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GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION

Updated 2017

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Global Strategy for Asthma Management and Prevention (2017 update)

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

This document should be cited as: Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2017. Available from: www.ginasthma.org

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

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

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

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

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

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

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

Methodology

GINA SCIENCE COMMITTEE

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

PROCESSES FOR UPDATES AND REVISIONS OF THE GINA REPORT

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

After initial screening by the Program Director and Chair of the Science Committee, each publication identified by the above search is reviewed for relevance and quality by members of the Science Committee. Each publication is allocated to at least two Committee members, but all members receive a copy of all of the abstracts and have the opportunity to provide comments. Members evaluate the abstract and, by his/her judgment, the full publication, and answer written questions about whether the scientific data impact on GINA recommendations, and if so, what specific changes should be made. A list of all publications reviewed by the Committee is posted on the GINA website.

During Committee meetings, each publication that was assessed by at least one member to potentially impact on the GINA report is discussed. Decisions to modify the report or its references are made by consensus by the full Committee, or, if necessary, by an open vote of the full Committee; members recuse themselves from decisions with which they have a conflict of interest. The Committee makes recommendations for therapies that have been approved for asthma by at least one regulatory agency, but decisions are based on the best available peer-reviewed evidence and not on labeling directives from government regulators. In 2009, after carrying out two sample reviews using the GRADE system,[2] GINA decided not to adopt this methodology for its general processes because of the major resource challenges that it would present. This decision also reflected that, unique among evidence based recommendations in asthma, and most other therapeutic areas, GINA conducts an ongoing twice-yearly update of the evidence base for its recommendations. As with all previous GINA reports, levels of evidence are assigned to management recommendations where appropriate. A description of the current criteria is found in Table A. Annual updates of the Global Strategy for Asthma Management and Prevention are based on evaluation of publications from July 1 of the previous year through June 30 of the year the update was completed.

In 2014, a major revision of the GINA report was published. It was developed in the context of major changes in our understanding of airways disease, a focus on risk reduction as well as on symptom control, widespread interest in personalized asthma treatment, and extensive evidence about how to effectively translate and implement evidence into changes in clinical practice.[3,4] There were also substantial changes to the structure and layout of the report in 2014, with many new tables and flow-charts to communicate key messages for clinical practice. To further improve the utility of the report, detailed background information was placed in an Appendix on the GINA website (www.ginasthma.org), rather

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than being included in the report itself. As with the previous major revisions published in 2002 and 2006, the 2014 GINA report underwent extensive external peer review prior to publication.

A review of GINA methodology was conducted in 2016. It was decided that, for future meetings, the literature search would be expanded to include EMBASE as well as PubMed. Since the literature search is primarily focused on therapeutic interventions, but the GINA report also includes considerable background and explanatory material, it was agreed that each year, each chapter of the report would be reviewed by at least two members to assess its currency and clinical relevance.

LITERATURE REVIEWED FOR GINA 2017 UPDATE

The GINA report has been updated in 2017 following the routine twice-yearly review of the literature by the GINA Science Committee. The literature searches for 'clinical trial' publication types (see above) and meta-analyses identified a total of 304 publications, of which 190 were screened out for relevance and/or quality. The remaining 114 publications were reviewed by at least two members of the Science Committee, and 66 were subsequently discussed at a face-to-face meeting (37 'clinical trials' and 29 meta-analyses). A list of key changes in GINA 2017 can be found on p.10, and a tracked changes copy of the 2016 report is archived on the GINA website.

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

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

FUTURE CHALLENGES

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

At the most fundamental level, patients in many areas may not have access even to low dose inhaled corticosteroids, which are the cornerstone of care for asthma patients of all severity. More broadly, medications remain the major

contributor to the overall costs of asthma management, so the pricing of asthma medications continues to be an issue of urgent need and a growing area of research interest.

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

What's new in GINA 2017?

The GINA report has been updated in 2017 following the routine twice-yearly review of the literature by the GINA Scientific Committee. Full details of the changes can be found on the GINA website. In summary, the key changes are:

- 'Asthma-COPD overlap' is the term now recommended by GINA and GOLD to describe patients who have features of both asthma and COPD. Such patients are commonly seen in clinical practice, but they are rarely included in therapeutic trials. Asthma-COPD overlap does *not* refer to a single disease entity, but, as for 'asthma' and 'COPD', it likely includes several different phenotypes caused by different underlying mechanisms. The previous term 'asthma-COPD overlap syndrome', or ACOS, is no longer advised, because this term has often been used as if it was a separate disease. More details are found in Chapter 5 (p.89), which provides a pragmatic safety-focused approach to diagnosis and management of these patients in clinical practice, and calls for research to identify underlying mechanisms and treatment options.
- The recommendation about frequency of measuring lung function after diagnosis has been clarified (see p.31).
- Additional information has been added about factors affecting the fraction of exhaled nitric oxide (FENO), its relationship with eosinophilic airway inflammation, and its predictive value (p.20, p.29, p.38, p.41 and p.104).
- As an extra option in Steps 3 and 4, add-on sub-lingual immunotherapy (SLIT) can now be considered in adult house-dust mite-sensitive patients with asthma and allergic rhinitis who have exacerbations despite ICS treatment, provided FEV_1 is >70% predicted (Box 3-5 p.43, p.51).
- For Step 5 treatment, reslizumab has been included as an additional anti-IL5 treatment for adults with severe eosinophilic asthma (see p.47 and Box 3-14, p.70).
- Add-on leukotriene receptor antagonist has been included as an option for helping to down-titrate ICS (p.49).
- For patients with chronic rhinosinusitis, it has been clarified that treatment of the nose may reduce nasal symptoms, but does not generally improve asthma outcomes (p.65).
- In infants, prolonged cough, and cough without cold symptoms, are associated with later parent-reported physician-diagnosed asthma, independent of infant wheeze (p.103).
- Information about the potential effect of poorly-controlled asthma and inhaled corticosteroid (ICS) treatment on growth in children is now in the main report, in addition to the detailed material already in the Appendix. ICS may reduce growth velocity in the first 1-2 years of treatment, but this is not progressive or cumulative. In the one study that showed a difference in adult height, it amounted to only 0.7% of adult height. See p.30, p.108 and p.109.
- Information has been added about the different lung function trajectories that have been observed between childhood and early adult life (see p.31).
- Examples of high impact implementation interventions have been added to the main report (p.130)

Several references have been updated as new meta-analyses and studies have become available. These are itemized in the tracked-changes copy of the report, available on the GINA website.

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Peer-reviewed publications about the GINA report

The following articles, summarizing key changes in the GINA report in 2014—15, have been published in peer-reviewed journals.

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

Boulet LP *et al*. The revised 2014 GINA strategy report: opportunities for change. Curr Opin Pulm Med 2015; 21: 1-7

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

Reddel HK *et al*. A summary of the new GINA strategy: a roadmap to asthma control. Eur Respir J 2015; 46: 622-39 (open access; doi 10.1183/13993003.00853-2015). It is suggested that this article should be read as a companion piece to the GINA report, as it explains the rationale behind many key recommendations.

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Chapter 1.

Definition, description, and diagnosis of asthma

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KEY POINTS

- Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.
- Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called 'asthma phenotypes'; however, these do not correlate strongly with specific pathological processes or treatment responses.
- The diagnosis of asthma should be based on the history of characteristic symptom patterns and evidence of variable airflow limitation. This should be documented from bronchodilator reversibility testing or other tests.
- Asthma is usually associated with airway hyperresponsiveness and airway inflammation, but these are not necessary or sufficient to make the diagnosis.
- If possible, the evidence for the diagnosis of asthma should be documented before starting controller treatment, as it is often more difficult to confirm the diagnosis afterwards.
- Additional strategies may be needed to confirm the diagnosis of asthma in particular populations, including patients already on controller treatment, the elderly, and those in low-resource settings.

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DEFINITION OF ASTHMA

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

This definition was reached by consensus, based on consideration of the characteristics that are typical of asthma and that distinguish it from other respiratory conditions.

DESCRIPTION OF ASTHMA

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

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

Asthma phenotypes

Asthma is a heterogeneous disease, with different underlying disease processes. Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called 'asthma phenotypes'.[5-7] In patients with more severe asthma, some phenotype-guided treatments are available. However, to date, no strong relationship has been found between specific pathological features and particular clinical patterns or treatment responses.[8] More research is needed to understand the clinical utility of phenotypic classification in asthma.

Many phenotypes have been identified.[5-7] Some of the most common include:

- *Allergic asthma*: this is the most easily recognized asthma phenotype, which often commences in childhood and is associated with a past and/or family history of allergic disease such as eczema, allergic rhinitis, or food or drug allergy. Examination of the induced sputum of these patients before treatment often reveals eosinophilic airway inflammation. Patients with this asthma phenotype usually respond well to inhaled corticosteroid (ICS) treatment.
- *Non-allergic asthma*: some adults 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 respond less well to ICS.
- *Late-onset asthma*: some adults, particularly women, present with asthma for the first time in adult life. These patients tend to be non-allergic, and often require higher doses of ICS or are relatively refractory to corticosteroid treatment.
- *Asthma with fixed airflow limitation*: some patients with long-standing asthma develop fixed airflow limitation that is thought to be due to airway wall remodeling.
- *Asthma with obesity*: some obese patients with asthma have prominent respiratory symptoms and little eosinophilic airway inflammation.

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

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MAKING THE INITIAL DIAGNOSIS

Making the diagnosis of asthma,[9] as shown in Box 1-1 (p16) is based on identifying both a characteristic pattern of respiratory symptoms such as wheezing, shortness of breath (dyspnea), chest tightness or cough, and variable expiratory airflow limitation. The pattern of symptoms is important, as respiratory symptoms may be due to acute or chronic conditions other than asthma. If possible, the evidence supporting a diagnosis of asthma (Box 1-2, p5) should be documented when the patient first presents, as the features that are characteristic of asthma may improve spontaneously or with treatment; as a result, it is often more difficult to confirm a diagnosis of asthma once the patient has been started on controller treatment.

Patterns of respiratory symptoms that are characteristic of asthma

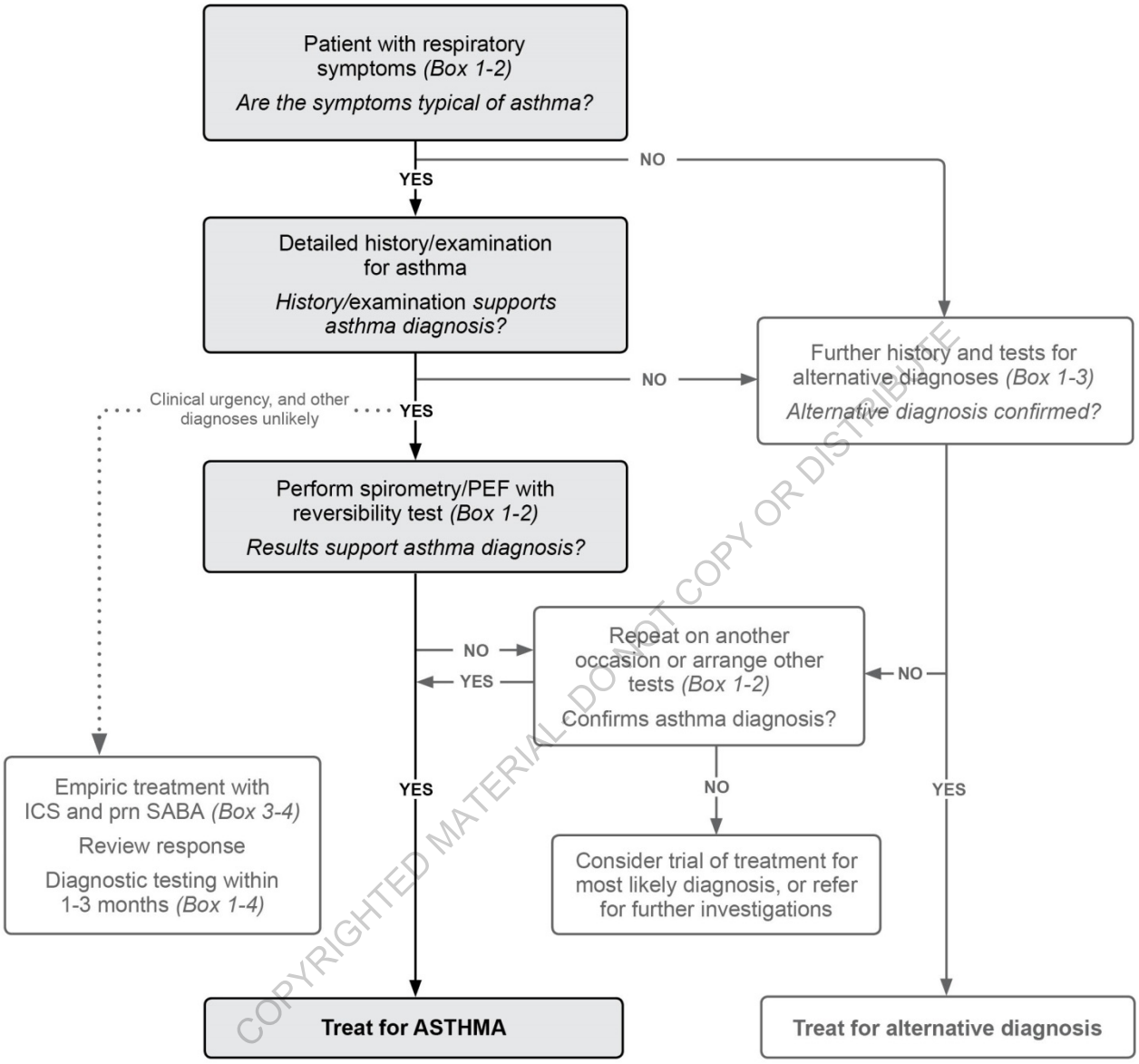
The following features are typical of asthma and, if present, *increase* the probability that the patient has asthma:[9]

- More than one symptom (wheeze, shortness of breath, cough, chest tightness), especially in adults
- Symptoms often worse at night or in the early morning
- Symptoms vary over time and in intensity
- Symptoms are triggered by viral infections (colds), exercise, allergen exposure, changes in weather, laughter, or irritants such as car exhaust fumes, smoke or strong smells.

