthpiece or facemask as appropriate.

If a child needs more than 4 puffs of salbutamol (albuterol) in less than 4 hours, urgent medical care should be sought. The treatment of acute asthma exacerbations in children 5 years and younger is described in Section 12 (see Acute asthma exacerbations in children 5 years and younger, p.205).

Box 11-2. Personalized management of asthma in children 5 years and younger



ICS: inhaled corticosteroid; LTRA: leukotriene receptor antagonist. For ICS doses in children, see Box 11-3 (p.195) †If prescribing LTRA, advise parent/caregiver about risk of neuropsychiatric adverse effects.

Box 11-3. Low daily doses of inhaled corticosteroids for children 5 years and younger

***This is not a table of equivalence*, but instead, suggestions for "low" total daily doses for the ICS treatment recommendations for children aged 5 years and younger in Box 11-2 (p.194), based on available studies and product information. Data on comparative potency are not readily available, particularly for children.**

***This table does NOT imply potency equivalence*. For example, if you switch a child's treatment from a "low" dose of one ICS to a "low" dose of another ICS, this may represent a decrease (or increase) in potency. The child's asthma may become unstable (or they may be at increased risk of adverse effects).**

Children should be monitored to ensure stability after any change of treatment. Doses and potency may also differ by country, depending on local products, inhaler devices, regulatory labelling and clinical guidelines. The doses listed here are the lowest approved doses for which safety and effectiveness have been adequately studied in this age group.

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.

Inhaled corticosteroid	Low total daily dose in mcg (age-group with adequate safety and effectiveness data)
BDP (pMDI, standard particle, HFA)	100 (ages 5 years and older)
BDP (pMDI, extrafine particle, HFA)	50 (ages 5 years and older)
Budesonide nebulized	500 (ages 1 year and older)
Fluticasone propionate (pMDI, standard particle, HFA)	50 (ages 4 years and older)
Fluticasone furoate (DPI)	Not sufficiently studied in children 5 years and younger
Mometasone furoate (pMDI, standard particle, HFA)	100 (ages 5 years and older)
Ciclesonide (pMDI, extrafine particle, HFA)	Not sufficiently studied in children 5 years and younger

In children, pMDI should always be used with a spacer

BDP : beclometasone dipropionate; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; pMDI: pressurized metered-dose inhaler. For new preparations, including generic ICS, the manufacturer's information should be reviewed carefully, as products containing the same molecule may not be clinically equivalent.

Note about ICS doses: Meta-analyses of placebo-controlled trials of daily ICS in children with recurrent wheezing and/or asthma, who at enrolment had frequent between-episode symptoms, demonstrated a significant reduction in symptoms and exacerbations.[841,857] Many of these studies used higher daily doses of ICS than those shown in this table (e.g., fluticasone propionate mean 200 mcg (interquartile range 150, 250 mcg) or equivalent. However, dose-response analyses have not been published to know whether lower doses are also effective in confirming the diagnosis of asthma.

Once the diagnosis of asthma is confirmed, the general principle should be the same as for older children and adults: for each patient, establish the minimal effective dose that controls their interval symptoms and, in combination with an action plan, reduces the risk of acute episodes and need for courses of oral corticosteroids.

Which children with asthma should be prescribed regular ICS treatment?

Daily low-dose ICS (Step 2, Box 11-2, p.194) is indicated for a child with either of the following:

- Respiratory symptoms not well controlled, (e.g., reliever needed more than twice a week on average; Box 11-1, p.191) (Evidence A)
- One or more exacerbations or episodes of wheezing in the past 12 months that required an acute care visit, a short course of rescue OCS, or a hospital admission (Evidence A).

Daily ICS treatment may also be indicated in a child with recurrent viral-induced asthma (Evidence D).

It is important to discuss the decision to prescribe controller treatment and the choice of treatment with the child's parents or caregivers. 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,[148] and the one study that examined long-term outcomes showed a difference of only 0.7% in adult height.[147,858] Poorly controlled asthma itself adversely affects adult height.[146] Effects of ICS on growth velocity are dose dependent, so the minimal effective ICS dose should be identified for each child.

ASTHMA TREATMENT STEPS FOR CHILDREN AGED 5 YEARS AND YOUNGER

Asthma treatment in young children follows a stepwise approach (Box 11-2), with medication adjusted up or down, in conjunction with an asthma action plan, 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.

Step 1: Preferred option: as-needed inhaled short-acting beta$_2$-agonist (SABA)

All children with asthma or suspected asthma should be provided with inhaled SABA for relief of symptoms (Evidence D). See Box 11-4 (p.195) for choice of inhaler device.

SABA as needed for the relief of symptoms may be the only asthma treatment indicated for some children with symptoms no more than twice a week on average. Symptoms more than twice a week over a 1-month period indicates the need for a trial of low-dose ICS treatment (see Step 2.)[859]

Other options

For children with intermittent viral-induced asthma and no interval symptoms, particularly those with underlying atopy (positive for modified API) in whom inhaled SABA medication is not sufficient, intermittent high-dose ICS may be considered[756,860,861] (see Management of worsening asthma and exacerbations, p.159). Due to the risk of side-effects, this should only be considered if the physician is confident that the treatment will be used appropriately.

Not recommended

Oral bronchodilator therapy (including in liquids/syrups) is not recommended due to its slower onset of action and higher rate of side-effects, compared with inhaled SABA (Evidence D).

Step 2: Preferred option: daily low-dose ICS plus as-needed SABA

Regular daily low-dose ICS (Box 11-3, p.195) is recommended as the preferred initial treatment to control asthma in children 5 years and younger whose asthma symptoms are not well controlled, or who have had one or more severe exacerbations in the previous year (Evidence A).[841,862,863] This treatment should be given initially for at least 2–3 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.[864] However, for young children with recurrent viral-induced wheezing/asthma, a review concluded that neither regular nor intermittent LTRA reduces the rate of exacerbations requiring systemic corticosteroid treatment (Evidence A).[865] A further systematic review found that in preschool children with asthma or recurrent wheezing, daily ICS was more effective in improving symptom control and reducing exacerbations than regular LTRA monotherapy.[857] Prescribers should counsel parents/caregivers about the potential adverse effects of montelukast on sleep and behavior, and healthcare providers should consider the benefits and risks of side effects before prescribing.[309]

For preschool children with asthma characterized by frequent viral-induced wheezing and interval asthma symptoms, as-needed (prn)[866] or episodic high-dose ICS[756,860,861,867] may be considered, but a trial of regular daily low-dose ICS should

be undertaken first. The effect on exacerbation risk seems similar for regular daily low-dose and episodic high-dose ICS.[841] See also Initial home management of asthma exacerbations (p.202).

Several clinical trials of anti-inflammatory reliever therapy with as-needed-only low-dose ICS-formoterol are underway, including some in children aged 5 years and younger.

If good asthma control is not achieved with the first treatment selected, trials of the alternative Step 2 therapies are recommended before moving to Step 3.[855]

Step 3: Double the "low" daily ICS dose plus as-needed SABA. Consider specialist referral

If symptoms are not well controlled after 2–3 months of initial treatment with a low dose of ICS, or if exacerbations continue to occur, check the following before considering any step up in treatment:

- Confirm that the symptoms are due to asthma rather than a concomitant or alternative condition (Box 10-4, p.185).
- Check and correct inhaler technique. Consider alternative delivery systems if indicated.
- Confirm good adherence to the prescribed dose.
- Ask parents/caregivers about risk factors, such as exposure to allergens or tobacco smoke (Box 11-1, p.191).

Preferred option: young children's medium-dose ICS (double the "low" daily dose)

Consider doubling the initial low dose of ICS (Evidence C). Assess response after 2–3 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.

Consider specialist referral.

Step 4: Continue controller treatment and refer for expert assessment

If asthma symptoms are still not well controlled, or acute episodes persist after doubling the initial dose of ICS, carefully reassess inhaler technique and adherence to medication, as these are common problems in this age group. Also reassess and address control of environmental factors, where relevant, and reconsider the asthma diagnosis. Refer for expert or specialist advice.

Other options

The best treatment for this population has not been established. If the diagnosis of asthma has been confirmed, the specialist may consider any of the following options:

- Add-on long-acting muscarinic agents (LAMA): There is insufficient evidence on the efficacy and safety of ICS in combination with a LAMA in this age group. A small 12-week trial in children aged 1–5 years with persistent asthma symptoms tested various daily doses of tiotropium (2.5 mcg vs 5 mcg vs placebo). No group difference in symptoms were observed and no safety concerns emerged.[868]
- Addition of LTRA to maintenance ICS: This option 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. Note the concern about potential neuropsychiatric adverse effects with montelukast.[309]
- ICS in combination with a long-acting beta$_2$-agonist (LABA): There are insufficient data from studies evaluating the efficacy and safety of ICS-LABA in children younger than 4 years.

The need for additional controller treatment should be re-evaluated at each visit and maintained for as short a period as possible, with consideration of potential risks and benefits. Treatment goals and their feasibility should be reconsidered and discussed with the child's family/carer.

REVIEWING RESPONSE AND ADJUSTING TREATMENT

Assessment at every visit should include asthma symptom control and risk factors (Box 11-1, p.191), 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 (p.,[869-871] 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 reinstituted (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/caregiver 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.

Before considering a step-up of controller treatment

If symptom control is poor and/or exacerbations persist despite 2–3 months of adequate controller therapy, check the following before considering any step up in treatment:

- Confirm that the symptoms are due to asthma rather than a concomitant or alternative condition (Box 10-4, p.185). Refer for expert assessment if the diagnosis is in doubt.
- Check and correct inhaler technique.
- Confirm good adherence to 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.
- Ask parents/caregivers about risk factors such as allergen or tobacco smoke exposure (Box 11-1, p.191).

CHOICE OF INHALER DEVICE

Asthma treatment in children aged 5 years and younger should be based on inhaled medicines. General information about inhaler devices, and the issues that should be considered, are found in Section 5 (p.108) and in Box 5-1 (p.109). These include, first choosing the right medication(s) for the child to control symptoms, allow normal activity, and reduce the risk of severe exacerbations, then considering which delivery device is available, whether they can use it correctly after training and, if more than one type of inhaler device is available, their relative environmental impact.

For children aged 5 years and younger, the preferred delivery system is a pressurized metered-dose inhaler (pMDI) with a valved spacer (Box 11-4, p.195), with a mouthpiece or face mask, depending on the child's age (Evidence A).[872] 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 (i.e., taking multiple breaths in and out through the spacer mouthpiece or face mask after each actuation is released into the spacer). 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 spacer, and the way it 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.
- Only 1 actuation of the pMDI should be delivered at a time, and the inhaler should be shaken before each actuation. 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

healthcare provider or a caregiver 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 and exposure of eyes. The skin on the nose and around the mouth should be cleaned immediately after the inhalations are finished.
- 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 healthcare 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; again, if a mask is used, clean the skin around mouth and nose afterwards. If a nebulizer is used, follow local infection control procedures.

Box 11-4. 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

If nebulizer is used, follow infection control procedures, as respiratory viruses can be dispersed by up to 1 meter. See p.109 and Box 5-1 (p.109) for other factors to consider in choice of an inhaler device.

ASTHMA SELF-MANAGEMENT EDUCATION FOR CAREGIVERS OF YOUNG CHILDREN

Asthma self-management education should be provided to family members and caregivers of children with asthma or suspected asthma. An educational program should contain:

- Basic information about asthma and the factors that influence it
- Training to achieve correct inhalation technique
- Information on the importance of the child's adherence to the prescribed medication regimen
- A written asthma action plan.

Crucial factors for a successful asthma education program include a partnership between patient/caregiver and healthcare providers, with a high level of agreement regarding the goals of treatment for the child, and intensive follow-up (Evidence D).[38]

Written asthma action plans

Asthma action plans should be provided for the family/caregivers of all children with asthma, including those aged 5 years and younger (Evidence D). Action plans, developed through collaboration between an asthma educator, the healthcare provider and the family, have been shown to be of value in older children,[873] 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 caregiver 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 departments and hospitals, ambulance services and emergency pharmacies).

Details of treatments that can be initiated at home are provided in Section 12.

12. Management of worsening asthma and exacerbations in children 5 years and younger

KEY POINTS

Symptoms of asthma exacerbation in young children

- Exacerbations in young children may be indicated by worsening of respiratory symptoms (dry cough, coughing spells with/without wheezing, difficult or heavy breathing, or breathlessness), especially during sleep, or after laughing, crying or activity, reduced exercise tolerance, impaired daily activities including feeding, and/or a poor response to reliever medication. Signs of a moderate exacerbation include accessory muscle use and/or audible wheezing.

Home management in a written asthma action plan

- Give a written asthma action plan to parents/caregivers of young children with asthma so they can recognize when it is worsening, start reliever treatment, and identify when urgent hospital treatment is required.
- Initial treatment at home is with inhaled short-acting beta$_2$-agonist (SABA), with monitoring of response.
- Parents/caregivers should seek urgent medical care if the child is acutely distressed (e.g., severe breathlessness, subcostal/intercostal retraction, cyanosis), is drowsy/lethargic, or is worsening despite administration of SABA.
- Medical care should be obtained on the same day if ≥4 puffs of SABA are needed in less than 4 hours or if SABA is needed on more than three occasions within 12 hours.
- There is no compelling evidence to support parent/caregiver-initiated oral corticosteroid treatment.

Management of exacerbations in primary care or acute care facility

- Assess severity of the exacerbation while initiating treatment with bronchodilator and oxygen if needed:
  - SABA: 4–6 puffs of salbutamol (albuterol) 100 mcg/actuation by pressurized metered-dose inhaler (pMDI) with spacer, or 0.25 mg by nebulizer, administered once for mild exacerbations and every 20 minutes up to total 3 doses in the first hour, if needed, for moderate or severe exacerbations
  - Oxygen (if needed) to maintain saturation ≥94%.
- Arrange immediate transfer to hospital if there is no response to repeated inhaled SABA within 1–2 hours, if the child is unable to speak or drink, has a respiratory rate >40/minute or is cyanosed, or if oxygen saturation is <92% on room air.
- For a moderately severe or severe exacerbation, add inhaled ipratropium bromide: 4 puffs (20 mcg/actuation) or nebulized (0.25 mg), administered with SABA every 20 minutes for 3 doses, if needed.
- Consider systemic corticosteroids for children attending an emergency department or admitted to hospital: oral prednisone/prednisolone 1–2 mg/kg/day up to a maximum of 20 mg/day for children aged 0–2 years; 30 mg/day for children aged 3–5 years, for up to 5 days, or dexamethasone 0.3 to 0.6 mg/kg/day for 1–2 days. If symptoms do not resolve, or recur, during dexamethasone treatment, consider switching to prednisolone.
- Oxygen saturation by pulse oximetry may be overestimated in people with dark skin color.

Arrange early follow-up after an exacerbation

- Instruct parent/caregiver to seek medical care if there is no improvement or a deterioration over the next 24–48 hours.
- If feasible, arrange follow-up within 1–3 days of an exacerbation and again 1–2 months later to plan ongoing asthma management.

Children who have experienced an asthma exacerbation are at risk of further exacerbations, so they should be assessed for management to reduce this risk.

DIAGNOSIS OF EXACERBATIONS

A flare-up (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. An exacerbations may necessitate a visit to a healthcare provider or require treatment with systemic corticosteroids. In pediatric resources, the term “episode” is commonly used.

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 beta$_2$-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.[874]

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.

INITIAL HOME MANAGEMENT OF ASTHMA EXACERBATIONS

Initial management includes an action plan to enable the child’s family members and caregivers 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/caregivers should be advised to seek medical attention immediately if:

- The child is acutely distressed (e.g., severe breathlessness, subcostal/intercostal retraction, cyanosis), is drowsy or lethargic or if their condition is deteriorating
- The child’s symptoms are not rapidly relieved 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/caregiver should initiate treatment with inhaled SABA: 2 puffs of inhaled salbutamol (albuterol) 200 mcg per actuation (or equivalent), given one puff at a time by pMDI via a spacer device with mouthpiece or facemask (Evidence D). This may be repeated two more times at 20-minute intervals, if needed. The child should be observed by the family/caregiver and, if improving, maintained in a restful and reassuring atmosphere for an hour or more. Medical attention should be obtained urgently if any of the features listed above apply, or on the same day if ≥4 puffs of inhaled SABA are required for symptom relief within 4 hours or if SABA is needed on >3 occasions within the first 12 hours.

Family/caregiver-initiated corticosteroids

Evidence to support the initiation of oral corticosteroid (OCS) treatment by family/caregivers in the home management of asthma exacerbations in children is weak,[875-879] despite this practice in some regions. Preemptive episodic high-dose nebulized ICS may reduce exacerbations in children with intermittent viral triggered wheezing.[841] However, because of the 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 healthcare provider is confident that the medications will be used appropriately, and the child is closely monitored for side-effects.