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

- Isolated cough with no other respiratory symptoms (see p.21)
- Chronic production of sputum
- Shortness of breath associated with dizziness, light-headedness or peripheral tingling (paresthesia)
- Chest pain
- Exercise-induced dyspnea with noisy inspiration.

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



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ICS: inhaled corticosteroids; PEF: peak expiratory flow (highest of three readings). When measuring PEF, use the same meter each time as the value may vary by up to 20% between different meters. SABA: short-acting beta$_2$-agonist.

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

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

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

DIAGNOSTIC FEATURE	CRITERIA FOR MAKING THE DIAGNOSIS OF ASTHMA
1. History of variable respiratory symptoms	
Wheeze, shortness of breath, chest tightness and cough Descriptors may vary between cultures and by age, e.g. children may be described as having heavy breathing	• Generally more than one type of respiratory symptom (in adults, isolated cough is seldom due to asthma) • Symptoms occur variably over time and vary in intensity • Symptoms are often worse at night or on waking • Symptoms are often triggered by exercise, laughter, allergens, cold air • Symptoms often appear or worsen with viral infections
2. Confirmed variable expiratory airflow limitation	
Documented excessive variability in lung function* (one or more of the tests below)	The greater the variations, or the more occasions excess variation is seen, the more confident the diagnosis
AND documented airflow limitation*	At least once during diagnostic process when FEV_1 is low, confirm that FEV_1/FVC is reduced (normally >0.75–0.80 in adults, >0.90 in children)
Positive bronchodilator (BD) reversibility test* (more likely to be positive if BD medication is withheld before test: SABA ≥4 hours, LABA ≥15 hours)	*Adults*: increase in FEV_1 of >12% and >200 mL from baseline, 10–15 minutes after 200–400 mcg albuterol or equivalent (greater confidence if increase is >15% and >400 mL). *Children*: increase in FEV_1 of >12% predicted
Excessive variability in twice-daily PEF over 2 weeks*	*Adults*: average daily diurnal PEF variability >10%** *Children*: average daily diurnal PEF variability >13%**
Significant increase in lung function after 4 weeks of anti-inflammatory treatment	*Adults*: increase in FEV_1 by >12% and >200 mL (or PEF† by >20%) from baseline after 4 weeks of treatment, outside respiratory infections
Positive exercise challenge test*	*Adults*: fall in FEV_1 of >10% and >200 mL from baseline *Children*: fall in FEV_1 of >12% predicted, or PEF >15%
Positive bronchial challenge test (usually only performed in adults)	Fall in FEV_1 from baseline of ≥20% with standard doses of methacholine or histamine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge
Excessive variation in lung function between visits* (less reliable)	*Adults*: variation in FEV_1 of >12% and >200 mL between visits, outside of respiratory infections *Children*: variation in FEV_1 of >12% in FEV_1 or >15% in PEF† between visits (may include respiratory infections)

BD: bronchodilator (short-acting SABA or rapid-acting LABA); FEV_1: forced expiratory volume in 1 second; LABA: long-acting $beta_2$-agonist; PEF: peak expiratory flow (highest of three readings); SABA: short-acting $beta_2$-agonist. See Box 1-4 for diagnosis in patients already taking controller treatment.

*These tests can be repeated during symptoms or in the early morning. **Daily diurnal PEF variability is calculated from twice daily PEF as ([day's highest minus day's lowest] / mean of day's highest and lowest), and averaged over one week. †For PEF, use the same meter each time, as PEF may vary by up to 20% between different meters. BD reversibility may be lost during severe exacerbations or viral infections.[10] If bronchodilator reversibility is not present at initial presentation, the next step depends on the availability of other tests and the urgency of the need for treatment. In a situation of clinical urgency, asthma treatment may be commenced and diagnostic testing arranged within the next few weeks (Box 1-4, p.22), but other conditions that can mimic asthma (Box 1-3) should be considered, and the diagnosis of asthma confirmed as soon as possible.

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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 upper airway dysfunction, chronic obstructive pulmonary disease (COPD), respiratory infections, tracheomalacia, or inhaled foreign body. Crackles (crepitations) and inspiratory wheezing are not features of asthma. Examination of the nose may reveal signs of allergic rhinitis or nasal polyposis.

Lung function testing to document variable expiratory airflow limitation

Asthma is characterized by variable expiratory airflow limitation, i.e. expiratory lung function varies over time and in magnitude to a greater extent than in healthy populations. In asthma, lung function may vary between completely normal and severely obstructed in the same patient. Poorly controlled asthma is associated with greater variability in lung function than well-controlled asthma.[10]

Lung function testing should be carried out by well-trained operators with well-maintained and regularly calibrated equipment.[9,11] Forced expiratory volume in 1 second (FEV_1) from spirometry is more reliable than peak expiratory flow (PEF). If PEF is used, the same meter should be used each time, as measurements may differ from meter to meter by up to 20%.[11]

A reduced FEV_1 may be found with many other lung diseases (or poor spirometric technique), but a reduced ratio of FEV_1 to FVC indicates airflow limitation. From population studies,[12] the FEV_1/FVC ratio is normally greater than 0.75 to 0.80, and usually greater than 0.90 in children. Any values less than these suggest airflow limitation. Many spirometers now include age-specific predicted values.

In clinical practice, once an obstructive defect has been confirmed, variation in airflow limitation 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 reversibility test. *'Reversibility'* 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,[13] or more sustained improvement over days or weeks after the introduction of effective controller treatment such as ICS.[13]

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

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

Specific criteria for demonstrating excessive variability in expiratory lung function are listed in Box 1-2 (p.17). A decrease in lung function during a respiratory infection, while commonly seen in asthma, does not necessarily indicate that a person has asthma, as it may also be seen in otherwise healthy individuals or people with COPD.

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

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How much variation in expiratory airflow is consistent with asthma?

There is overlap in bronchodilator reversibility and other measures of variation between health and disease.[14] 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.17). 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.

Diurnal PEF variability is calculated from twice daily readings as the daily amplitude percent mean, i.e. ([Day's highest – day's lowest]/mean of day's highest and lowest) x 100, then the average of each day's value is calculated over 1–2 weeks. The upper 95% confidence limit of diurnal variability (amplitude percent mean) from twice daily readings is 9% in healthy adults,[15] and 12.3% in healthy children,[16] so in general, diurnal variability >10% for adults and >13% for children is regarded as excessive.

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 controller treatment. Predicted normal ranges (especially for PEF) have limitations, so the patient's own best reading ('personal best') is recommended as their 'normal' value.

When can variable airflow limitation be documented?

If possible, evidence of variable airflow limitation should be documented before treatment is started. This is because variability usually decreases with treatment as lung function improves; and in some patients airflow limitation may become fixed or irreversible over time. In addition, any increase in lung function with treatment can help to confirm the diagnosis of asthma. Bronchodilator reversibility may not be present during viral infections or if the patient has used a $beta_2$-agonist within the previous few hours.

If spirometry is not available, or variable airflow limitation is not documented, a decision about whether to investigate further or start controller treatment immediately depends on clinical urgency and access to other tests. Box 1-4 (p.22) describes how to confirm the diagnosis of asthma in a patient already taking controller treatment.

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Other tests

Bronchial provocation tests

Airflow limitation may be absent at the time of initial assessment in some patients. As documenting variable airflow limitation is a key part of establishing an asthma diagnosis, one option is to refer the patient for bronchial provocation testing to assess airway hyperresponsiveness. This is most often established with inhaled methacholine, but histamine, exercise,[17] eucapnic voluntary hyperventilation or inhaled mannitol may also be used. These tests are moderately sensitive for a diagnosis of asthma but have limited specificity;[18,19] for example, airway hyperresponsiveness to inhaled methacholine has been described in patients with allergic rhinitis,[20] cystic fibrosis,[21] bronchopulmonary dysplasia[22] and COPD.[23] 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.17) and other clinical features (Box 1-3, p.20) must also be taken into account.

Allergy tests

The presence of atopy increases the probability that a patient with respiratory symptoms has allergic asthma, but this is not specific for asthma nor is it present in all asthma phenotypes. Atopic status can be identified by skin prick testing or by measuring the level of specific immunoglobulin E (sIgE) in serum. Skin prick testing with common environmental allergens is simple and rapid to perform and, when performed by an experienced tester with standardized extracts, is inexpensive and has a high sensitivity. Measurement of sIgE is no more reliable than skin tests and is more expensive, but may be preferred for uncooperative patients, those with widespread skin disease, or if the history suggests a risk of anaphylaxis.[24] 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.

Exhaled nitric oxide

Measurement of the fractional concentration of exhaled nitric oxide (FENO) is becoming more widely available. It is modestly associated with eosinophilic airway inflammation.[25] FENO has not been established as useful for ruling or ruling out a diagnosis of asthma, as defined on p.14. FENO is higher in eosinophilic asthma but also in non-asthma conditions (e.g. eosinophilic bronchitis, atopy, allergic rhinitis, eczema), and it is not elevated in some asthma phenotypes (e.g. neutrophilic asthma). Several other factors affect FENO levels:[26] it is lower in smokers and is decreased during bronchoconstriction and in the early phases of allergic response;[27] it may be increased or decreased during viral respiratory infections[26]

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

DIFFERENTIAL DIAGNOSIS

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

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

Age	Condition	Symptoms
6–11 years	Chronic upper airway cough syndrome	Sneezing, itching, blocked nose, throat-clearing
	Inhaled foreign body	Sudden onset of symptoms, unilateral wheeze
	Bronchiectasis	Recurrent infections, productive cough
	Primary ciliary dyskinesia	Recurrent infections, productive cough, sinusitis
	Congenital heart disease	Cardiac murmurs
	Bronchopulmonary dysplasia	Pre-term delivery, symptoms since birth
	Cystic fibrosis	Excessive cough and mucus production, gastrointestinal symptoms
12–39 years	Chronic upper airway cough syndrome	Sneezing, itching, blocked nose, throat-clearing
	Vocal cord dysfunction	Dyspnea, inspiratory wheezing (stridor)
	Hyperventilation, dysfunctional breathing	Dizziness, paresthesia, sighing
	Bronchiectasis	Productive cough, recurrent infections
	Cystic fibrosis	Excessive cough and mucus production
	Congenital heart disease	Cardiac murmurs
	Alpha$_1$-antitrypsin deficiency	Shortness of breath, family history of early emphysema
	Inhaled foreign body	Sudden onset of symptoms
40+ years	Vocal cord dysfunction	Dyspnea, inspiratory wheezing (stridor)
	Hyperventilation, dysfunctional breathing	Dizziness, paresthesia, sighing
	COPD*	Cough, sputum, dyspnea on exertion, smoking or noxious exposure
	Bronchiectasis	Productive cough, recurrent infections
	Cardiac failure	Dyspnea with exertion, nocturnal symptoms
	Medication-related cough	Treatment with angiotensin converting enzyme (ACE) inhibitor
	Parenchymal lung disease	Dyspnea with exertion, non-productive cough, finger clubbing
	Pulmonary embolism	Sudden onset of dyspnea, chest pain
	Central airway obstruction	Dyspnea, unresponsive to bronchodilators

*For more detail, see Chapter 5 (p.89). Any of the above conditions may also contribute to respiratory symptoms in patients with confirmed asthma.

MAKING THE DIAGNOSIS OF ASTHMA IN SPECIAL POPULATIONS

Patients presenting with cough as the only respiratory symptom

Diagnoses to be considered are cough variant asthma, cough induced by angiotensin converting enzyme (ACE) inhibitors, gastroesophageal reflux, chronic upper airway cough syndrome (often called 'postnasal drip'), chronic sinusitis, and vocal cord dysfunction.[29] Patients with cough-variant asthma have chronic cough as their principal, if not only, symptom, associated with airway hyperresponsiveness. It is more common in children and often more problematic at night; lung function may be normal. For these patients, documentation of variability in lung function (Box 1-2, p.17) is important.[30] Cough-variant asthma must be distinguished from eosinophilic bronchitis in which patients have cough and sputum eosinophils but normal spirometry and airway responsiveness.[30]

Occupational asthma and work-aggravated asthma

Asthma acquired in the workplace is frequently missed. Asthma may be induced or (more commonly) aggravated by exposure to allergens or other sensitizing agents at work, or sometimes from a single, massive exposure. Occupational rhinitis may precede asthma by up to a year and early diagnosis is essential, as persistent exposure is associated with worse outcomes.[31]

An estimated 5–20% of new cases of adult-onset asthma can be attributed to occupational exposure.[31] Adult-onset asthma requires a systematic inquiry about work history and exposures, including hobbies.[32] Asking patients whether their symptoms improve when they are away from work (weekends or vacation) is an essential screening question.[33] It is important to confirm the diagnosis of occupational asthma objectively as it may lead to the patient changing their occupation, which may have legal and socioeconomic implications. Specialist referral is usually necessary, and frequent PEF monitoring at and away from work is often used to help confirm the diagnosis. Further information about occupational asthma is found in Chapter 3 (p.67) and in specific guidelines.[31]

Athletes

The diagnosis of asthma in athletes should be confirmed by lung function tests, usually with bronchial provocation testing.[17] Conditions that may either mimic or be associated with asthma, such as rhinitis, laryngeal disorders (e.g. vocal cord dysfunction), dysfunctional breathing, cardiac conditions and over-training, must be excluded.[34]

Pregnant women

Pregnant women and women planning a pregnancy should be asked whether they have asthma so that appropriate advice about asthma management and medications can be given (see Chapter 3: *Managing asthma in special populations or settings*, p.66).[35] If objective confirmation of the diagnosis is needed, it would not be advisable to carry out a bronchial provocation test or to step down controller treatment until after delivery.