Leukotriene receptor antagonists

In children aged 2–5 years with intermittent viral wheezing, one study found that an oral leukotriene receptor antagonist (LTRA) given for 7–20 days, commenced at the start of an URTI or the first sign of asthma symptoms, reduced symptoms, healthcare utilization and time off work for the caregiver.[880] In contrast another study found no significant effect with LTRA, compared with placebo, on episode-free days (primary outcome), OCS use, healthcare 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.[881] Parents/caregivers should be counseled about the risk of adverse effects on sleep, behavior and mental health with montelukast.[309]

PRIMARY CARE OR HOSPITAL MANAGEMENT OF ACUTE ASTHMA EXACERBATIONS IN CHILDREN 5 YEARS OR YOUNGER

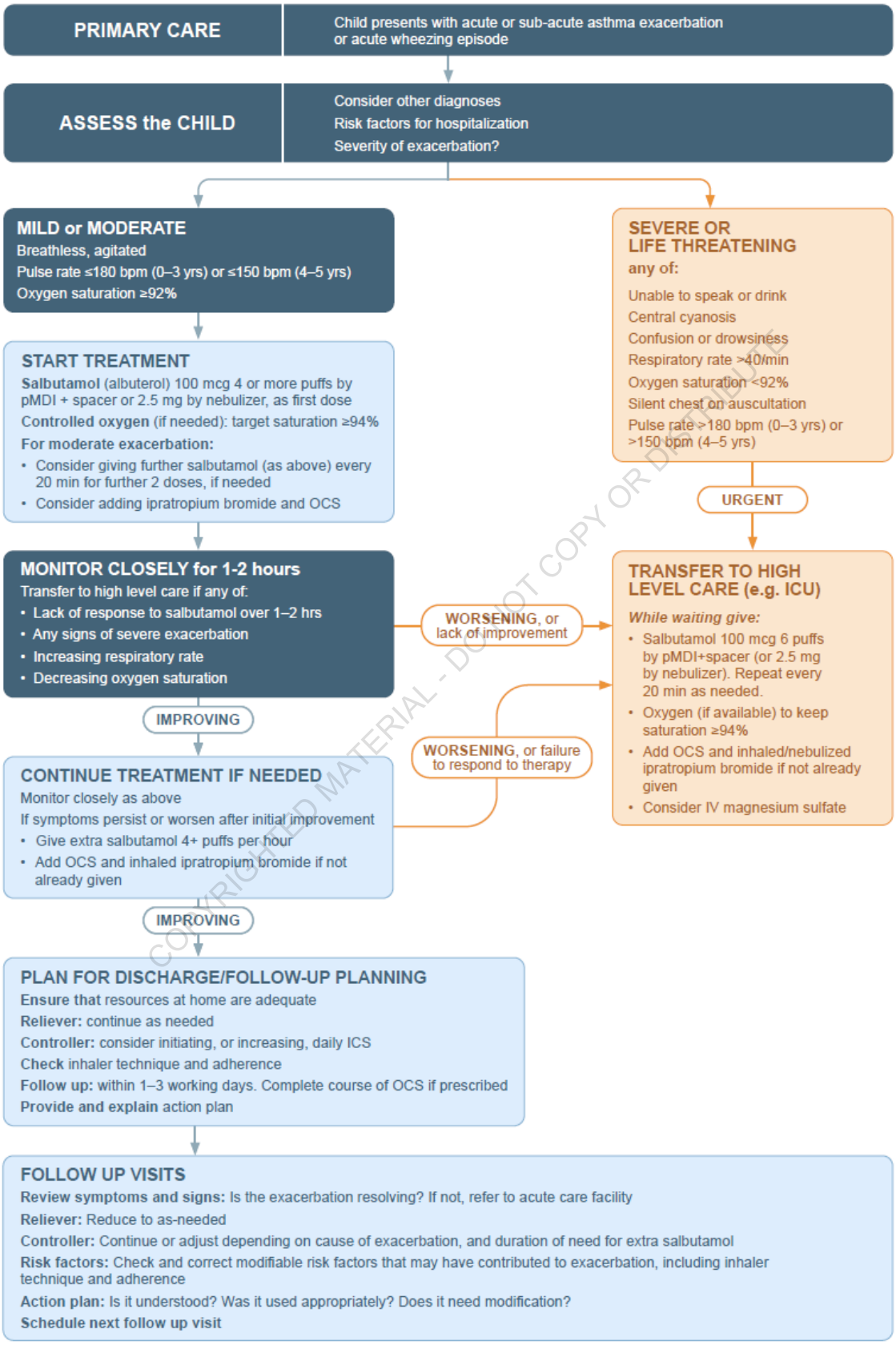
Assessment of exacerbation severity

Conduct a brief history and examination concurrently with the initiation of therapy (Box 12-1, p.204). The presence of any of the features of a severe exacerbation listed in Box 12-2 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.[780] Note that oxygen saturation by pulse oximetry may be overestimated in people with dark skin color.[761] Oxygen saturation targets should be adjusted for altitude, where appropriate.[762]

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 Preschool Respiratory Assessment Measure (PRAM) and Pediatric Asthma Severity Score (PASS) have been developed for assessing the severity of acute asthma exacerbations in children.[882,883]

Box 12-1. Management of acute asthma or wheezing in children 5 years and younger



bpm: beats/minute; IV: intravenous; OCS: oral corticosteroids; pMDI: pressurized metered dose inhaler.

Box 12-2. 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)**	>94%	<92%
Speech†	Sentences	Words
Pulse rate	<100 beats/minute	>180 beats/minute (0–3 years) >150 beats/minute (4–5 years)
Respiratory rate	≤40/minute	>40/minute
Accessory muscle use (suprasternal, supraclavicular or intercostal retractions and, in severe cases, nasal flaring)	Absent	Present
Central cyanosis	Absent	Likely to be present
Wheeze intensity	Variable	Chest may be quiet

O_2: oxygen. *Any of these features indicates a severe asthma exacerbation. **Oximetry before treatment with oxygen or bronchodilator. Note potential for overestimation of oxygen saturation with pulse oximetry in people with dark skin color.[761] Oxygen saturation targets should be adjusted for altitude, where appropriate.[762] † The child's developmental stage and usual capability must be considered.

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 must be referred to hospital for observation and further treatment (Evidence D; Box 12-3). 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 younger than 2 years, as the risk of dehydration and respiratory fatigue is increased (Box 12-4, p.206).

Box 12-3. 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
- Respiratory rate >40 per minute
- Oxygen saturation <92% when breathing room air (note potential for overestimation of oxygen saturation with pulse oximetry in people with dark skin color)
- Quiet chest on auscultation

Lack of response to initial bronchodilator treatment:

- Lack of response to 12 puffs of inhaled salbutamol (albuterol), administered as 4 separate puffs every 20 minutes for 3 times, over 1 hour
- Persisting tachypnea* despite three administrations of inhaled salbutamol, even if the child shows other clinical signs of improvement

Social environment that limits delivery of acute treatment, or parent/caregiver unable to manage asthma at home.

During transfer to hospital, continue to give inhaled salbutamol, oxygen (if available and required to maintain saturation ≥94%), and give systemic corticosteroids (see Box 12-1, p.204)

*Normal respiratory rate: <50 breaths/minute in children 2–12 months; <40 breaths/minute in children 1–5 years.

Box 12-4. Initial emergency department management of asthma exacerbations in children 5 years and younger

Therapy	Dose and administration
Supplemental oxygen	Delivered by face nasal prongs or mask, as indicated to maintain oxygen saturation at ≥94%
Short-acting beta$_2$-agonist (SABA)	4 or more puffs of salbutamol (albuterol) by spacer, or 2.5 mg by nebulizer. For moderate or severe exacerbation, consider giving SABA every 20 minutes for 3 doses, then reassess severity. If symptoms persist or deteriorate, give an additional 4 puffs or more per hour.
Systemic corticosteroids	For moderate or severe exacerbation, 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 oral dexamethasone 0.3–0.6 mg/kg (max 12 mg) OR intravenous methylprednisolone 1 mg/kg 6-hourly on day 1
Additional options within or after the first hour of treatment	
Ipratropium bromide	For moderately severe or severe exacerbation, give 4 puffs of 20 mcg ipratropium bromide by pMDI and spacer or 250 mcg by nebulization every 20 minutes with SABA for 3 doses. For mild exacerbation, if poor response to SABA in the initial hour, consider adding ipratropium as described above (if not already given).
Magnesium sulfate	Consider intravenous isotonic magnesium sulfate (40–50 mg/kg, maximum 2 g over 10–20 minutes for children aged ≥2 years with severe exacerbation (Box 12-2, p.205)

pMDI: pressurized metered dose inhaler; SABA: short-acting beta$_2$-agonist. If a nebulizer is used, follow infection control procedures to reduce transmission of respiratory viruses. Oxygen saturation targets should be adjusted for altitude, where appropriate.[762] See below for additional and ongoing treatment, including maintenance inhaled corticosteroids.

Emergency treatment and initial pharmacotherapy

Oxygen

Manage hypoxemia urgently with oxygen by face mask to achieve and maintain percutaneous oxygen saturation ≥94% (Evidence A). Note the potential for overestimation of oxygen saturation in people with dark skin color. Oxygen saturation targets should be adjusted for altitude, where appropriate.[762]

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 and required). 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.

Inhaled bronchodilator therapy

The initial dose of inhaled SABA may be given by a pMDI with spacer and either mask or mouthpiece, or by 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 delivery (Evidence A),[884] and nebulizers can spread infectious particles. The initial dose of SABA is four puffs of salbutamol ([albuterol], 100 mcg per puff) or equivalent, except in severe acute asthma when six puffs should be given. When a nebulizer is used, a dose of 2.5 mg salbutamol solution is recommended, and infection control procedures should be followed. The frequency of dosing depends on the response observed over 1–2 hours (see below).