The elderly

Asthma is frequently undiagnosed in the elderly,[36] due to poor perception of airflow limitation; acceptance of dyspnea as being 'normal' in old age; lack of fitness; and reduced activity. The presence of comorbid diseases also complicates the diagnosis. 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.[37] Measurement of plasma brain natriuretic polypeptide (BNP) and assessment of cardiac function with echocardiography may also be helpful.[38] In older people with a history of smoking or biomass fuel exposure, COPD and overlapping asthma and COPD (asthma–COPD overlap, ACO) should be considered (Chapter 5, p.89).

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Smokers and ex-smokers

Asthma and COPD may be difficult to distinguish in clinical practice, particularly in older patients and smokers and ex-smokers, and these conditions may overlap (asthma-COPD overlap, or ACO). The *Global Strategy for Diagnosis, Management and Prevention of COPD (GOLD)*[39] *defines COPD* on the basis of chronic respiratory symptoms, exposure to a risk factor such as smoking, and post-bronchodilator FEV_1/FVC <0.7. Clinically important bronchodilator reversibility (>12% and >200 mL) is often found in COPD.[40] Low diffusion capacity is more common in COPD than asthma. The history and pattern of symptoms and past records can help to distinguish these patients from those with long-standing asthma who have developed fixed airflow limitation (see Chapter 5, p.89). Uncertainty in the diagnosis should prompt early referral for specialized investigation and treatment recommendations, as patients with asthma-COPD overlap have worse outcomes than those with asthma or COPD alone.[41]

Confirming the diagnosis of asthma in patients already taking controller treatment

If the basis of a patient's diagnosis of asthma has not previously been documented, confirmation with objective testing should be sought. Many patients (25–35%) with a diagnosis of asthma in primary care cannot be confirmed as having asthma.[42-45]

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

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Box 1-4. Confirming the diagnosis of asthma in a patient already taking controller treatment

Current status	Steps to confirm the diagnosis of asthma
Variable respiratory symptoms and variable airflow limitation	Diagnosis of asthma is confirmed. Assess the level of asthma control (Box 2-2, p.29) and review controller treatment (Box 3-5, p.43).
Variable respiratory symptoms but no variable airflow limitation	Repeat BD reversibility test again after withholding BD (SABA: 4 hours; LABA: 12+ hours) or during symptoms. If normal, consider alternative diagnoses (Box 1-3, p.20). *If FEV_1 is >70% predicted*: consider a bronchial provocation test. If negative, consider stepping down controller treatment (see Box 1-5) and reassess in 2–4 weeks *If FEV_1 is <70% predicted*: consider stepping up controller treatment for 3 months (Box 3-5), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation
Few respiratory symptoms, normal lung function, and no variable airflow limitation	Repeat BD reversibility test again after withholding BD (SABA: 4 hours; LABA: 12+ hours) or during symptoms. If normal, consider alternative diagnoses (Box 1-3). Consider stepping down controller treatment (see Box 1-5): • *If symptoms emerge and lung function falls*: asthma is confirmed. Step up controller treatment to lowest previous effective dose. • *If no change in symptoms or lung function at lowest controller step*: consider ceasing controller, and monitor patient closely for at least 12 months (Box 3-7).
Persistent shortness of breath and fixed airflow limitation	Consider stepping up controller treatment for 3 months (Box 3-5, p.43), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation. Consider asthma–COPD overlap syndrome (Chapter 5, p.89).

BD: bronchodilator; LABA: long-acting $beta_2$-agonist; SABA: short-acting $beta_2$-agonist

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

1. ASSESS
• Document the patient's current status including asthma control (Box 2-2, p.29) and lung function. If the patient has risk factors for asthma exacerbations (Box 2-2B), do not step down treatment without close supervision. • Choose a suitable time (e.g. no respiratory infection, not going away on vacation, not pregnant). • Provide a written asthma action plan (Box 4-2, p.77) so the patient knows how to recognize and respond if symptoms worsen. Ensure they have enough medication to resume their previous dose if their asthma worsens.
2. ADJUST
• Show the patient how to reduce their ICS dose by 25–50%, or stop extra controller (e.g. LABA, leukotriene receptor antagonist) if being used (Box 3-7, p.49) • 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.17). • If symptoms increase and variable airflow limitation is confirmed after stepping down treatment, the diagnosis of asthma is confirmed. The controller dose should be returned to the lowest previous effective dose. • If, after stepping down to a low dose controller treatment, symptoms do not worsen and there is still no evidence of variable airflow limitation, consider ceasing controller treatment and repeating asthma control assessment and lung function tests in 2–3 weeks, but follow the patient for at least 12 months

COPD: chronic obstructive pulmonary disease; LABA: long-acting beta$_2$-agonist.

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Obese patients

While asthma is more common in obese than non-obese people,[46] respiratory symptoms associated with obesity can mimic asthma. In obese patients with dyspnea on exertion, it is important to confirm the diagnosis of asthma with objective measurement of variable airflow limitation. One study found that non-obese patients were just as likely to be over-diagnosed with asthma as obese patients (around 30% in each group).[42] Another study found both over- and under-diagnosis of asthma in obese patients.[47]

Low resource settings

Communities with limited resources are found not only in low and middle income countries (LMIC), but also in affluent nations. In low resource settings, diagnosis of respiratory symptoms commences with a symptom-based or syndromic approach. Questions about duration of symptoms and about fever, chills, sweats, weight loss, pain on breathing and hemoptysis help to distinguish chronic respiratory infections such as tuberculosis, HIV/AIDS and parasitic or fungal lung diseases from asthma and COPD.[48,49] Variable airflow limitation can be confirmed using PEF meters; these have been proposed by the World Health Organization as essential tools in the Package of Essential Non-communicable Diseases Interventions.[50] In low resource settings, documentation of symptoms and PEF before and after a therapeutic trial with as-needed SABA and regular ICS, often together with a 1 week course of oral corticosteroids, can help to confirm the diagnosis of asthma before long-term treatment is commenced.[51]

In low and middle-income countries, a comparison between the prevalence of asthma symptoms and of a doctor's diagnosis of asthma among adolescents and young adults suggests that, at the population level, as many as 50% of cases may be undiagnosed.[52,53] In a recent review, it has been reported that, among doctors working in primary care health services, the precision of the diagnosis of asthma is far from ideal, varying from 54% under-diagnosis to 34% over-diagnosis.[54] Poverty is commonly associated with restrictive spirometry, so where possible, both FEV_1 and FVC should be recorded.[55] These observations demonstrate how important it is to build capacity of primary care physicians for asthma diagnosis and management.

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Chapter 2.

Assessment of asthma

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KEY POINTS

- Assess the two domains of asthma control: symptom control (previously called 'current clinical control') and future risk of adverse outcomes, as well as treatment issues such as inhaler technique and adherence, side-effects and comorbidities.
- Assess symptom control from the frequency of daytime and night-time asthma symptoms and reliever use, and from activity limitation. Poor symptom control is burdensome to patients and is a risk factor for future exacerbations.
- Assess the patient's future risk for exacerbations, fixed airflow limitation and medication side-effects, even when symptom control is good. Identified risk factors for exacerbations that are independent of symptom control include a history of ≥1 exacerbations in the previous year, poor adherence, incorrect inhaler technique, low lung function, smoking, and blood eosinophilia.
- Once the diagnosis of asthma has been made, lung function is most useful as an indicator of future risk. It should be recorded at diagnosis, 3–6 months after starting treatment, and periodically thereafter. Discordance between symptoms and lung function should prompt further investigation.
- Poor control of symptoms and poor control of exacerbations may have different contributory factors and may need different treatment approaches.
- Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations. It is important to distinguish between severe asthma and asthma that is uncontrolled, e.g. due to incorrect inhaler technique and/or poor adherence.

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OVERVIEW

For every patient, assessment of asthma should include the assessment of asthma control (both symptom control and future risk of adverse outcomes), treatment issues particularly inhaler technique and adherence, and any comorbidities that could contribute to symptom burden and poor quality of life (Box 2-1, p27). Lung function, particularly forced expiratory volume in 1 second (FEV_1) as a percentage of predicted, is an important part of the assessment of future risk.

What is meant by 'asthma control'?

The level of asthma control is the extent to which the manifestations of asthma can be observed in the patient, or have been reduced or removed by treatment.[15,56] 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.[56]

Asthma control has two domains: symptom control (previously called 'current clinical control') and future risk of adverse outcomes (Box 2-2, p.29). Both should always be assessed. Lung function is an important part of the assessment of future risk; it should be measured at the start of treatment, after 3–6 months of treatment (to identify the patient's personal best), and periodically thereafter for ongoing risk assessment.

How to describe a patient's asthma control

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

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

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

What does the term 'asthma control' mean to patients?

Many studies describe discordance between the patient's and health provider's assessment of the patient's level of asthma control. This does not necessarily mean that patients 'over-estimate' their level of control or 'under-estimate' its severity, but that patients understand and use the word 'control' differently from health professionals, e.g. based on how quickly their symptoms resolve when they take reliever medication.[56,57] If the term 'asthma control' is used with patients, the meaning should always be explained.

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

1. Assess asthma control = symptom control and future risk of adverse outcomes
• Assess symptom control over the last 4 weeks (Box 2-2A) • Identify any other risk factors for exacerbations, fixed airflow limitation or side-effects (Box 2-2B) • Measure lung function at diagnosis/start of treatment, 3–6 months after starting controller treatment, then periodically
2. Assess treatment issues
• Document the patient's current treatment step (Box 3-5, p.43) • Watch inhaler technique, assess adherence and side-effects • Check that the patient has a written asthma action plan • Ask about the patient's attitudes and goals for their asthma and medications
3. Assess comorbidities
• Rhinitis, rhinosinusitis, gastroesophageal reflux, obesity, obstructive sleep apnea, depression and anxiety can contribute to symptoms and poor quality of life, and sometimes to poor asthma control

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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.[58-60]

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

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

Asthma symptom control tools for adults and adolescents

Simple screening tools: these can be used in primary care to quickly identify patients who need more detailed assessment. Examples include the consensus-based GINA symptom control tool (Part A, Box 2-2A). This classification correlates with assessments made using numerical asthma control scores.[61,62] It can be used, together with a risk assessment (Box 2-2B), to guide treatment decisions (Box 3-5, p.43). Other examples are the Primary Care Asthma Control Screening Tool (PACS),[63] and the 30-second Asthma Test, which also includes time off work/school.[64]

Categorical symptom control tools: examples include the consensus-based 'Royal College of Physicians (RCP) Three Questions' tool,[65] which asks about difficulty sleeping, daytime symptoms and activity limitation due to asthma in the previous month.