For children with moderate or severe exacerbations or those with a poor response to SABA in the initial hour, inhaled ipratropium bromide 4 puffs of 20 mcg/actuation (or 250 mcg by nebulizer) can be added to SABA every 20 minutes for 3 doses.[884]

Magnesium sulfate

Intravenous $MgSO_4$ in a single dose of 40–50 mg/kg (maximum 2 g) by slow infusion (20–60 minutes) may be considered in addition to standard treatment with salbutamol, ipratropium, and oral corticosteroids, after the first hour of treatment for children ≥2 years old with severe acute asthma (e.g., oxygen saturation <92%, Box 6-10, p.206).[806] A 2024 systematic review and meta-analysis in children found a reduced risk of hospitalization in children treated with $MgSO_4$ intravenously as second-line therapy, compared with placebo or standard of care. By contrast, nebulized $MgSO_4$ was not associated with clinically significant improvement in respiratory rate; there was a modest improvement in peak expiratory flow (PEF), but not forced expiratory flow in 1 second (FEV_1).[811]

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(s)*: a further 4–6 puffs of salbutamol (depending on severity) may be given 20 minutes after the first dose and repeated at 20-minute intervals for total 3 doses. If not already administered, add 4 puffs of 20 mcg of inhaled (or 250 mcg nebulized) ipratropium bromide for 3 doses with each salbutamol dose, and commence oral corticosteroids. Failure to respond at 1 hour, or earlier deterioration, should prompt consideration for admission to hospital and/or administration of intravenous magnesium sulfate (Evidence D).
- *If symptoms have improved by 1 hour but persist*: the child may be given further doses of bronchodilator (4 puffs or more of salbutamol each hour, as needed). Oral corticosteroids should be given, if not yet administered. The child need to remain in the emergency department until significant improvement is reached to be discharged home. Children with signs/symptoms that fail to respond to above therapy within 3–4 hours should be referred immediately to hospital (Evidence D).
- *If symptoms resolve and do not recur for 1–2 hours*: no further acute care treatment may be required. When discharged home, the child should be observed by the family/caregiver and have ready access to emergency care. Further SABA may be given as needed up to every 4 hours (up to a total of 12 puffs/24 hours). Continue short course of oral corticosteroids and consider adding inhaled corticosteroids as indicated (Evidence D), as outlined below.

Additional acute treatment

When treatment in addition to SABA is required for an exacerbation, options available for treatment of the acute exacerbation in children aged 5 years or younger include ICS as add-on to the short course of oral corticosteroid (see p.202).[885] However, there is not strong evidence of clinical benefit (e.g., reduction in hospitalizations) with this strategy.

Maintain current controller treatment (if prescribed)

Children who have been prescribed maintenance therapy with ICS should continue to take it during and after an exacerbation (Evidence D), but the dose may need to be increased depending on assessment of the context of the exacerbation (see Discharge and follow up, p.208). If the child was previously prescribed daily LTRA, consider switching to daily ICS; parents/caregivers should be informed about the potential neuropsychiatric adverse effects associated with LTRA.[309]

Inhaled corticosteroids

In ED management, addition of ICS to standard care (including OCS) does not reduce risk of hospitalization but reduces length of stay and acute asthma scores in children in the ED.[885] For those children already on ICS, doubling the dose was not effective in a small study of mild-moderate exacerbations in children aged 6–14 years,[886] nor was quintupling the dose in children aged 5–11 years who had good pre-exacerbation ICS adherence. This approach should be reserved mainly for individual cases, and should always involve regular follow-up and monitoring of adverse effects (Evidence D).

Oral corticosteroids

For children with moderately severe or 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).[887,888] A course of 3–5 days is sufficient in most children of this age, and can be stopped without tapering (Evidence D). Alternatively, dexamethasone 0.3 to 0.6 mg/kg (maximum 12 mg) in 1 dose with/without a second dose the next day can be considered. (Evidence A).[798] A 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.[888] Several studies have failed to show any benefits when oral corticosteroids were given by parents or caregivers during periods of worsening wheeze managed in an outpatient setting (Evidence D).[875-878,889,890]

In children discharged from the emergency department, an intramuscular corticosteroid may be an alternative to a course of OCS for preventing relapse,[788] but the risk of long-term adverse effects must be considered. There is insufficient evidence to recommend intramuscular over oral corticosteroids.[788]

Regardless of treatment, the severity of symptoms must be carefully monitored after discharge (as below) to confirm they are recovering. 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., 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).

Before discharge from the emergency department or hospital, family/caregivers 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
- SABAs should be used on an as-needed basis, rather than regularly, to avoid masking worsening asthma, but the daily requirement should be recorded to ensure it is being decreased over time to pre-exacerbation levels.
- Confirm that ICS has been initiated where appropriate (at twice the low initial dose in Box 11-3 (p.195) for the first month after discharge, then adjusted as needed) or continued, for those previously prescribed controller medication.
- Provide a supply of SABA and, where applicable, the remainder of the course of oral corticosteroid, together with a supply of ICS or LTRA.
- A follow-up appointment within 1–3 days and another within 1–2 months, depending on the clinical, social and practical context of the exacerbation.

13. Primary prevention of asthma

KEY POINTS

The development and persistence of asthma are driven by gene–environment interactions. There is a "window of opportunity" *in utero* and in early life to prevent asthma in children, 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 are:

- To avoid exposure to environmental tobacco smoke during pregnancy and the first year of life.
- To encourage vaginal delivery where possible.
- To avoid use of broad-spectrum antibiotics during the first year of life, where possible.

Breastfeeding is advised, not for prevention of allergy and asthma, but for its other positive health benefits.

For adults with adult-onset asthma, always ask about occupational or domestic exposures, as these exposures may explain 5–20% of new cases of asthma.

In adults and adolescents, the early identification and elimination of occupational sensitizers and the removal of sensitized patients from any further exposure are important aspects of the prevention and management of occupational asthma.

FACTORS ASSOCIATED WITH INCREASED OR DECREASED RISK OF ASTHMA IN CHILDREN

Asthma is a heterogeneous disease whose inception and persistence are driven by gene–environment interactions that are not yet fully understood. 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 from studies investigating the role of environmental risk factors for the development of asthma support further research on prevention strategies focusing on nutrition, allergens (both inhaled and ingested), pollutants (particularly environmental tobacco smoke), microbes, and psychosocial factors.

"Primary prevention" refers to preventing the onset of disease.

DIETARY FACTORS: NUTRITION AND SUPPLEMENT USE BY MOTHER AND/OR CHILD

Nutrition of mother and/or child

Maternal diet

A large body of research investigating the development of allergy and asthma in children has focused on the mother's diet during pregnancy. Current evidence does not clearly demonstrate that ingestion of any specific foods during pregnancy increases the risk for asthma. However, a 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.[891] 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.[892,893] 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.[894-897] Dietary changes during pregnancy are therefore not recommended for prevention of allergies or asthma.

Breastfeeding

Despite the existence of many studies reporting a beneficial effect of breastfeeding on asthma prevention, results are conflicting,[898] and caution should be taken in advising families that breastfeeding will prevent asthma. Breastfeeding decreases wheezing episodes in early life; however, it may not prevent development of persistent asthma (Evidence D). Regardless of any effect on development of asthma, breastfeeding should be encouraged for its other positive benefits (Evidence A).

Timing of introduction of solids

Beginning in the 1990s, many national pediatric agencies and societies recommended delayed introduction of solid food, especially for children at a high risk for developing allergy. However, meta-analyses have found no evidence that this practice reduces the risk of allergic disease (including asthma).[899] Early introduction of peanuts may prevent peanut allergy in high-risk infants.[899]

Dietary supplements for mother and/or child

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.[900] This was not confirmed in two randomized controlled trials (RCTs) of vitamin D supplementation in pregnancy, which compared standard-dose with high-dose vitamin D; however, a significant effect was not disproven.[901,902] 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.[903] The effect was greatest among women who maintained 25(OH)vitamin D levels of at least 30 ng/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,[903] although in both trials, no effects of vitamin D supplementation on the development of asthma and recurrent wheeze were evident at the age of 6 years.[904] Secondary analysis of the VDAART study[902] suggested that earlier supplementation may be more effective in reducing the risk of asthma.[905]

Fish oil and long-chain polyunsaturated fatty acids

Systematic reviews of cohort studies about maternal dietary intake of fish or seafood during pregnancy[894,906] and of RCTs on maternal dietary intake of fish or long-chained polyunsaturated fatty acids during pregnancy[894] showed no consistent effects on the risk of wheeze, asthma or atopy in the child. One study demonstrated decreased wheeze/asthma in preschool children at high risk for asthma when mothers were given a high-dose fish oil supplement in the third trimester;[907] 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).[908]

ENVIRONMENTAL FACTORS

Inhalant allergens

Allergic sensitization is the best predictor for development of persistent asthma.[909] Sensitization to indoor inhaled aeroallergens 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,[910,911] the relationship for animal allergen appears to be more complex.[898] Some studies have found that exposure to pet allergens is associated with increased risk of sensitization to these allergens,[912,913] and of asthma and wheezing.[914,915] By

contrast, other studies have demonstrated a decreased risk of developing allergy with exposure to pets.[916,917] Analyses of data from large populations of school-age children from birth cohorts in Europe have found no association between pets in the homes early in life and higher or lower prevalence of asthma in children.[918,919] For children at risk of asthma, dampness, visible mold and mold odor in the home environment are associated with increased risk of developing asthma.[920] Overall, there are insufficient data to recommend efforts to either reduce or increase prenatal 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,[921] the Canadian Asthma Primary Prevention Study,[922] and the Prevention of Asthma in Children study[923] were associated with lower risk of asthma diagnosis in children younger than 5 years.[924] Two multifaceted studies that followed children beyond age 5 years demonstrated a significant protective effect both before and after the age of 5 years.[921,925] The Isle of Wight study has shown a continuing positive benefit for early-life intervention through to age 18 years;[926] however, it remains unclear which components of the intervention contributed to the effects reported, and the precise mechanism of these effects.