Numerical 'asthma control' tools: these tools provide scores and cut points to distinguish different levels of symptom control, validated against health care provider assessment. Many translations are available. These scores may be useful for assessing patient progress; they are commonly used in clinical research, but may be subject to copyright restrictions. Numerical asthma control tools are more sensitive to change in symptom control than categorical tools.[61]

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

- *Asthma Control Questionnaire (ACQ)*.[66,67] Scores range from 0–6 (higher is worse). A score of 0.0–0.75 is classified as well-controlled asthma; 0.75–1.5 as a 'grey zone'; and >1.5 as poorly controlled asthma. The ACQ score is calculated as the average of 5, 6 or 7 items: all versions of the ACQ include five symptom questions; ACQ-6 includes reliever use; and in ACQ-7, a score for pre-bronchodilator FEV_1 is averaged with symptom and reliever items. The minimum clinically important difference is 0.5.[68]
- *Asthma Control Test (ACT)*.[62,69,70] Scores range from 5–25 (higher is better). Scores of 20–25 are classified as well-controlled asthma; 16–20 as not well-controlled; and 5–15 as very poorly controlled asthma. The ACT includes four symptom/reliever questions plus a patient self-assessed level of control. The minimum clinically important difference is 3 points.[70]

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

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

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

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

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

- *Childhood Asthma Control Test* (c-ACT)[71] with separate sections for parent and child to complete
- *Asthma Control Questionnaire* (ACQ)[72,73]

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

- Test for Respiratory and Asthma Control in Kids (TRACK)[74-76]
- Composite Asthma Severity Index (CASI)[77]

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

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

A. Asthma symptom control		**Level of asthma symptom control**		
In the past 4 weeks, has the patient had:		**Well controlled**	**Partly controlled**	**Uncontrolled**
• 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☐			
• Reliever needed 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, particularly for patients experiencing exacerbations. Measure FEV_1 at start of treatment, after 3–6 months of controller treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment.	
Potentially modifiable independent risk factors for flare-ups (exacerbations) • Uncontrolled asthma symptoms[78] • High SABA use[79] (with increased mortality if >1 x 200-dose canister/month[80]) • Inadequate ICS: not prescribed ICS; poor adherence;[81] incorrect inhaler technique[82] • Low FEV_1, especially if <60% predicted[83,84] • Major psychological or socioeconomic problems[85] • Exposures: smoking;[84] allergen exposure if sensitized[84] • Comorbidities: obesity;[86] rhinosinusitis;[87] confirmed food allergy[88] • Sputum or blood eosinophilia;[89,90] elevated FENO (in adults with allergic asthma)[91] • Pregnancy[92] Other major independent risk factors for flare-ups (exacerbations) • Ever intubated or in intensive care unit for asthma[93] • ≥1 severe exacerbation in last 12 months[94]	**Having one or more of these risk factors increases the risk of exacerbations even if symptoms are well controlled.**
Risk factors for developing fixed airflow limitation • Lack of ICS treatment[95] • Exposures: tobacco smoke;[96] noxious chemicals; occupational exposures[31] • Low initial FEV_1;[97] chronic mucus hypersecretion;[96,97] sputum or blood eosinophilia[97]	
Risk factors for medication side-effects • *Systemic*: frequent OCS; long-term, high dose and/or potent ICS; also taking P450 inhibitors[98] • *Local*: high-dose or potent ICS;[98,99] poor inhaler technique[100]	

FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; OCS: oral corticosteroid; P450 inhibitors: cytochrome P450 inhibitors such as ritonavir, ketoconazole, itraconazole; SABA: short-acting $beta_2$-agonist.

*Excludes reliever taken before exercise. For children 6–11 years, also refer to Box 2-3, p.30. See Box 3-8, p.50 for specific risk reduction strategies.

This consensus-based GINA control classification corresponds to that in GINA 2010–2012, except that lung function now appears only in the 'future risk' assessment. 'Current clinical control' has been renamed 'symptom control', to emphasize that these measures are not sufficient for assessment of disease control – future risk assessment for adverse outcomes is also needed. 'Independent' risk factors are those that are significant after adjustment for the level of symptom control. Poor symptom control and exacerbation risk should not be simply combined numerically, as they may have different causes and may need different treatment strategies.

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

Asthma symptom control	
Day symptoms	How often does the child have cough, wheeze, dyspnea or heavy breathing (number of times per week or day)? What triggers the symptoms? How are they handled?
Night symptoms	Cough, awakenings, tiredness during the day? (If the only symptom is cough, consider rhinitis or gastroesophageal reflux disease).
Reliever use	How often is reliever medication used? (check date on inhaler or last prescription) Distinguish between pre-exercise use (sports) and use for relief of symptoms.
Level of activity	What sports/hobbies/interests does the child have, at school and in their spare time? How does the child's level of activity compare with their peers or siblings? Try to get an accurate picture of the child's day from the child without interruption from the parent/carer.
Future risk factors	
Exacerbations	How do viral infections affect the child's asthma? Do symptoms interfere with school or sports? How long do the symptoms last? How many episodes have occurred since their last medical review? Any urgent doctor/emergency department visits? Is there a written action plan?
Lung function	Check curves and technique. Main focus is on FEV_1 and FEV_1/FVC ratio. Plot these values as percent predicted to see trends over time.
Side-effects	Check the child's height at least yearly, as poorly-controlled asthma can affect growth,[101] and growth velocity may be lower in the first 1-2 years of ICS treatment.[102] Ask about frequency and dose of ICS and OCS.
Treatment factors	
Inhaler technique	Ask the child to show how they use their inhaler. Compare with a device-specific checklist.
Adherence	On how many days does the child use their controller in a week (e.g. 0, 2, 4, 7 days)? Is it easier to remember to use it in the morning or evening? Where is inhaler kept – is it in plain view to reduce forgetting? Check date on inhaler.
Goals/concerns	Does the child or their parent/carer have any concerns about their asthma (e.g. fear of medication, side-effects, interference with activity)? What are the child's/parent's/carer's goals for asthma 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[88])
Obesity	Check age-adjusted BMI. Ask about diet and physical activity.
Other investigations (if needed)	
2-week diary	If no clear assessment can be made based on the above questions, ask the child or parent/carer to keep a daily diary of asthma symptoms, reliever use and peak expiratory flow (best of three) for 2 weeks (Appendix Chapter 4).
Exercise challenge in respiratory laboratory	Provides information about airway hyperresponsiveness and fitness (Box 1-2, p.17). Only undertake a challenge if it is otherwise difficult to assess asthma control.

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; ICS: inhaled corticosteroids; OCS: oral corticosteroids.

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ASSESSING FUTURE RISK OF ADVERSE OUTCOMES

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

- Asthma symptoms can be controlled by placebo or sham treatments[103,104] or by inappropriate use of long-acting beta$_2$-agonist (LABA) alone,[105] which leaves airway inflammation untreated.
- Respiratory symptoms may be due to other conditions such as lack of fitness, or comorbidities such as upper airway dysfunction.
- Anxiety or depression may contribute to symptom reporting.
- Some patients have few symptoms despite low lung function.

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

Exacerbations

Poor asthma symptom control itself substantially increases the risk of exacerbations.[58-60] However, several additional independent risk factors have been identified, i.e. factors, that, when present, increase the patient's risk of exacerbations even if symptoms are few. These risk factors (Box 2-2B) include a history of ≥1 exacerbations in the previous year, poor adherence, incorrect inhaler technique and smoking.

'Fixed' airflow limitation

The average rate of decline in FEV_1 in non-smoking healthy adults is 15–20 mL/year.[106] People with asthma may have an accelerated decline in lung function and develop airflow limitation that is not fully reversible. This is often associated with more persistent dyspnea. Independent risk factors that have been identified for fixed airflow limitation include exposure to cigarette smoke or noxious agents, chronic mucus hypersecretion, and asthma exacerbations in patients not taking ICS[95] (see Box 2-2B). Children with persistent asthma may have reduced growth in lung function, and some are at risk of accelerated decline in lung function in early adult life.[107]

Medication side-effects

Choices with any medication are based on the balance of benefit and risk. Most people using asthma medications do not experience any side-effects. The risk of side-effects increases with higher doses of medications, but these are needed in few patients. Systemic side-effects that may be seen with long-term, high-dose ICS include easy bruising; an increase beyond the usual age-related risk of osteoporosis, cataracts and glaucoma; and adrenal suppression. Local side effects of ICS include oral thrush and dysphonia. Patients are at greater risk of ICS side-effects with higher doses or more potent formulations,[98,99] and, for local side-effects, with incorrect inhaler technique.[100]

ROLE OF LUNG FUNCTION IN ASSESSING ASTHMA CONTROL

The relationship of lung function with other asthma control measures

Lung function does not correlate strongly with asthma symptoms in adults[108] or children.[109] In some asthma control tools, lung function is numerically averaged or added with symptoms,[66,110] but if the tool includes several symptom items, these can outweigh clinically important differences in lung function.[111] 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 controller treatment to assess the patient's personal best FEV_1; and periodically thereafter. For example, in most adult patients, lung function should be recorded at least every 1-2 years, but more frequently in higher risk patients including those with exacerbations and

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

Once the diagnosis of asthma has been confirmed, it is not generally necessary to ask patients to withhold their regular or as-needed medications before visits,[15] but preferably the same conditions should apply at each visit.

Interpreting interval lung function 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.[83,84,112,113]
- Is a risk factor for lung function decline, independent of symptom levels.[97]
- If symptoms are few, suggests limitation of lifestyle, or poor perception of airflow limitation,[114] which may be due to untreated airway inflammation.[115]

A 'normal' or high 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.20).

Persistent bronchodilator reversibility:

- Finding significant bronchodilator reversibility (increase in FEV_1 >12% and >200 mL from baseline[13]) in a patient taking controller treatment, or who has taken a short-acting $beta_2$-agonist within 4 hours, or a LABA within 12 hours, suggests uncontrolled asthma.

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

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Interpreting 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.[116] 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 'fixed' (incompletely reversible) airflow limitation. While a trial of higher-dose ICS/LABA and/or systemic corticosteroids may be appropriate to see if FEV_1 can be improved, high doses should not be continued if there is no response.

The between-visit variability of FEV_1 (≤12% week to week or 15% year to year in healthy individuals[13]) limits its use in adjusting asthma treatment 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%.[117,118]

PEF monitoring

Once the diagnosis of asthma is made, short-term PEF monitoring may be used to assess response to treatment, to evaluate triggers (including at work) for worsening symptoms, or to establish a baseline for action plans. After starting ICS, personal best PEF (from twice daily readings) is reached on average within 2 weeks.[119] Average PEF continues to increase, and diurnal PEF variability to decrease, for about 3 months.[108,119] Excessive variation in PEF suggests sub-optimal asthma control, and increases the risk of exacerbations.[120]

Long-term peak expiratory flow (PEF) monitoring is now generally only recommended for patients with severe asthma, or those with impaired perception of airflow limitation[115,121-124] (Appendix Chapter 4). For clinical practice, displaying PEF results on a standardized chart may improve accuracy of interpretation.[125]

ASSESSING ASTHMA SEVERITY

How to assess asthma severity in clinical practice

Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations.[15,56,126] It can be assessed once the patient has been on controller treatment for several months and, if appropriate, treatment step down has been attempted to find the patient's minimum effective level of treatment. Asthma severity is not a static feature and may change over months or years.

Asthma severity can be assessed when the patient has been on regular controller treatment for several months:[15,126]

- *Mild asthma* is asthma that is well controlled with Step 1 or Step 2 treatment (Box 3-5, p.43), i.e. with as-needed reliever medication alone, or with low-intensity controller treatment such as low dose ICS, leukotriene receptor antagonists or chromones.
- *Moderate asthma* is asthma that is well controlled with Step 3 treatment e.g. low dose ICS/LABA.
- *Severe asthma* is asthma that requires Step 4 or 5 treatment (Box 3-5, p.43), e.g. high-dose ICS/LABA, to prevent it from becoming 'uncontrolled', or asthma that remains 'uncontrolled' despite this treatment. While many patients with uncontrolled asthma may be difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, the European Respiratory Society/American Thoracic Society Task Force on Severe Asthma considered that the definition of severe asthma should be reserved for patients with refractory asthma and those in whom response to treatment of comorbidities is incomplete.[126]

Describing asthma severity in other contexts

For descriptions of participants in epidemiological studies and clinical trials, asthma severity has often been based on prescribed treatment step (Box 3-5, p.43). For example, patients prescribed Step 2 treatments are often described as having mild asthma; those prescribed Step 3–4 as having moderate asthma; and those prescribed Step 4–5 as having moderate-to-severe asthma. This approach is based on the assumption that patients are receiving appropriate treatment, and that those prescribed more intense treatment are likely to have more severe underlying disease. However, this is only a surrogate measure, and it causes confusion since most studies also require participants to have uncontrolled symptoms at entry. For epidemiological studies or clinical trials, it is preferable to categorize patients by the treatment step that they are prescribed, without inferring severity.

For low resource countries that do not currently have access to medications such as ICS, the World Health Organization definition of severe asthma[127] includes a category of 'untreated severe asthma'. This category corresponds to other classifications of uncontrolled asthma in patients not taking controller treatment.

Other language about asthma severity

'Severe' is often also used to describe the intensity of asthma symptoms, the magnitude of airflow limitation, or the nature of an exacerbation. In older asthma literature, many different severity classifications have been used; many of these were similar to current concepts of asthma control.[56]

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

How to distinguish between uncontrolled and severe asthma

Although most asthma patients can achieve good symptom control and minimal exacerbations with regular controller treatment, some patients will not achieve one or both of these goals even with maximal therapy.[110] In some patients this is due to truly refractory severe asthma, but in many others, it is due to comorbidities, persistent environmental exposures, or psychosocial factors.

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

- Poor inhaler technique (up to 80% of community patients)[82] (Box 3-11, p.56)
- Poor medication adherence[128] (Box 3-12, p.58)
- Incorrect diagnosis of asthma, with symptoms due to alternative conditions such as upper airway dysfunction, cardiac failure or lack of fitness (Box 1-3, p.20)
- Comorbidities and complicating conditions such as rhinosinusitis, gastroesophageal reflux, obesity and obstructive sleep apnea (Chapter 3, Part D, p.62)
- Ongoing exposure to sensitizing or irritant agents in the home or work environment.