Treatment with grass pollen sublingual allergen immunotherapy (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 aged 5–12 years with grass-allergic rhinoconjunctivitis, but asthma symptoms and asthma medication use were reduced. [927] At present, there is insufficient evidence to make a recommendation for SLIT in children with grass allergic rhinoconjunctivitis for the purpose of asthma prevention. More studies are needed.

Pollutants

Maternal smoking during pregnancy is the most direct route of prenatal environmental tobacco smoke exposure.[928] A meta-analysis concluded that prenatal smoking had its strongest effect on young children, whereas postnatal maternal smoking appeared only to affect asthma development in older children.[929] Exposure to outdoor pollutants, such as living near a main road, is associated with increased risk of asthma.[930,931] A 2019 study suggested that up to 4 million new pediatric asthma cases (13% of the global incidence) may be attributable to exposure to traffic-related air pollution.[932] Prenatal NO_2, SO2, and PM_{10} exposures are associated with an increased risk of asthma in childhood,[933] but it is difficult to separate effects of prenatal and postnatal exposure.

Microbial effects

The “hygiene hypothesis”, and the more recently coined “microflora hypothesis” and “biodiversity hypothesis”,[934] 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.[935] The risk of asthma is also reduced in children whose bedrooms have high levels of bacterial-derived lipopolysaccharide endotoxin.[936,937] Similarly, children in homes with ≥2 dogs or cats are less likely to be allergic than those in homes without dogs or cats.[917] 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.[938,939] This may relate to differences in the infant gut microbiota according to their mode of delivery.[940]

Respiratory syncytial virus (RSV) infection in infancy is associated with recurrent wheeze at age 5 years.[832] Preventative treatment of premature infants with monthly injections of palivizumab, a monoclonal antibody prescribed for prophylaxis of severe RSV infection, was associated with a reduction in recurrent wheezing in the first year of life.[941] However, 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.[942] The long-term effect of RSV-specific monoclonal antibodies in the prevention of asthma remains uncertain.[943] Studies of RSV vaccination of pregnant women[944] and healthy infants[945] suggest a reduction in RSV infection requiring medical attention in the first year of life. However, it has not yet been established whether these interventions will lead to a reduced risk of further wheezing episodes, or will prevent development of asthma.

Medications and other factors

Antibiotic use during pregnancy and in infants and toddlers has been associated with the development of asthma later in life,[946] although not all studies have shown this association.[947] Intake of the analgesic, paracetamol (acetaminophen), may be associated with an increased risk of asthma in both children and adults,[948] although exposure during infancy may be confounded by use of paracetamol for respiratory tract infections.[948] Frequent use of paracetamol by pregnant women has been associated with increased risk of asthma in their children.[949]

Maternal folic acid supplementation during pregnancy at higher than recommended doses may be associated with a small increase in the risk of childhood asthma in offspring.[950] However, this small risk is far outweighed by the well-established role of folate supplementation in reducing the risk of clinically important neural tube defects. Women should therefore be advised and encouraged to follow recommendations by local health authorities on folic acid supplementation during pregnancy.

There is no evidence that vaccinations increase a child's risk of developing asthma.

PSYCHOSOCIAL AND PHYSICAL FACTORS

Maternal distress

The social environment to which children are exposed may also contribute to the development and severity of asthma. Maternal distress during pregnancy[951] or during the child's early years[952] has been associated with an increased risk of the child developing asthma.

Obesity

Maternal obesity and weight gain during pregnancy

Data from observational studies suggest that maternal obesity and weight gain during pregnancy pose an increased risk for asthma in children. A meta-analysis[953] showed that maternal obesity in pregnancy was associated with higher odds of ever asthma or wheeze or current asthma or wheeze; each 1 kg/m^2 increase in maternal body-mass index (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.

Obesity in children

A meta-analysis of 18 studies found that being either overweight or obese was a risk factor for childhood asthma and wheeze, particularly in girls.[547] In adults, there is evidence suggesting that obesity affects the risk of asthma, but that asthma does not affect the risk of obesity.[954,955]

Pre-term birth and low birth weight

Pre-term birth (<37 weeks) and low birthweight (<2.5 kg) are associated with increased risk of wheezing disorders in infancy and early childhood, and increased risk of asthma in childhood.[956]

ADVICE ABOUT PRIMARY PREVENTION OF ASTHMA

Prevention of asthma in children

Based on the results of cohort and observational studies,[957] and a GRADE-based analysis conducted for the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines,[898] parents/caregivers enquiring about how to reduce the risk of their children developing asthma can be provided with the advice summarized in Box 13-1.

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 13-1. Advice about primary prevention of asthma in children 5 years and younger

Parents/caregivers enquiring about how to reduce the risk of their child developing asthma can be given the following advice:

- Children should not be exposed to environmental tobacco smoke during pregnancy or after birth.
- Identification and correction of Vitamin D insufficiency in women with asthma who are pregnant, or planning pregnancy, may reduce the risk of early life wheezing episodes.
- Where possible, vaginal delivery should be encouraged.
- Where possible, the use of broad-spectrum antibiotics during the first year of life should be discouraged.
- Breastfeeding is advised, not for prevention of allergy or asthma, but for its other positive health benefits.

Prevention of occupational asthma in adults

An estimated 5–20% of new cases of adult-onset asthma can be attributed to occupational exposure.[65] 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. Early diagnosis is essential, as persistent exposure is associated with worse outcomes.[65,66]

Asthma acquired in the workplace is frequently missed. The occurrence of adult-onset asthma requires a systematic inquiry about work history and exposures, including hobbies. An essential screening question is to ask patients whether their symptoms improve when they are away from work (weekends or vacation).[67] 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 peak expiratory flow (PEF) monitoring at and away from work is often used to help confirm the diagnosis.

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.[65] For example, cost-effective minimization of latex sensitization can be achieved by using non-powdered low-allergen gloves instead of powdered latex gloves.[65]

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).

There is more information about occupational asthma in specific guidelines.[65,68]

14. Implementing asthma management strategies into health systems

KEY POINTS

- 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 consider 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 can be aided by tools developed for this purpose.

INTRODUCTION

Due to the exponential increase in medical research publications, practical syntheses are needed to guide policy makers and healthcare providers in delivering evidence-based care. When asthma care is consistent with evidence-based recommendations, outcomes improve.[228,958,959] This Strategy Report is a resource document for healthcare providers, intended to set out 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. These objectives can only be realized through local implementation in each country, region and healthcare organization.

The use of rigorous methodologies such as Grading of Recommendations Assessment, Development and Evaluation (GRADE)[10] for the development of clinical practice recommendations, and of ADAPTE[960] 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.[961] Further, there is generally very limited high quality evidence addressing the many decision nodes in comprehensive clinical practice guidelines, particularly in developing countries.

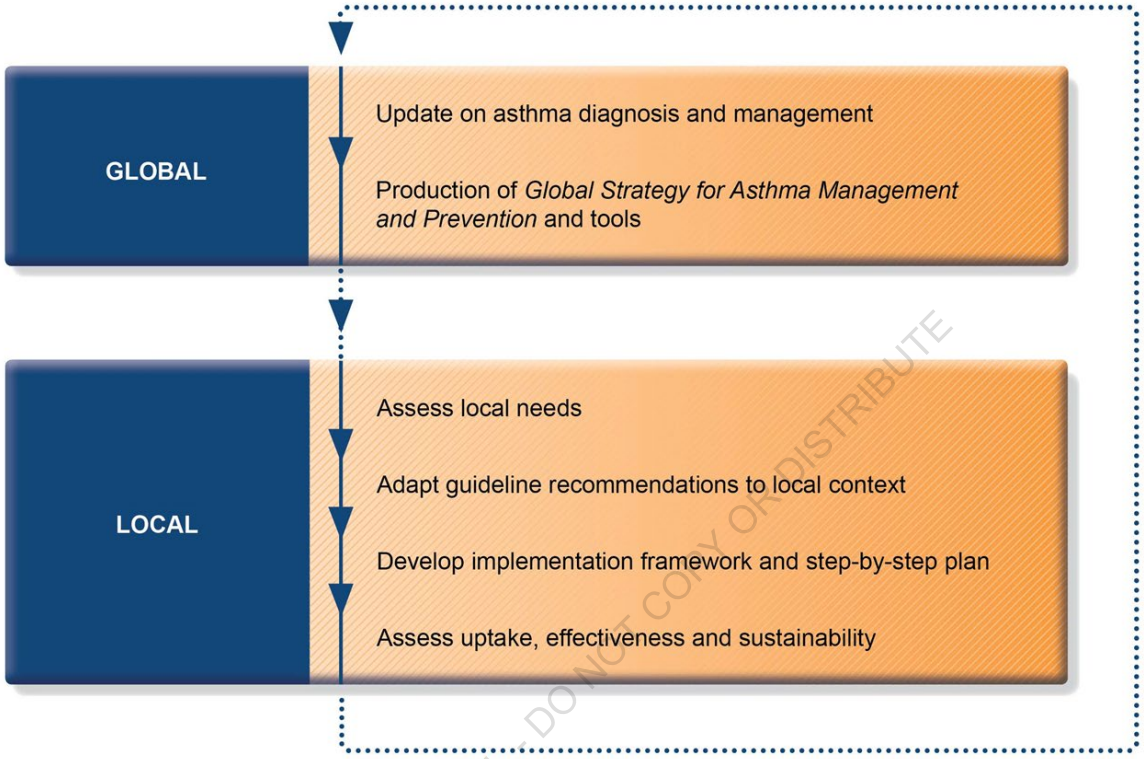
The GINA annual report is not a formal guideline but an evidence-based strategy, updated yearly from a review of the evidence published in the last 18 months. Each year's report is an update on the entire strategy, so it does not use individual PICOT questions and GRADE, but the review process includes systematic reviews using these methodologies. (See section on methodology at www.ginasthma.org). As with other evidence-based clinical recommendations, the GINA strategy must be adapted to the local context for implementation in clinical practice.