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

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Watch patient using their inhaler **Discuss adherence and barriers to use**	• Watch patient use their inhaler(s), check against inhaler checklist. Show correct method, and recheck, up to 3 times. Re-check each visit. • Have empathic discussion to identify poor adherence, e.g. *"Many patients don't use their inhaler as prescribed. In the last 4 weeks, how many days a week have you taken it?" (0 days, 1, 2, 3 etc)* and/or: *"Do you find it easier to remember your inhaler in the morning or the evening?"* Ask about beliefs, cost of medications, and refill frequency.
Confirm the diagnosis of asthma	• If no evidence of variable airflow limitation on spirometry or other testing *(Box 1-2)*, consider halving ICS dose and repeating lung function after 2–3 weeks *(Box 1-5)*; check patient has action plan. Consider referring for challenge test.
If possible remove potential risk factors **Assess and manage comorbidities**	• Check for risk factors or inducers such as smoking, beta-blockers or NSAIDs, or occupational or domestic allergen exposure *(Box 2-2)*, and address as possible *(Box 3-8 – Treating modifiable risk factors).* • Check for and manage comorbidities (e.g. rhinitis, obesity, GERD, obstructive sleep apnea, depression/anxiety) that may contribute to symptoms
Consider treatment step-up	• Consider step up to next treatment level or alternative option on present level *(Box 3-5)*. • Use shared decision-making, and balance potential benefits and risks
Refer to a specialist or severe asthma clinic	• If asthma still uncontrolled after 3–6 months on high dose ICS/LABA, or with ongoing risk factors, refer to a specialist or severe asthma clinic *(Box 3-14)*. • Refer earlier than 6 months if asthma very severe or difficult to manage, or if doubts about diagnosis.

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

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

Chapter 3.

Treating asthma to control symptoms and minimize risk

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This chapter is divided into four parts:

Part A. General principles of asthma management

Part B. Medications and strategies for asthma symptom control and risk reduction

- Medications
- Treating modifiable risk factors
- Non-pharmacological therapies and strategies

Part C. Guided asthma self-management education and skills training

- Information, inhaler skills, adherence, written asthma action plan, self-monitoring, regular review

Part D. Managing asthma with comorbidities and in special populations

Management of worsening and acute asthma is described in Chapter 4 (p.73).

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PART A. GENERAL PRINCIPLES OF ASTHMA MANAGEMENT

KEY POINTS

- The long-term goals of asthma management are to achieve good symptom control, and to minimize future risk of exacerbations, fixed airflow limitation and side-effects of treatment. The patient's own goals regarding their asthma and its treatment should also be identified.
- Effective asthma management requires a partnership between the person with asthma (or the parent/carer) and their health care providers.
- Teaching communication skills to health care providers may lead to increased patient satisfaction, better health outcomes, and reduced use of health care resources.
- The patient's 'health literacy' – that is, the patient's ability to obtain, process and understand basic health information to make appropriate health decisions – should be taken into account.
- Control-based management means that treatment is adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk (of exacerbations and side-effects)
- For population-level decisions about asthma treatment, the 'preferred option' at each step represents the best treatment for most patients, based on group mean data for efficacy, effectiveness and safety from randomized controlled trials, meta-analyses and observational studies, and net cost.
- For individual patients, treatment decisions should also take into account any patient characteristics or phenotype that predict the patient's likely response to treatment, together with the patient's preferences and practical issues (inhaler technique, adherence, and cost to the patient).

LONG-TERM GOALS OF ASTHMA MANAGEMENT

The long-term goals of asthma management are:

- To achieve good control of symptoms and maintain normal activity levels
- To minimize future risk of exacerbations, fixed airflow limitation and side-effects.

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

THE PATIENT-HEALTH CARE PROVIDER PARTNERSHIP

Effective asthma management requires the development of a partnership between the person with asthma (or the parent/carer) and health care providers. 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[129] (Evidence A) and children[130] (Evidence A).

There is emerging evidence that a shared-care approach is associated with improved outcomes.[131] Patients should be encouraged to participate in decisions about their treatment, and given the opportunity to express their expectations and concerns. This partnership needs to be individualized to each patient. A person's willingness and ability to engage in self-management may vary depending on factors such as ethnicity, literacy, understanding of health concepts (health literacy), numeracy, beliefs about asthma and medications, desire for autonomy, and the health care system.

Good communication

Good communication by health care providers is essential as the basis for good outcomes[132-134] (Evidence B). Teaching health care providers to improve their communication skills (Box 3-1) can result in increased patient satisfaction, better health outcomes, and reduced use of health care resources[132-134] without lengthening consultation times.[135] It can also enhance patient adherence.[135] Training patients to give information clearly, seek information, and check their understanding of information provided is also associated with improved adherence with treatment recommendations.[135]

Health literacy and asthma

There is increasing recognition of the impact of low health literacy on health outcomes, including in asthma.[136,137] 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'.[136] Low health literacy is associated with reduced knowledge and worse asthma control.[138] In one study, low numeracy among parents of children with asthma was associated with higher risk of exacerbations.[137] Interventions adapted for cultural and ethnicity perspectives have been associated with improved knowledge and significant improvements in inhaler technique.[139] Suggested communication strategies for reducing the impact of low health literacy are shown in Box 3-1.

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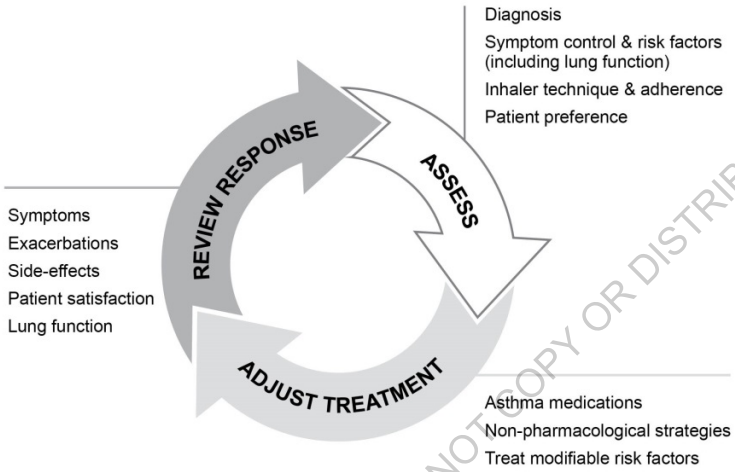
Box 3-1. Communication strategies for health care providers

Key strategies to facilitate good communication[133,134]
• A congenial demeanor (friendliness, humor and attentiveness) • Allowing the patient to express their goals, beliefs and concerns • Empathy, reassurance, and prompt handling of any concerns • Giving encouragement and praise • Giving appropriate (personalized) information • Providing feedback and review
Specific strategies for reducing the impact of impaired health literacy[136]
• Order information from most to least important • Speak slowly and use simple words (avoid medical language, if possible) • Simplify numeric concepts (e.g. use numbers instead of percentages) • Frame instructions effectively (use illustrative anecdotes, drawings, pictures, table or graphs) • Confirm understanding by using the 'teach-back' method (ask patients to repeat instructions) • Ask a second person (e.g. nurse, family member) to repeat the main messages • Pay attention to non-verbal communication by the patient (e.g. poor eye contact) • Make patients feel comfortable about asking questions

CONTROL-BASED ASTHMA MANAGEMENT

In control-based asthma management, pharmacological and non-pharmacological treatment is adjusted in a continuous cycle that involves assessment, treatment and review (Box 3-2). Asthma outcomes have been shown to improve after the introduction of control-based guidelines[140,141] or practical tools for implementation of control-based management strategies.[131,142] The concept of control-based management is also supported by the design of most randomized controlled medication trials, with patients identified for a change in asthma treatment on the basis of features of poor symptom control with or without other risk factors such as low lung function or a history of exacerbations.

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



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For many patients in primary care, symptom control is a good guide to a reduced risk of exacerbations.[143] When inhaled corticosteroids (ICS) were introduced into asthma management, large improvements were observed in symptom control and lung function, and exacerbations and asthma-related mortality decreased. However, with other asthma therapies (including ICS/long-acting beta$_2$-agonists (LABA)[144,145]) or different treatment regimens (such as ICS/formoterol maintenance and reliever therapy[146]), and in patients with severe asthma, there may be discordance between responses for symptom control and exacerbations. In addition, some patients continue to have exacerbations despite well-controlled symptoms, and for patients with ongoing symptoms, side-effects may be an issue if ICS doses continue to be stepped up. Therefore, in control-based management, *both* domains of asthma control (symptom control and future risk – see Box 2-2, p.29) should be taken into account when choosing asthma treatment and reviewing the response.[15,56]

Alternative strategies for adjusting asthma treatment

Some alternative strategies have been evaluated, mainly in severe or difficult-to-treat asthma.

- *Sputum-guided treatment*: this approach, when compared with guidelines-based treatment, is associated with a reduced risk of exacerbations and similar levels of symptom control and lung function.[147] However, only a limited number of centers have routine access to induced sputum analysis, and the benefits have primarily been seen in patients requiring secondary care.[143]
- *Fractional concentration of exhaled nitric oxide* (FENO): treatment guided by FENO has not generally been found to be effective.[147,148] In several of these studies, there have been problems with the design of the intervention and/or control algorithms, that make comparisons and conclusions difficult.[149] Results of FENO measurement at a single point in time should be interpreted with caution (see p.20).[26,28]

At present, neither sputum- nor FENO-guided treatment is recommended for the general asthma population. Sputum-guided treatment is recommended for patients with moderate or severe asthma who are managed in centers experienced in this technique (Box 3-14, p.70)[126] (Evidence A).

Choosing between asthma treatment options

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

- *Population-level medication choices*, e.g. for national formularies or managed care organizations. These aim to represent the best option for most patients in the population. For each treatment step, a 'preferred' controller medication is recommended that provides the best benefit to risk ratio (including cost) for both symptom control and risk reduction. Choice of the preferred controller is based on group mean data from efficacy studies (highly controlled studies in well-characterized populations) and effectiveness studies (from pragmatically controlled studies, or studies in broader populations, or strong observational data),[150] as well as on safety data and cost.
- *Patient-level medication choices*: choices at this level also take into account any patient characteristics or phenotype that may predict a clinically important difference in their response compared with other patients, together with the patient's preferences and practical issues (cost, ability to use the medication and adherence).

The extent to which asthma treatment can be individualized according to patient characteristics or phenotypes depends on the health system, the clinical context, the potential magnitude of difference in outcomes, cost and available resources. At present, most research activity about individualized treatment is focused on severe asthma.[151,152]

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

Choosing between treatment options at a population level
(e.g. national formularies, health maintenance organizations, national guidelines)

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

- Efficacy
- Effectiveness
- Safety

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

Choosing between controller options for individual patients

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

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

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

KEY POINTS

- At present, Step 1 treatment is with as-needed short-acting beta$_2$-agonist (SABA) alone. However, chronic airway inflammation is found even in patients with infrequent or recent-onset asthma symptoms, and there is a striking lack of studies of inhaled corticosteroids (ICS) in such populations.
- Treatment with regular daily low dose ICS is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization and death
- For patients with persistent symptoms and/or exacerbations despite low dose ICS, consider step up but first check for common problems such as inhaler technique, adherence, persistent allergen exposure and comorbidities
  - For adults and adolescents, the preferred step-up treatment is combination ICS/long-acting beta$_2$-agonist (LABA).
  - For adults and adolescents with exacerbations despite other therapies, the risk of exacerbations is reduced with combination low dose ICS/formoterol (with beclometasone or budesonide) as both maintenance and reliever, compared with maintenance controller treatment plus as-needed SABA.
  - For children 6–11 years, increasing the ICS dose is preferred over combination ICS/LABA.
- Consider step down once good asthma control has been achieved and maintained for about 3 months, to find the patient's lowest treatment that controls both symptoms and exacerbations
  - Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit
  - Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma.
- For all patients with asthma:
  - Provide inhaler skills training: this is essential for medications to be effective, but technique is often incorrect
  - Encourage adherence with controller medication, even when symptoms are infrequent
  - Provide training in asthma self-management (self-monitoring of symptoms and/or PEF, written asthma action plan and regular medical review) to control symptoms and minimize the risk of exacerbations and need for health care utilization.
- For patients with one or more risk factors for exacerbations:
  - Prescribe regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients
  - Identify and address modifiable risk factors, (e.g. smoking, low lung function)
  - Consider non-pharmacological strategies and interventions to assist with symptom control and risk reduction, (e.g. smoking cessation advice, breathing exercises, some avoidance strategies)

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ASTHMA MEDICATIONS

Categories of asthma medications

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

- *Controller medications*: these are used for regular maintenance treatment. They reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and decline in lung function.
- *Reliever (rescue) medications*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment.

- *Add-on therapies for patients with severe asthma* (Box 3-14, p.70): these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications (usually a high dose ICS and a LABA) and treatment of modifiable risk factors (see Box 3-8, p.50).

Initial controller treatment

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

- Early initiation of low dose ICS in patients with asthma leads to a greater improvement in lung function than if symptoms have been present for more than 2–4 years.[153,154] One study showed that after this time, higher ICS doses were required, and lower lung function was achieved.[155]
- Patients not taking ICS who experience a severe exacerbation have a greater long-term decline in lung function than those who have already started ICS.[95]
- For patients with occupational asthma, early removal from exposure to the sensitizing agent and early treatment increase the probability of recovery.[31]

Recommended options for initial controller treatment in adults and adolescents, based on evidence (where available) and consensus, are listed in Box 3-4. The patient's response should be reviewed, and treatment stepped down once good control is achieved. Recommendations for a stepwise approach to ongoing treatment are found in Box 3-5 (p.43).

FENO >50 parts per billion (ppb) has been associated with a good short-term response to ICS.[28] However, there are no studies examining the long-term safety of withholding ICS in patients with low initial FENO. Consequently, in patients with a diagnosis or suspected diagnosis of asthma, FENO cannot be recommended at present for deciding against treatment with ICS. Based on current evidence, GINA recommends treatment with low-dose ICS for most patients with asthma, even those with infrequent symptoms (Box 3-2), to reduce the risk of serious exacerbations.