ADAPTING AND IMPLEMENTING ASTHMA CLINICAL PRACTICE GUIDELINES

Implementation of asthma management strategies may be carried out at a national, regional or local level.[962] Ideally, implementation should be a multidisciplinary effort involving many stakeholders, and using cost-effective methods of knowledge translation.[962-964] Each implementation initiative needs to consider the nature of the local health system and its resources, including human resources, infrastructure, and available treatments (Box 14-1). 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 14-2.

Box 14-1. Approach to implementation of the Global Strategy for Asthma Management and Prevention



Box 14-2. 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 (e.g., primary care health providers, specialists, nurses, pharmacists, patients, community members).

2. Assess the current status of asthma care delivery, outcomes e.g., exacerbations, admissions, deaths, 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.

In treatment recommendations, consider environmental issues (planetary health) in addition to patient health

4. Identify barriers to implementation and facilitators of implementation.

5. Select an implementation framework and its component strategies.

6. Develop a step-by-step implementation plan:

- Select target populations and evaluable outcomes, and specify data coding requirements (if relevant).
- Identify local resources to support implementation.
- Set timelines.
- Distribute tasks to members.
- Evaluate outcomes.

7. Continually 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.[964-967] Some of the barriers to implementation of evidence-based asthma management relate to the delivery of care, while others occur at individual or community level (see Box 14-3). Cultural and economic barriers can particularly affect the application of recommendations.

Box 14-3. Examples of barriers to the implementation of evidence-based recommendations

Healthcare providers	Patients
• Insufficient knowledge of recommendations • Lack of agreement with recommendations or expectation that they will be effective • Resistance to change • External barriers (organizational, health policies, financial constraints) • Lack of time and resources • Medico-legal issues • Lack of accurate coding (diagnosis, exacerbations, emergency department and hospital admissions, and deaths)	• Low health literacy • Insufficient understanding of asthma and its management • Lack of agreement with recommendations • Cultural and economic barriers • Peer influence • Attitudes, beliefs, preferences, fears and misconceptions

High-impact implementation interventions

Ideally, interventions should be applied at the level of both the patient and the healthcare provider and, where relevant, the health system. Studies of the most effective means of medical education show that it may be difficult to change clinical practice. Examples of highly effective implementation interventions are shown in Box 14-4.

Box 14-4. Examples of high-impact implementation interventions in asthma management

- Free inhaled corticosteroids (ICS) for patients with a recent hospital admission and/or severe asthma[968]
- Early treatment with ICS, guided self-management, reduction in exposure to tobacco smoke, improved access to asthma education[228]
- Checklist memory aid for primary care, prompting assessment of asthma control and treatment strategies[969]
- Use of individualized written asthma action plans as part of self-management education[540]
- An evidence-based care process model for acute and chronic pediatric asthma management, implemented at multiple hospitals[970]

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. 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 healthcare system. Each country should determine its own minimum sets of data to audit health outcomes.

How can GINA help with implementation?

The GINA Strategy 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 report provides approaches for consideration. The GINA Dissemination Group assists in the dissemination of the recommendations in the Strategy Report. GINA can be contacted via the website (www.ginasthma.org/contact-us).

Appendix A: Overview of Type 2 biomarkers in the diagnosis and management of asthma in adolescents and adults

Numerous biomarkers have been investigated in the blood, urine, induced sputum, exhaled air and bronchoalveolar lavage fluid of people with asthma. Biomarkers must be measured and interpreted in the appropriate clinical context. In the clinical management of asthma, the most useful and widely used biomarkers are those reflecting Type 2 airway inflammation and allergy: blood eosinophil count, fractional exhaled nitric oxide (FeNO), serum total immunoglobulin E (IgE), and allergen-specific IgE. These biomarkers have roles in diagnosis, phenotyping, monitoring, prognosis and prediction of treatment response in asthma. Sputum eosinophil count is useful in directing corticosteroid therapy in patients with moderate–severe asthma, but it is not generally available in clinical practice.

This Appendix brings together and expands on information about Type 2 biomarkers that has been included in previous GINA reports, with additional information about sources of variability in blood eosinophils and FeNO.

Table A1. High blood eosinophils and FeNO, and factors affecting their levels, in adults and adolescents

Biomarker	Typical criteria for 'high' in adults/adolescents	Factors affecting measurement
Blood eosinophil count (BEC)	For diagnosis of asthma: BEC ≥ upper limit of normal for the population from regional or national laboratory reference values. In severe asthma patients taking high-dose ICS: • BEC ≥150/μL suggests presence of Type 2 inflammation; • BEC ≥300/μL is a common threshold for eligibility for Type 2-targeted biologics.	BEC levels are influenced by multiple factors, including age, sex, time of day, smoking, and allergen exposure in sensitized individuals.[53,700] Within a population, BEC is higher: • in males than females • in the morning than the afternoon • in current smokers • with parasitic infections (e.g., helminths) • in allergic diseases (e.g., atopic dermatitis, allergic rhinitis, drug hypersensitivity) • with allergen exposure in sensitized individuals • in other non-asthma conditions (e.g., eosinophilic bronchitis, EGPA). Within a population, BEC is lower: • in some asthma phenotypes • in patients taking corticosteroids (particularly oral corticosteroids, but also inhaled and intranasal).
Fractional exhaled nitric oxide (FeNO)	Population reference values are not possible at present.[50] In the interim, the following levels are suggested as indicating high FeNO: • ICS-naïve: >50 ppb • Medium-dose ICS: ≥25 ppb • High-dose ICS: ≥20 ppb	FeNO levels are influenced by multiple factors, including age, sex, time of day, and by allergen exposure in sensitized individuals, as well as by measuring device and site.[50,313] Within a population, FeNO is higher: • in males than females • in the afternoon than the morning • in allergic diseases, e.g., atopic dermatitis, allergic rhinitis • approximately 24 hours after allergen exposure in sensitized individuals. Within a population, FeNO is lower: • in current smokers • during bronchoconstriction and with lower lung function • during the early allergic response • with inhaled corticosteroids (dose-dependent) but also with oral or nasal corticosteroids.

Implications for use of Type 2 biomarkers in clinical practice

Given the many sources of variation listed above, blood eosinophil counts and FeNO levels should be interpreted with caution in clinical practice, especially by comparison with specific threshold values. This is particularly important outside the context of clinical trials, in which study visits (and hence biomarker measurements) are often standardized with regard to time of day.

For patients with severe asthma who are being assessed for eligibility for Type 2-directed biologic therapy, if blood eosinophils and/or FeNO are not initially above the target threshold, they should be measured at least 3 times; additional details are on p.150 and p.152.

Table A2. Clinical utility of Type 2 biomarkers

Biomarker	Clinical context or population	Clinical utility of biomarker
1. INITIAL DIAGNOSIS OF ASTHMA		
Blood eosinophil count (BEC)	Adults with typical symptoms of asthma, but normal or obstructive spirometry without a positive bronchodilator responsiveness test	In a patient with typical asthma symptoms, high BEC may support a diagnosis of Type 2 asthma, but consider non-asthma causes of elevated BEC (as above). Low BEC does not rule out asthma.[46,700,971-974] Diagnosis of asthma is further supported if there is a clinical response to asthma treatment (see Box 1-1 [p.24] and Box 1-2 [25]).
FeNO	Adults with typical symptoms of asthma, but normal or obstructive spirometry without a positive bronchodilator responsiveness test	In a patient with typical asthma symptoms, a high FeNO may support a diagnosis of Type 2 asthma, but there are non-asthma causes of elevated FeNO (as above), and a low FeNO does not rule out asthma.[46,49,313,973,975-984] Diagnosis of asthma is further supported if there is a clinical response to asthma treatment (see Box 1-1 [p.24] and Box 1-2 [25]).
2. PHENOTYPING OF ASTHMA		
2.1 *Mild-to-moderate asthma*		
BEC	Identification of asthma phenotypes in adults and adolescents	High BEC in a patient with an established diagnosis of asthma is consistent with eosinophilic asthma.[19,47,985]
FeNO	Identification of asthma phenotypes in adults and adolescents	High FeNO in a patient with an established diagnosis of asthma is consistent with Type 2 asthma.[19,47,985]
Serum total IgE Allergen-specific IgE	Identification of asthma phenotypes in adults, adolescents and children	One or more positive tests for a clinically-relevant allergen-specific IgE (or skin prick tests) in a patient with an established diagnosis of asthma is consistent with allergic asthma,[19,47,985] when consistent with a medical history of symptoms triggered by exposure to specific aeroallergen(s).
2.2 *Severe asthma*		
See GINA 2025 Chapter 8: Difficult-to-treat and Severe Asthma (p.139). To identify Type 2-high severe asthma in patients taking high-dose ICS-containing therapy, BEC and FeNO may need to be repeated up to 3 times. For patients taking OCS, the biomarkers should be measured, if possible, at least 1–2 weeks after cessation of a burst of OCS, or on the lowest possible maintenance dose; a pause of 2 days in maintenance OCS dose can allow BEC to increase (p.150).[702]		