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

Once asthma treatment has been commenced (Box 3-4), ongoing treatment decisions are based on a cycle of assessment, adjustment of treatment, and review of the response. Controller medication is adjusted up or down in a stepwise approach (Box 3-5) to achieve good symptom control and minimize future risk of exacerbations, fixed airflow limitation and medication side-effects. Once good asthma control has been maintained for 2–3 months, treatment may be stepped down in order to find the patient's minimum effective treatment (Box 3-7, p.49).

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

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

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Box 3-4. Recommended options for initial controller treatment in adults and adolescents

Presenting symptoms	Preferred initial controller
Asthma symptoms or need for SABA less than twice a month; no waking due to asthma in last month; and no risk factors for exacerbations (Box 2-2B, p17), including no exacerbations in the last year	No controller (Evidence D)*
Infrequent asthma symptoms, but the patient has one or more risk factors for exacerbations (Box 2-2B); e.g. low lung function, or exacerbation requiring OCS in the last year, or has ever been in intensive care for asthma	Low dose ICS** (Evidence D)*
Asthma symptoms or need for SABA between twice a month and twice a week, or patient wakes due to asthma once or more a month	Low dose ICS** (Evidence B)
Asthma symptoms or need for SABA more than twice a week	Low dose ICS** (Evidence A) Other less effective options are LTRA or theophylline
Troublesome asthma symptoms most days; or waking due to asthma once a week or more, especially if any risk factors exist (Box 2-2B)	Medium/high dose ICS[†] (Evidence A), or Low dose ICS/LABA[†#] (Evidence A)
Initial asthma presentation is with severely uncontrolled asthma, or with an acute exacerbation	Short course of oral corticosteroids AND Start regular controller treatment; options are • High-dose ICS (Evidence A), or • Moderate-dose ICS/LABA[#] (Evidence D)
Before starting initial controller treatment	
• Record evidence for the diagnosis of asthma, if possible • Record the patient's level of symptom control and risk factors, including lung function (Box 2-2, p17) • Consider factors influencing choice of treatment (Box 3-3, p27) • Ensure that the patient can use the inhaler correctly • Schedule an appointment for a follow-up visit	
After starting initial controller treatment	
• Review patient's response (Box 2-2) after 2–3 months, or earlier depending on clinical urgency • See Box 3-5 for recommendations for ongoing treatment and other key management issues • Step down treatment once good control has been maintained for 3 months (Box 3-7, p.49).	

ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist .

This table is based on evidence from available studies and consensus, including considerations of cost.
* These recommendations reflect the evidence for chronic airway inflammation in asthma even when symptoms are infrequent, the known benefit of low dose ICS in reducing serious exacerbations in broad asthma populations, and the lack of large studies comparing the effect of ICS and as-needed SABA alone on exacerbations in these populations.
**Corresponds to starting at Step 2 in Box 3-5.
[†] Corresponds to starting at Step 3 in Box 3-5.
Not recommended for initial treatment in children 6–11 years.

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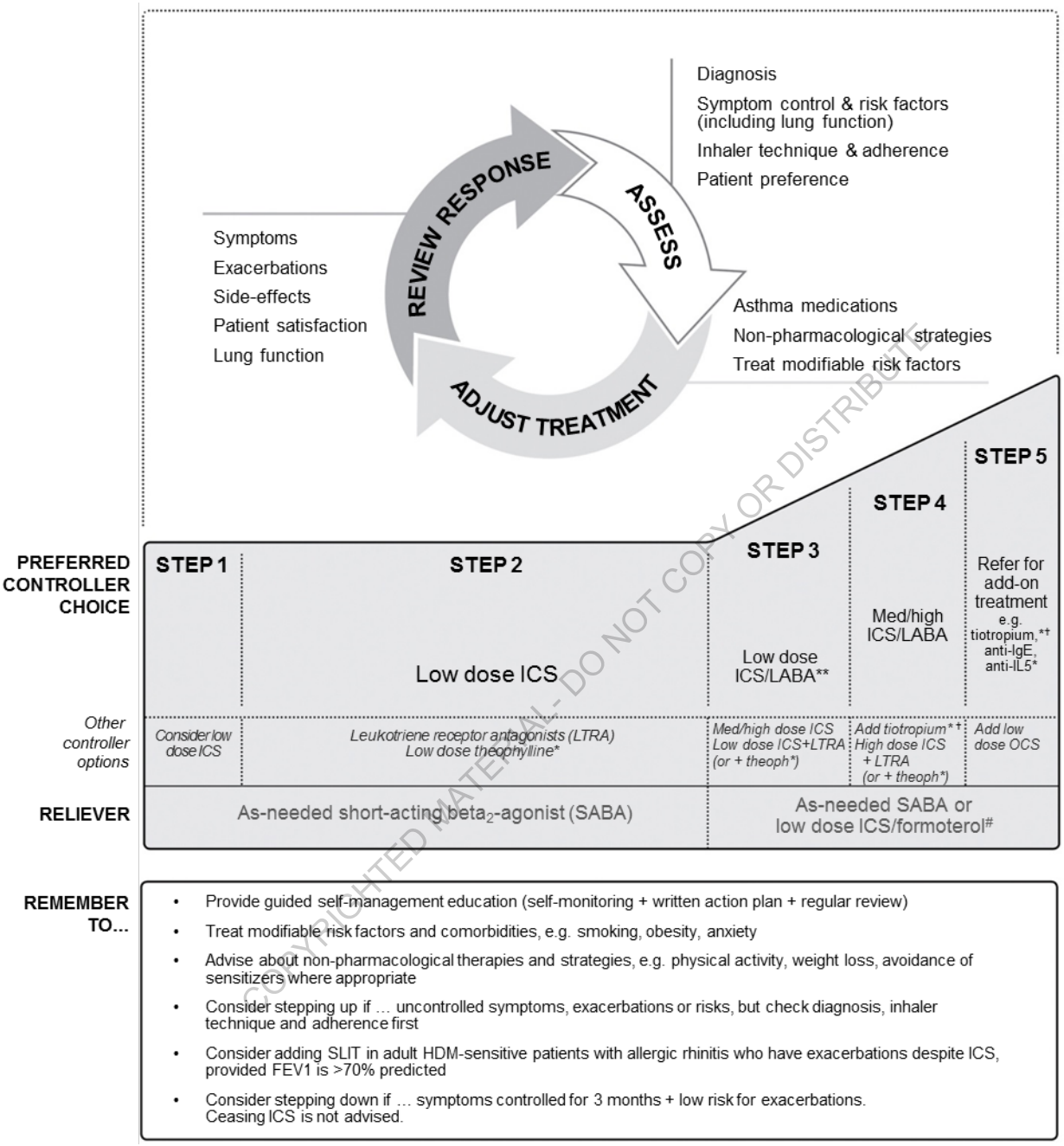
Box 3-5. Stepwise approach to control symptoms and minimize future risk



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ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; med: medium dose; OCS: oral corticosteroids; SLIT: sublingual immunotherapy. See Box 3-6 (p.44) for low, medium and high doses of ICS for adults, adolescents and children 6–11 years. See Chapter 3 Part D (p.66) for management of exercise-induced bronchoconstriction.

* Not for children <12 years.
** For children 6–11 years, the preferred Step 3 treatment is medium dose ICS.
\# Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol maintenance and reliever therapy.
† Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years.

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

Adults and adolescents (12 years and older)			
Drug	**Daily dose (mcg)**		
	Low	Medium	High
Beclometasone dipropionate (CFC)*	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate(DPI)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000
Children 6–11 years (for children 5 years and younger, see Box 6-6, p.112)			
Beclometasone dipropionate (CFC)*	100–200	>200–400	>400
Beclometasone dipropionate (HFA)	50-100	>100-200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide	80	>80-160	>160
Fluticasone furoate (DPI)	n.a.	n.a.	n.a.
Fluticasone propionate (DPI)	100–200	>200–400	>400
Fluticasone propionate (HFA)	100–200	>200–500	>500
Mometasone furoate	110	≥220–<440	≥440
Triamcinolone acetonide	400–800	>800–1200	>1200

CFC: chlorofluorocarbon propellant; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; n.a. not applicable
*Beclometasone dipropionate CFC is included for comparison with older literature.

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

For new preparations, manufacturer’s information should be reviewed carefully; products containing the same molecule may not be clinically equivalent. For more detailed discussion see Raissy et al.[98]

In clinical practice, the choice of medication, device and dose should be based on assessment of symptom control, risk factors, patient preference, and practical issues (cost, ability to use the device, and adherence) (Box 3-3, p27). It is important to monitor the response to treatment and any side-effects, and to adjust the dose accordingly (Box 3-5, p31). Once good symptom control has been maintained for 3 months, the ICS dose should be carefully titrated to the minimum dose, taken regularly, that will maintain good symptom control and minimize exacerbation risk, while reducing the potential for side-effects (Box 3-7). Patients who are being considered for a high daily dose of ICS (except for short periods) should be referred for expert assessment and advice, where possible (Box 3-14, p55).

More detail about asthma medications is provided in Appendix Chapter 5 (adults: Part A; children 6–11 years: Part B).

***STEP 1*: As-needed reliever inhaler**

Preferred option: as-needed inhaled short-acting beta$_2$-agonist (SABA)

SABAs are highly effective for the quick relief of asthma symptoms[156] (Evidence A). However, there is insufficient evidence about the safety of treating asthma with SABA alone, so this option should be reserved for patients with occasional daytime symptoms (e.g. less than twice a month) of short duration (a few hours), with no night waking and with normal lung function. More frequent symptoms, or the presence of any exacerbation risk factors such as FEV_1 <80% personal best or predicted or an exacerbation in the previous 12 months, indicate that regular controller treatment is needed[157-159] (Evidence B).

Other options

Regular low dose ICS should be considered, in addition to as-needed SABA, for patients at risk of exacerbations[157,159] (Evidence B).

Other options not recommended for routine use

In adults, inhaled anticholinergic agents like ipratropium, oral SABA or short-acting theophylline are potential alternatives to SABA for relief of asthma symptoms; however, these agents have a slower onset of action than inhaled SABA (Evidence A), and oral SABA and theophylline have a higher risk of side-effects.

The rapid-onset LABA, formoterol, is as effective as SABA as a reliever medication in adults and children,[160] but use of regular or frequent LABA without ICS is strongly discouraged because of the risk of exacerbations (Evidence A).

***STEP 2*: Low dose controller medication plus as-needed reliever medication**

Preferred option: regular low dose ICS plus as-needed SABA

Treatment with ICS at low doses reduces asthma symptoms, increases lung function, improves quality of life, and reduces the risk of exacerbations and asthma-related hospitalizations or death[157,159,161,162] (Evidence A). Box 3-6 lists doses that are considered to be low, medium and high for different ICS products.

Other options

Leukotriene receptor antagonists (LTRA) are less effective than ICS[163] (Evidence A). They may be appropriate for initial controller treatment for some patients who are unable or unwilling to use ICS; for patients who experience intolerable side-effects from ICS; or for patients with concomitant allergic rhinitis[164,165] (Evidence B).

For adult or adolescent patients not previously using controller treatment, combination low dose ICS/LABA as the initial maintenance controller treatment reduces symptoms and improves lung function compared with low dose ICS alone. However, it is more expensive and does not further reduce the risk of exacerbations compared with ICS alone[166] (Evidence A).

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

Options not recommended for routine use

Sustained-release theophylline has only weak efficacy in asthma[167-169] (Evidence B) and side-effects are common, and may be life-threatening at higher doses.[170] Chromones (nedocromil sodium and sodium cromoglycate) have a favorable safety profile but low efficacy[171,172] (Evidence A), and their inhalers require burdensome daily washing to avoid blockage.

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***STEP 3*: One or two controllers plus as-needed reliever medication**

Preferred option (adults/adolescents): combination low dose ICS/LABA as maintenance treatment plus as-needed SABA OR combination low dose ICS/formoterol (budesonide or beclometasone) as both maintenance and reliever treatment

Preferred option (children 6–11 years): moderate dose ICS plus as-needed 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, p22).

The options at this step differ depending on age. For adults and adolescents, there are two 'preferred' Step 3 options: combination low dose ICS/LABA as maintenance treatment with as-needed SABA as reliever, and low dose ICS/ formoterol as both maintenance and reliever treatment. Currently approved combination ICS/LABA inhalers for Step 3 treatment of asthma include low doses of fluticasone propionate/formoterol, fluticasone furoate/vilanterol, fluticasone propionate/salmeterol, beclometasone/ formoterol, budesonide/formoterol and mometasone/formoterol (see Box 3-6, p.44). The maintenance and reliever regimen can be prescribed with low dose beclometasone/formoterol or budesonide/formoterol. Adding LABA to the same dose of ICS provides additional improvements in symptoms and lung function with a reduced risk of exacerbations[173] (Evidence A). In at-risk patients, the ICS/formoterol maintenance and reliever regimen significantly reduces exacerbations and provides similar levels of asthma control at relatively low doses of ICS, compared with a fixed dose of ICS/LABA as maintenance treatment or a higher dose of ICS, both with as-needed SABA[174-178] (Evidence A). For adult patients with allergic rhinitis and sensitized to house dust mite, with exacerbations despite low-high dose ICS, consider adding sublingual allergen immunotherapy (SLIT), provided FEV_1 is >70% predicted.[179,180] (see p.51).

In children, the preferred option is to increase ICS to medium dose (see Box 3-6, p.44),[181] and in this age group, the effect may be similar to[182] or more effective[183,184] than adding LABA.