Biomarker	Clinical context or population	Clinical utility of biomarker
3. PROGNOSIS OF ASTHMA		
BEC	Patients with a history of ≥1 asthma exacerbation in the previous year	A high BEC is associated with a higher risk of (future) asthma exacerbations, particularly in patients taking a medium/high dose of ICS or OCS.[14,986,987]
FeNO	Patients with a history of ≥1 asthma exacerbation in the previous year	In ICS-treated patients, a high FeNO is associated with a higher risk of (future) asthma exacerbations.[14,986,987]
BEC and FeNO	Patients with a history of ≥1 asthma exacerbation in the previous year	BEC and FeNO provide complementary prognostic information in patients with asthma; risk of future asthma exacerbations is highest when both BEC and FeNO are high.[14]
4.SELECTING ASTHMA TREATMENT, OR PREDICTING RESPONSE		
4.1 Mild asthma		
BEC	Adults with mild asthma taking low-dose ICS or no ICS	The reduction in severe exacerbations seen with as-needed-only ICS-formoterol (AIR-only) compared with as-needed SABA or daily ICS plus as-needed SABA is independent of baseline BEC, i.e., patients with either low or high BEC have a significant reduction in severe exacerbations with AIR-only compared with these other regimens.[195,196]
FeNO	Adults with mild asthma taking low-dose ICS or no ICS	The reduction in severe exacerbations seen with as-needed-only ICS-formoterol vs SABA-only or daily ICS plus as-needed SABA is independent of baseline FeNO, i.e., patients with either low or high FeNO have a significant reduction in severe exacerbations with AIR-only compared with these other regimens.
4.2 Moderate asthma		
BEC	Adults with uncontrolled asthma despite prescription of GINA step 3 or 4 treatment	The reduction in severe exacerbations with maintenance-and-reliever therapy (MART) with ICS-formoterol is independent of baseline BEC, (i.e., patients with low BEC have a significant reduction in severe exacerbations with MART compared with SABA-based regimens), but the benefit increases with higher BEC.[988] If BEC is high, first check adherence and inhaler technique first; consider switching to anti-inflammatory reliever therapy (GINA Track 1) or (if reliever is SABA) increasing ICS dose.[368]
FeNO	Adults with uncontrolled asthma despite prescription of GINA step 3 or 4 treatment	In patients with difficult-to-treat asthma and persistently high FeNO despite prescribing of medium-high dose ICS-LABA, directly observed or monitored corticosteroid therapy suppresses FeNO in approximately two-thirds of patients, and is associated with previous poor adherence.[236,506] If FeNO is high, check adherence and inhaler technique first;[236,506] if asthma remains uncontrolled, consider switching to anti-inflammatory reliever therapy (GINA Track 1) or, if reliever is SABA, increasing ICS dose.[368]

Biomarker	Clinical context or population	Clinical utility of biomarker
BEC and FeNO	Adults with uncontrolled asthma despite prescription of GINA step 3 or 4 treatment	If both BEC and FeNO are low, either in stable state or during exacerbations, consider other treatment options (pharmacological and non-pharmacological) before increasing ICS dose.[368]
4.3 Severe asthma		
BEC	Adults with severe asthma who experience exacerbations despite treatment with high dose ICS-LABA	A high BEC predicts a better asthma response to add-on treatment with all biologics licensed for treatment of asthma than a lower BEC.[398,403,989]
FeNO	Adults with severe asthma who experience exacerbations despite treatment with high-dose ICS-LABA	For patients with high FeNO, first check adherence, because FeNO suppression with directly observed administration of corticosteroid identifies poor adherence in two-thirds of patients with persistently high FeNO despite prescription of high-dose ICS-LABA.[236,506] A high FeNO predicts a better asthma response to add-on treatment with dupilumab, omalizumab and tezepelumab than a lower FeNO.[398,403,989] The efficacy of anti-IL5 (mepolizumab, reslizumab) and anti-IL5R (benralizumab) is independent of FeNO levels.[989]
BEC and FeNO	Adults with severe asthma who experience exacerbations despite treatment with high-dose ICS-LABA	BEC and FeNO provide complementary theragnostic information in severe asthma; patients with severe asthma treated with dupilumab or tezepelumab have the best clinical response if both BEC and FeNO (pre-biologic) are high.[398,403,989]

AIR: anti-inflammatory reliever (ICS-formoterol); BDR: bronchodilator responsiveness; BEC: blood eosinophil count; EGPA: eosinophilic granulomatosis with polyangiitis; FeNO: fractional exhaled nitric oxide; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist.

Appendix B. Overview of asthma medication classes

For more details about medications, see Product Information from manufacturers. Always check local eligibility criteria.

ANTI-INFLAMMATORY RELIEVER MEDICATIONS	
Low-dose combination ICS-formoterol	
Medications	Beclometasone-formoterol or budesonide-formoterol
Delivery	pMDI or DPI
Indications	This is the anti-inflammatory reliever inhaler for GINA Track 1, for patients prescribed maintenance-and-reliever therapy (MART) with maintenance ICS-formoterol in Steps 3-5, or for patients prescribed as-needed-only ICS-formoterol in Steps 1-2. In both settings, it reduces the risk of severe exacerbations, compared with using SABA as reliever, with similar symptom control. In patients with mild asthma, as-needed-only ICS-formoterol reduces emergency visits/hospitalizations by 65%, compared with SABA alone, and by 37% when compared with daily ICS plus as-needed SABA. See Box 4-8, p.84 for details of medications and doses for AIR-only and MART. Low-dose ICS-formoterol can be taken before exercise to reduce exercise-induced bronchoconstriction, and before or during allergen exposure to reduce allergic responses.
Recommended maximum doses in any day	For adults and adolescents, the maximum total number of inhalations in a single day (maintenance plus reliever doses) for budesonide-formoterol gives 72 mcg metered dose (delivered dose 54 mcg) of the formoterol component. Since the safety and efficacy of budesonide-formoterol up to this maximum total daily use has been established from large studies (>50,000 patients), GINA suggests that the same maximum total daily dose should also apply for beclometasone-formoterol. For children 6–11 years prescribed MART with budesonide-formoterol, the maximum total dose recommended in a single day gives 48 mcg metered dose (delivered dose 36 mcg) of the formoterol component. See Box 4-7, p.78 for details of medications and doses for different age-groups.
Adverse effects	As for ICS-formoterol above
Low-dose combination ICS-SABA	
Medications	Budesonide-salbutamol (also described as albuterol-budesonide); beclometasone-salbutamol
Delivery	pMDI or DPI
Indications	Anti-inflammatory reliever option (instead of SABA) for GINA Track 2. Budesonide-salbutamol 100/100 mcg (delivered dose 80/90 mcg), 2 inhalations taken as needed for symptom relief on top of maintenance ICS or ICS-LABA, reduced the risk of severe exacerbations in adults, compared with SABA reliever; most of the benefit was seen in Step 3. ICS-SABA cannot be used for maintenance-and-reliever therapy. No published evidence for as-needed-only use of budesonide-salbutamol in Steps 1–2.
Recommended maximum doses in any day:	Maximum 6 doses, each of 2 inhalations, in any day
Adverse effects	As for ICS and SABA