Other options

Another option for adults and adolescents is to increase ICS to medium dose (see Box 3-6, p.44), but this is less effective than adding a LABA[118,185,186] (Evidence A). Other less efficacious options are low dose ICS plus either LTRA[187] (Evidence A) or low dose, sustained-release theophylline[188] (Evidence B).

***STEP 4*: Two or more controllers plus as-needed reliever medication**

Preferred option (adults/adolescents): combination low dose ICS/formoterol as maintenance and reliever treatment, OR combination medium dose ICS/LABA plus as-needed SABA

Preferred option (children 6–11 years): refer for expert assessment and advice

The selection of Step 4 treatment depends on the prior selection at Step 3. Before stepping up, check for common problems such as incorrect inhaler technique, poor adherence, and environmental exposures, and confirm that the symptoms are due to asthma (Box 2-4, p22).

For adult and adolescent patients with ≥1 exacerbations in the previous year, combination low dose ICS/formoterol as maintenance and reliever treatment is more effective in reducing exacerbations than the same dose of maintenance ICS/LABA or higher doses of ICS[178] (Evidence A). This regimen can be prescribed with low dose budesonide/formoterol or beclometasone/formoterol as in Step 3; the maintenance dose may be increased if necessary. For patients taking low dose maintenance ICS/LABA with as-needed SABA, whose asthma is not adequately controlled, treatment may be increased to medium dose ICS/LABA[145] (Evidence B); combination ICS/LABA medications are as for Step 3.

For children 6–11 years, if asthma is not well controlled on moderate dose ICS (see Box 3-6, p.44), the recommendation is to refer the child for expert assessment and advice.

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Other options

Tiotropium (long-acting muscarinic antagonist) by mist inhaler may be used as add-on therapy for adult or adolescent patients with a history of exacerbations (Evidence A);[189] it is not indicated in children <12 years.

For adult patients with allergic rhinitis and sensitization to house dust mite, with exacerbations despite low-high dose ICS, consider adding sublingual allergen immunotherapy (SLIT), provided FEV_1 is >70% predicted.[179,180] (see p.51).

Combination high-dose ICS/LABA may be considered in adults and adolescents, but the increase in ICS dose generally provides little additional benefit[110,118,186,190] (Evidence A), and there is an increased risk of side-effects, including adrenal suppression.[191] A high dose is recommended only on a trial basis for 3–6 months when good asthma control cannot be achieved with medium dose ICS plus LABA and/or a third controller (e.g. LTRA or sustained-release theophylline,[159,168,192] Evidence B). Theophylline should not be used in children.

For medium or high dose budesonide, efficacy may be improved with dosing four times daily[193,194] (Evidence B), but adherence may be an issue. For other ICS, twice-daily dosing is appropriate (Evidence D). Other options for adults or adolescents that can be added to a medium- or high-dose ICS but that are less efficacious than adding LABA, include LTRA[192,195-198] (Evidence A), or low dose sustained-release theophylline[168] (Evidence B).

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***STEP 5*: Higher level care and/or add-on treatment**

Preferred option: referral for specialist investigation and consideration of add-on treatment

Patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered, should be referred to a specialist with expertise in management of severe asthma[126] (Evidence D)

Treatment options that may be considered at Step 5 (if not already tried) are described in Box 3-14 (p.70). They include:

- Add-on tiotropium (long-acting muscarinic antagonist) in patients aged ≥12 years with a history of exacerbations despite Step 4 treatment. Add-on tiotropium by mist inhaler improves lung function and increases the time to severe exacerbation (Evidence B).[189]
- Add-on anti-immunoglobulin E (anti-IgE) (omalizumab) treatment: for patients aged ≥6 years with moderate or severe allergic asthma that is uncontrolled on Step 4 treatment[199,200] (Evidence A).
- Add-on anti-interleukin-5 treatment (subcutaneous mepolizumab, intravenous reslizumab): for patients aged ≥12 years with severe eosinophilic asthma that is uncontrolled on Step 4 treatment (Evidence B).[201-203]
- Sputum-guided treatment: for patients 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[147] (Evidence A).
- Add-on treatment with bronchial thermoplasty: may be considered for some adult patients with severe asthma [126] (Evidence B). Evidence is limited and in selected patients (see p.51 and Appendix Chapter 6). The long term effects compared with control patients, including for lung function, are not known.
- Add-on low dose oral corticosteroids (≤7.5 mg/day prednisone equivalent): may be effective for some adults with severe asthma[126] (Evidence D); but are often associated with substantial side effects[204,205] (Evidence B). They should only be considered for adults with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence with Step 4 treatment, and after exclusion of other contributory factors. Patients should be counseled about potential side-effects (Evidence D).[205] They should be assessed and monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).[206]

REVIEWING RESPONSE AND ADJUSTING TREATMENT

How often should asthma be reviewed?

Patients with asthma should be reviewed regularly to monitor their symptom control, risk factors and occurrence of exacerbations, as well as to document the response to any treatment changes. For most controller medications, improvement begins within days of initiating treatment, but the full benefit may only be evident after 3–4 months.[207] In severe and chronically under-treated disease, it may take longer.[208]

All health care providers should be encouraged to assess asthma control, adherence and inhaler technique at every visit, not just when the patient presents because of their asthma.[209] 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[210] (Evidence D).

Stepping up asthma treatment

Asthma is a variable condition, and periodic treatment adjustments by the clinician and/or the patient may be needed.[211]

- *Sustained step up (for at least 2–3 months)*: some patients may fail to respond adequately to initial treatment. A step up in treatment may be recommended (Box 3-5, p31) if the symptoms are confirmed to be due to asthma; inhaler technique and adherence are satisfactory; and modifiable risk factors such as smoking have been addressed (Box 3-8, p38). Any step-up should be regarded as a therapeutic trial, and the response reviewed after 2–3 months. If there is no response, treatment should be reduced to the previous level, and alternative treatment options or referral considered.
- *Short-term step up (for 1–2 weeks)*: an occasional short-term increase in maintenance ICS dose for 1–2 weeks may be necessary; for example, during viral infections or seasonal allergen exposure. This may be initiated by the patient according to their written asthma action plan (Box 4-2, p61), or by the health care provider.
- *Day-to-day adjustment:* for patients prescribed combination budesonide/formoterol or beclometasone/formoterol as maintenance and reliever treatment, the patient adjusts the number of as-needed doses of ICS/formoterol from day to day according to their symptoms, while continuing the maintenance dosage.

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Stepping down treatment when asthma is well controlled

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

- To find the patient's minimum effective treatment, i.e. to maintain good control of symptoms and exacerbations, and to minimize the costs of treatment and potential for side-effects
- To encourage the patient to continue regular controller treatment. Patients often experiment with intermittent treatment through concern about the risks or costs of daily treatment.[212] It may be helpful to inform them that lower doses can be achieved if controller treatment is taken every day.

The approach to stepping down will differ from patient to patient depending on their current treatment, risk factors and preferences. There are few experimental data on the optimal timing, sequence and magnitude of treatment reductions in asthma. If treatment is stepped down too far or too quickly, exacerbation risk may increase even if symptoms remain reasonably controlled[213] (Evidence B). Complete cessation of ICS is associated with a significant risk of exacerbations[214] (Evidence A). Predictors of loss of control during dose reduction include airway hyperresponsiveness and sputum eosinophilia,[215] but these tests are not readily available in primary care. Any step-down of asthma treatment should be considered as a therapeutic trial, with the response evaluated in terms of both symptom control and exacerbation frequency. Prior to stepping down treatment, the patient should be provided with a written asthma action plan and instructions for how and when to resume their previous treatment if their symptoms worsen. Step-down strategies for different controller treatments are summarized in Box 3-7; these are based on current evidence, but more research is needed. Only a small number of step-down studies have been performed in children.

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

General principles of stepping down asthma treatment
• Consider stepping down when asthma symptoms have been well controlled and lung function has been stable for 3 or more months (Evidence D). If the patient has risk factors for exacerbations (Box 2-2, p17) or fixed airflow limitation, do not step down without close supervision. • Choose an appropriate time (no respiratory infection, patient not travelling, not pregnant). • Approach each step as a therapeutic trial. Engage the patient in the process; document their asthma status (symptom control, lung function and risk factors, Box 2-2); provide clear instructions; provide written asthma action plan (Box 4-2, p61) and ensure 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[216] (Evidence A).

Current step	Current medication and dose	Options for stepping down	Evidence
Step 5	High dose ICS/LABA plus oral corticosteroids (OCS)	• Continue high dose ICS/LABA and reduce OCS dose • Use sputum-guided approach to reducing OCS • Alternate-day OCS treatment • Replace OCS with high dose ICS	D B D D
	High dose ICS/LABA plus other add-on agents	• Refer for expert advice	D
Step 4	Moderate to high dose ICS/LABA maintenance treatment	• Continue combination ICS/LABA with 50% reduction in ICS component, by using available formulations • Discontinuing LABA may lead to deterioration[217]	B 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[216]	B
Step 3	Low dose ICS/LABA maintenance	• Reduce ICS/LABA to once daily • Discontinuing LABA may lead to deterioration[217]	D 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
	Moderate- or high-dose ICS	• Reduce ICS dose by 50%[216]	A
Step 2	Low dose ICS	• Once-daily dosing (budesonide, ciclesonide, mometasone)[218,219] • Adding LTRA may allow ICS dose to be stepped down[220] • Insufficient evidence to support step-down to as-needed ICS with SABA[221]	A B -
	Low dose ICS or LTRA	• Consider stopping controller treatment only if there have been no symptoms for 6–12 months, and patient has no risk factors (Box 2-2, p17). Provide a written asthma action plan, and monitor closely. • Complete cessation of ICS in adults is not advised as the risk of exacerbations is increased[214]	D A

BDP: beclometasone dipropionate; ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids.
*ICS/formoterol maintenance and reliever treatment can be prescribed with low dose budesonide/formoterol or BDP/formoterol.

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TREATING OTHER MODIFIABLE RISK FACTORS

Some patients continue to experience exacerbations even with maximal doses of current treatment. Having even one exacerbation increases the risk that a patient will have another within the next 12 months.[94] There is increasing research interest in identifying at-risk patients (Box 2-2B, p.29), and in investigating new strategies to further reduce exacerbation risk.

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

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

Risk factor	Treatment strategy	Evidence
Any patient with ≥1 risk factor for exacerbations (including poor symptom control)	• Ensure patient is prescribed regular ICS-containing controller • Ensure patient has a written action plan appropriate for their health literacy • Review patient more frequently than low-risk patients • Check inhaler technique and adherence frequently • Identify any modifiable risk factors (Box 2-2, p17)	A A A A D
≥1 severe exacerbation in last year	• Consider alternative controller regimens to reduce exacerbation risk, e.g. ICS/formoterol maintenance and reliever regimen • Consider stepping up treatment if no modifiable risk factors • Identify any avoidable triggers for exacerbations	A A C
Exposure to tobacco smoke	• Encourage smoking cessation by patient/family; provide advice and resources • Consider higher dose of ICS if asthma poorly-controlled	A B
Low FEV_1, especially if <60% predicted	• Consider trial of 3 months' treatment with high-dose ICS and/or 2 weeks' OCS • Exclude other lung disease, e.g. COPD • Refer for expert advice if no improvement	B D D
Obesity	• Strategies for weight reduction • Distinguish asthma symptoms from symptoms due to deconditioning, mechanical restriction, and/or sleep apnea	B D
Major psychological problems	• Arrange mental health assessment • Help patient to distinguish between symptoms of anxiety and asthma; provide advice about management of panic attacks	D D
Major socioeconomic problems	• Identify most cost-effective ICS-based regimen	D
Confirmed food allergy	• Appropriate food avoidance; injectable epinephrine	A
Allergen exposure if sensitized	• Consider trial of simple avoidance strategies; consider cost • Consider step up of controller treatment • The efficacy of allergen immunotherapy in asthma is limited	C D A
Sputum eosinophilia (limited centers)	• Increase ICS dose independent of level of symptom control	A*

FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; OCS: oral corticosteroids.
* Based on evidence from relatively small studies in selected populations. Also see Box 3-9 and Appendix Chapter 6 for more information about non-pharmacological interventions.

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The potential for local and/or systemic side-effects of medications can be minimized by ensuring correct inhaler technique (Box 3-11, p.42), by reminding patients to rinse and spit out after using ICS, and, after good asthma control has been maintained for 3 months, by finding each patient's minimum effective dose (the lowest dose that will maintain good symptom control and minimize exacerbations, Box 3-7, p.37).

OTHER THERAPIES

Allergen Immunotherapy

Allergen-specific immunotherapy may be an option if allergy plays a prominent role, e.g. asthma with allergic rhinoconjunctivitis. There are currently two approaches: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Overall, most studies have been in mild asthma, and few studies have compared immunotherapy with pharmacological therapy, or used standardized outcomes such as exacerbations.

SCIT: In people with asthma and allergic sensitization, SCIT is associated with a reduction in symptom scores and medication requirements, and improved allergen-specific and nonspecific airway hyperresponsiveness.[222] Adverse effects include uncommon anaphylactic reactions which may be life-threatening.