MEDICATIONS for MAINTENANCE TREATMENT	
Inhaled corticosteroids (ICS)	
Medications	Beclometasone, budesonide, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone, triamcinolone
Delivery	pMDI or DPI
Indications	ICS-containing medications are the most effective anti-inflammatory medications for asthma. ICS reduce symptoms, increase lung function, reduce airway hyperresponsiveness, improve quality of life, and reduce the risk of exacerbations, asthma-related hospitalizations and death. ICS differ in their potency and bioavailability, but most of the benefit is seen at low doses (see Box 4-2, p.71) for low, medium and high doses of different ICS). Adherence with ICS alone is usually very poor because the patient does not perceive any immediate benefit.
Adverse effects	Most patients do not experience side-effects. Local side-effects include oropharyngeal candidiasis and dysphonia; these can be reduced by use of a spacer with pMDIs, and rinsing with water and spitting out after inhalation. Long-term high doses increase the risk of systemic side-effects such as osteoporosis, cataract and glaucoma. Concomitant treatment with cytochrome P450 inhibitors such as ketoconazole, ritonavir, itraconazole, erythromycin and clarithromycin may increase the risk of ICS adverse effects such as adrenal suppression.
ICS in combination with a long-acting beta$_2$-agonist bronchodilator (ICS-LABA)	
Medications	Beclometasone-formoterol, budesonide-formoterol, fluticasone furoate-vilanterol, fluticasone propionate formoterol, fluticasone propionate-salmeterol, mometasone-formoterol and mometasone-indacaterol
Delivery	pMDI or DPI
Indications	When a low-dose of ICS alone fails to achieve good control of asthma, the addition of LABA to maintenance ICS improves symptoms, lung function and reduces exacerbations in more patients, more rapidly, than doubling the dose of ICS. Two regimens are available for adults and adolescents: low-dose combination beclometasone or budesonide with low-dose formoterol for both maintenance-and-reliever treatment (MART, GINA Track 1), and maintenance ICS-LABA with SABA or ICS-SABA as reliever (Track 2). MART with low-dose ICS-formoterol reliever is preferred as it reduces exacerbations, compared with conventional maintenance therapy with SABA as reliever, and is a simpler regimen. For as-needed-only use of ICS-formoterol in mild asthma, see section on anti-inflammatory relievers below; and for ICS-LABA-LAMA, see section on add-on medications. See box 4-2, p.71 for low, medium and high doses of ICS in combination with LABA. See Box 4-8, p.84 for medications and doses for anti-inflammatory reliever therapy with ICS-formoterol.
Adverse effects	The LABA component may be associated with tachycardia, headache or cramps. LABA is safe for asthma when used in combination with ICS, but LABA and/or LAMA should not be used without ICS in asthma (or in patients with asthma+COPD) due to increased risk of serious adverse outcomes. Concomitant treatment with cytochrome P450 inhibitors such as ketoconazole, ritonavir, itraconazole, erythromycin and clarithromycin may increase the risk of ICS adverse effects such as adrenal suppression.

Leukotriene receptor antagonists (LTRA) and leukotriene modifiers	
Medications	Montelukast, pranlukast, zafirlukast, zileuton
Delivery	Tablets
Indications	Target one part of the inflammatory pathway in asthma. Sometimes used as an option for maintenance therapy, mainly only in children. When used alone: less effective than low-dose ICS. When added to ICS: less effective than ICS-LABA.
Adverse effects	Few in placebo-controlled studies except elevated liver function tests with zileuton and zafirlukast. There are concerns in adults and children about risk of serious behavioral and mood changes, including suicidal ideation, associated with montelukast; this should be discussed with patients/parents/caregivers.
ADD-ON MAINTENANCE MEDICATIONS	
Long-acting muscarinic antagonists (LAMA) (check your local eligibility criteria)	
Medications	Tiotropium, ≥6 years, by mist inhaler, added to separate ICS-LABA Combination ICS-LABA-LAMA inhalers for adults ≥18 years: beclometasone-formoterol-glycopyrronium; fluticasone furoate-vilanterol-umeclidinium; mometasone-indacaterol-glycopyrronium
Delivery	pMDI or DPI or mist inhaler
Indications	An add-on option at Step 5 (or at Step 4, non-preferred because of weaker evidence for benefit) in combination or separate inhalers for patients with uncontrolled asthma despite ICS-LABA. Modestly improves lung function but not symptoms or quality of life; small reduction in exacerbations. For patients with exacerbations, ensure that ICS is increased to at least medium dose before considering need for add-on LAMA.
Adverse effects	Uncommon, but include dry mouth, urinary retention.
Anti-IgE (check your local eligibility criteria)	
Medications	Omalizumab, ≥6 years
Delivery	Syringe or pen for subcutaneous injection
Indications	An add-on option for patients with severe allergic asthma uncontrolled on high-dose ICS-LABA. May also be indicated for nasal polyps, confirmed IgE-mediated food allergy, and chronic spontaneous (idiopathic) urticaria. Self-administration may be an option.
Adverse effects	Reactions at the site of injection are common but minor. Anaphylaxis is rare.
Anti-IL5 and anti-IL5Rα (check your local eligibility criteria)	
Medications	Anti-IL5: mepolizumab (≥6 years, SC injection) or reslizumab (≥18 years, intravenous infusion); Anti-IL5 receptor benralizumab (≥12 years, SC injection)
Delivery	Depends on the specific medication, as above
Indications	Add-on options for patients with severe eosinophilic asthma uncontrolled on high-dose ICS-LABA. Maintenance OCS dose can be significantly reduced with benralizumab and mepolizumab. Mepolizumab and benralizumab may also be indicated for eosinophilic granulomatosis with

	polyangiitis (EGPA), and mepolizumab also for hypereosinophilic syndrome or chronic rhinosinusitis with nasal polyps. For mepolizumab and benralizumab, self-administration may be an option.
Adverse effects	Headache, and reactions at injection site are common but minor.
Anti-IL4Rα (check your local eligibility criteria)	
Medications	Dupilumab, ≥6 years
Delivery	Syringe or pen for subcutaneous injection
Indications	An add-on option for patients with severe eosinophilic or Type 2 asthma uncontrolled on high-dose ICS-LABA, or patients requiring maintenance OCS. Not advised for patients with current or historical blood eosinophils ≥1500/μL. May also be indicated for treatment of skin conditions including moderate–severe atopic dermatitis, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis. Self-administration may be an option.
Adverse effects	Reactions at injection site are common but minor. Transient blood eosinophilia occurs in 4–13% of patients. Rarely, cases of eosinophilic granulomatosis with polyangiitis (EGPA) may be unmasked following reduction/cessation of OCS treatment on dupilumab.
Anti-TSLP (check your local eligibility criteria)	
Medications	Tezepelumab, SC injection, ≥12 years
Delivery	Syringe or pen for subcutaneous injection
Indications	An add-on option for patients with severe asthma uncontrolled on high-dose ICS-LABA. In patients taking maintenance OCS, no significant reduction in OCS dose, compared with placebo.
Adverse effects	Injection-site reactions; anaphylaxis is rare; adverse events generally similar between active and placebo groups.
Systemic corticosteroids	
Medications	e.g., prednisone, prednisolone, methylprednisolone, hydrocortisone tablets, dexamethasone
Delivery	Given by tablets or suspension or by IM or IV injection
Indications	Short-term treatment (usually 5–7 days in adults) is important in the treatment of severe acute exacerbations, with main effects seen after 4–6 hours. For severe acute exacerbations, oral corticosteroid (OCS) therapy is preferred to IM or IV therapy and is effective in preventing short-term relapse. Tapering is required if OCS given for more than 2 weeks. Patients should be reviewed after any exacerbation, to optimize their inhaled treatment to reduce the risk of future exacerbations requiring OCS. As a last resort, long-term treatment with OCS may be required for some patients with severe asthma, but serious side-effects are problematic. Patients for whom this is considered should be referred for specialist review if available, to have treatment optimized and phenotype assessed.

Adverse effects	Short courses: adverse effects include sepsis, thromboembolism, sleep disturbance, reflux, appetite increase, hyperglycemia, mood changes. Even 4–5 lifetime courses increase cumulative risk of long-term adverse effects e.g., diabetes, osteoporosis, cataract, glaucoma, heart failure. Maintenance use: consider only as last resort, because of significant adverse effects e.g., cataract, glaucoma, hypertension, diabetes, adrenal suppression osteoporosis. Assess for these risks and treat appropriately.
SHORT-ACTING BRONCHODILATOR RELIEVER MEDICATIONS	
Short-acting inhaled beta$_2$-agonist bronchodilators (SABA)	
Medications	e.g., salbutamol (albuterol), terbutaline
Delivery	Administered by pMDI, DPI or, rarely, as solution for nebulization or injection
Indications	Inhaled SABAs provide quick relief of asthma symptoms and bronchoconstriction, and for pre-treatment before exercise. SABAs should be used only as-needed (not regularly) and at the lowest dose and frequency required. SABA-only treatment is not recommended because of the risk of severe exacerbations and asthma-related death, compared with use of any ICS. Currently, inhaled SABAs are the most commonly used bronchodilator for acute exacerbations requiring urgent primary care visit or ED presentation. Fenoterol is not recommended because of its association with increased cardiovascular adverse effects and increased risk of asthma mortality.
Adverse effects	Tremor and tachycardia are commonly reported with initial use of SABA. Tolerance develops rapidly with even 1–2 weeks of regular use, with increased airway hyperresponsiveness, reduced bronchodilator effect, and increased airway inflammation. Excess use, or poor response indicate poor asthma control and risk of exacerbations. Dispensing of 3 or more 200-dose canisters per year is associated with increased risk of exacerbations, and dispensing of 12 or more canisters per year is associated with markedly increased risk of death.
Short-acting antimuscarinics (anticholinergics)	
Medications	e.g., ipratropium bromide, oxitropium bromide. May be in combination with SABA
Delivery	pMDI or DPI
Indications	As-needed use: ipratropium is a less effective reliever medication than SABA, with slower onset of action. Short-term use in severe acute asthma, where adding ipratropium to SABA reduces the risk of hospital admission.
Adverse effects	Dryness of the mouth or a bitter taste

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