SLIT: Modest benefits have been seen in adults and children,[223] but there is concern about the design of many of the previous studies.[224] A study of SLIT for house dust mites (HDM) in patients with asthma and HDM allergic rhinitis demonstrated a modest reduction of ICS with high dose SLIT.[180] In patients sensitized to HDM, with allergic rhinitis and persistent asthma requiring ICS, with FEV_1>70% predicted, SLIT for HDM showed benefit in decreasing mild to moderate asthma exacerbations.[179] In such patients with exacerbations despite taking Step 3 or Step 4 therapy, SLIT can now be considered as an add-on therapy. Adverse effects include mild oral and gastrointestinal symptoms.[224]

Compared to pharmacological and avoidance options, potential benefits of allergen immunotherapy must be weighed against the risk of adverse effects, and the inconvenience and cost of the prolonged course of therapy (Evidence D).

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Vaccinations

Influenza causes significant morbidity and mortality in the general population, and the risk can be reduced by annual vaccination. Influenza contributes to some acute asthma exacerbations, and patients with moderate-severe asthma are advised to receive an influenza vaccination every year, or when vaccination of the general population is advised (Evidence D). However, patients should be advised that vaccination is not expected to reduce the frequency or severity of asthma exacerbations (Evidence A).[225] There is no evidence for an increase in asthma exacerbations after vaccination with inactivated trivalent vaccines compared to placebo.

People with asthma, particularly children and the elderly, are at higher risk of pneumoccal disease,[226] but there is insufficient evidence to recommend routine pneumococcal vaccination in people with asthma (Evidence D).[227]

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.[104] The treatment is associated with a large placebo effect.[104] In patients taking high-dose ICS/LABA, bronchial thermoplasty was associated with an increase in asthma exacerbations during the 3 month treatment period, and a subsequent decrease in exacerbations, but no beneficial effect on lung function or asthma symptoms compared with sham-controlled patients.[104] Extended follow up of some treated patients reported a sustained reduction in exacerbations compared with pre-treatment.[228] However, longer-term follow up of larger cohorts comparing effectiveness and safety, including for lung function, in both active and sham-treated patients is needed. Caution should be used in selecting patients for this procedure. The number of studies is small, and people with chronic sinus disease, frequent chest infections or FEV_1 <60% predicted were excluded from the sham-controlled study.[104] The 2014 ERS/ATS Task Force on Severe Asthma recommends that 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.[126]

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.[229] In a meta-analysis, benefit for asthma worsenings was seen in some studies, but to date, there is no good-quality evidence that Vitamin D supplementation leads to improvement in asthma control or reduction in exacerbations.[230,231] More studies are needed.

NON-PHARMACOLOGICAL INTERVENTIONS

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

Box 3-9. Non-pharmacological interventions - summary (continued next page; detail in Appendix Chapter 6)

Intervention	**Advice/recommendation** (continued on next page)	Evidence
Cessation of smoking and ETS exposure	• At every visit, strongly encourage people with asthma who smoke to quit. Provide access to counseling and smoking cessation programs (if available)	A
	• Advise parents/carers of children with asthma not to smoke and not to allow smoking 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 overlap, ACO, Chapter 5, p.89), 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 and management of exercise-induced bronchoconstriction (p50)	A
	• Regular physical activity improves cardiopulmonary fitness, but confers no other specific benefit on lung function or asthma symptoms, with the exception of swimming in young people with asthma	B
	• There is little evidence to recommend one form of physical activity over another	D
Avoidance of occupational exposures	• Ask all patients with adult-onset asthma about their work history and other exposures	A
	• In management of occupational asthma, identify and eliminate occupational sensitizers as soon as possible, and remove sensitized patients from any further exposure to these agents	A
	• Patients with suspected or confirmed occupational asthma should be referred 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	A
	• 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.69)	A
	• Decide about prescription of oral or intra-ocular beta-blockers on a case-by-case basis. Initiate treatment under close medical supervision by a specialist	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

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

Intervention	Advice/recommendation	Evidence
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 no evidence of clinical benefit for asthma 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 multi-component 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
Allergen immunotherapy	• For adult patients with allergic rhinitis and sensitized to HDM, with exacerbations despite low to high dose ICS, consider adding sublingual immunotherapy (SLIT), provided FEV_1 is >70% predicted	B
	• Compared to pharmacological and avoidance options, potential benefits of allergen immunotherapy (SCIT or SLIT) must be weighed against the risk of adverse effects and the inconvenience and cost of the prolonged course of therapy, including for SCIT the minimum half-hour wait required after each injection.	D
Breathing exercises	• Breathing exercises may be a useful supplement to asthma pharmacotherapy	B
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
Vaccinations	• People with asthma, particularly children and the elderly, are at higher risk of pneumococcal disease, but there is insufficient evidence to recommend routine pneumococcal vaccination in people with asthma	B
	• Advise patients with moderate-severe asthma to have an influenza vaccination every year, or at least when vaccination of the general population is advised	D
Bronchial thermoplasty	• For highly-selected adult patients with uncontrolled asthma despite use of recommended therapeutic regimens and referral to an asthma specialty center (Step 5), bronchial thermoplasty is a potential treatment option in some countries.	B
	• Caution should be used in selecting patients for this procedure, as the number of studies is small, and people with chronic sinus disease, frequent chest infections or FEV_1 <60% predicted were excluded.	D
Avoidance of outdoor allergens	• For sensitized patients, when pollen and mold counts are highest, closing windows and doors, remaining indoors, and using air conditioning may reduce exposure to outdoor allergens	D

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

Intervention	Advice/recommendation	Evidence
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
Avoidance of outdoor air pollutants/ weather conditions	• In general, when asthma is well-controlled, there is no need for patients to modify their lifestyle to avoid unfavorable outdoor (air pollutants, weather).	D
	• It may be helpful during unfavorable environmental conditions (very cold weather, low humidity or high air pollution) to avoid strenuous outdoors physical activity and stay indoors in a climate-controlled environment; and during viral infections to avoid polluted environments	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 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

NSAID: non-steroidal anti-inflammatory drugs; SABA: short-acting beta$_2$-agonist.
Interventions with highest level evidence are shown first. More details are provided in Appendix Chapter 6.

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INDICATIONS FOR REFERRAL FOR EXPERT ADVICE

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

Box 3-10. 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.20) (immediate referral recommended) • Diagnosis is unclear even after a trial of therapy with ICS or systemic corticosteroids • Patients with features of both asthma and COPD, if there is doubt about priorities for treatment
Suspected occupational asthma
• Refer for confirmatory testing and identification of sensitizing or irritant agent, specific advice about eliminating exposure and pharmacological treatment. See specific guidelines (e.g.[31]) for details.
Persistent uncontrolled asthma or frequent exacerbations
• Patient's symptoms remain uncontrolled, or patient has ongoing exacerbations or low lung function despite correct inhaler technique and good adherence with Step 4 treatment (moderate or high-dose ICS/LABA, Box 3-5, p.43). Before referral, depending on the clinical context, identify and treat modifiable risk factors (Box 2-2, p.29; Box 3-8, p.50) and comorbidities (p.62) • Patient has frequent asthma-related health care utilization (e.g. multiple ED visits or urgent primary care visits)
Any risk factors for asthma-related death (see Box 4-1, p.75)
• Near-fatal asthma attack (ICU admission, or mechanical ventilation for asthma) at any time in the past • Anaphylaxis or confirmed food allergy in a patient with asthma
Evidence of, or risk of, significant treatment side-effects
• Patients with significant side-effects from treatment • Need for long-term oral corticosteroid use • Frequent courses of oral corticosteroids (e.g. two or more courses a year)
Symptoms suggesting complications or sub-types of asthma
• e.g. aspirin-exacerbated respiratory disease (p.69); allergic bronchopulmonary aspergillosis
Additional reasons for referral in children 6–11 years
• Doubts about diagnosis of asthma e.g. respiratory symptoms are not responding well to treatment in a child who was born prematurely • Symptoms or exacerbations remain uncontrolled despite moderate dose ICS (Box 3-6B, p.44) with correct inhaler technique and good adherence • Suspected side-effects of treatment (e.g. growth delay) • Asthma and confirmed food allergy

ICS: inhaled corticosteroids; ICU: intensive care unit. For indications for referral in children 0–5 years, see Chapter 6, p.104.

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

OVERVIEW

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

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

SKILLS TRAINING FOR EFFECTIVE USE OF INHALER DEVICES

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

Poor inhaler technique leads to poor asthma control, increased risk of exacerbations and increased adverse effects.[82] Most patients (up to 70–80%) are unable to use their inhaler correctly. Unfortunately, many health care providers are unable to correctly demonstrate how to use the inhalers they prescribe.[232] Most people with incorrect technique are unaware that they have a problem. There is no 'perfect' inhaler – patients can have problems using any inhaler device.

Strategies for ensuring effective use of inhaler devices are summarized in Box 3-11.

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Box 3-11. Strategies to ensure effective use of inhaler devices

CHOOSE
• Choose the most appropriate inhaler device for the patient before prescribing. Consider the medication options (Box 3-5, p.43), the available devices, patient skills and cost. • If different options are available, encourage the patient to participate in the choice • For pMDIs, use of a spacer improves delivery and (with ICS) reduces the potential for side-effects • Ensure that there are no physical barriers, e.g. arthritis, that limit use of the inhaler • Avoid use of multiple different inhaler types where possible, to avoid confusion
CHECK
• 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 • Check technique again, paying attention to problematic steps. You may need to repeat this process 2–3 times.[233] • Only consider an alternative device if the patient cannot use the inhaler correctly after several repeats of training • Re-check inhaler technique frequently. After initial training, errors often recur within 4–6 weeks.[234]
CONFIRM
• Clinicians should be able to demonstrate correct technique for each of the inhalers they prescribe • Pharmacists and nurses can provide highly effective inhaler skills training[235,236]

The above principles apply to all types of inhaler devices. For patients prescribed pressurized metered dose inhalers (pMDIs), use of a spacer improves delivery and (for ICS) reduces the potential for local side-effects such as dysphonia and oral candidiasis. 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[233,237] (Evidence A). A physical demonstration is essential to improve inhaler technique.[238] This is easiest if the health care provider has placebo inhalers and a spacer. After training, inhaler technique falls off with time, so checking and re-training must be repeated regularly. This is particularly important for patients with poor symptom control or a history of exacerbations. Pharmacists and nurses can provide highly effective inhaler skills training.[235,236]

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

ADHERENCE WITH MEDICATIONS AND OTHER ADVICE

Identifying poor adherence

Poor adherence is defined as the failure of treatment to be taken as agreed upon by the patient and the health care provider. There is increasing awareness of the importance of poor adherence in chronic diseases, and of the potential to develop interventions to improve adherence.[239] Approximately 50% of adults and children on long-term therapy for asthma fail to take medications as directed at least part of the time.[128]

In clinical practice, poor adherence may be identified by an empathic question that acknowledges the likelihood of incomplete adherence and encourages an open discussion. See Box 3-12, p.58 for examples.

Checking the date of the last prescription or the date on the inhaler may assist in identifying poor adherence. In some health systems, pharmacists can assist in identifying poorly adherent patients by monitoring dispensing records. In clinical studies, poor adherence may be identified by short adherence behavior questionnaires, or from dispensing records; dose or pill counting; electronic inhaler monitoring;[240] and drug assay such as for prednisolone.[241]

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Factors contributing to poor adherence

It is important to elicit patients' beliefs and concerns about asthma and asthma medications in order to understand the reasons behind their medication-taking behavior. Specific drug and non-drug factors involved in poor adherence are listed in Box 3-12, p.58. They include both intentional and unintentional factors. Issues such as ethnicity,[242] health literacy,[243,244] and numeracy[137] are often overlooked. Patients' concerns about side-effects may be either real or perceived.[212,245]

Interventions to improve adherence in asthma

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

- Shared decision-making for medication/dose choice improved adherence and asthma outcomes.[131]
- Inhaler reminders for missed doses improved adherence and reduced exacerbations.[246,247]
- 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.[248]
- 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.[249]
- 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.[250]

Further studies are needed of adherence strategies that are feasible for implementation in primary care.

Box 3-12. Poor medication adherence 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. multiple 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 health care providers
• Stigmatization
• Cultural or religious issues
• Cost
	Ask an empathic question
	• Acknowledge the likelihood of incomplete adherence and encourage an open non-judgemental 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?'[251]
	  • 'Do you find it easier to remember your inhaler in the morning or the evening?'
	Check medication usage
	• Check the date of the last controller prescription
	• Check the date and dose counter on the inhaler
	• In some health systems, prescribing and dispensing frequency can be monitored electronically by clinicians and/or pharmacists
	• See review articles for more detail.[128,252]

Examples of successful adherence interventions	
• Shared decision-making for medication/dose choice[131] • Inhaler reminders for missed doses[246,247] • Prescribing ICS once-daily versus twice-daily[253] • Home visits for a comprehensive asthma program by an asthma nurse[248]	

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ASTHMA INFORMATION

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

For young children, the focus of asthma education will be on the parent/carer, but young children can be taught simple asthma management skills. Adolescents may have unique difficulties regarding adherence, and peer support group education may help in addition to education provided by the health care provider.[254] Regional issues and the adolescent's developmental stage may affect the outcomes of such programs.[255]

The key features and components of an asthma education program are provided in Box 3-13. Information alone improves knowledge but does not improve asthma outcomes.[256] 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[257,258] information about asthma and its treatment. The GINA website (www.ginasthma.org) contains patient educational materials as well as links to several asthma websites. Patients and their families should be encouraged to make a note of any questions that arise from reading this information or as a result of the consultation, and should be given time to address these during the next consultation.

Asthma education and training can be delivered effectively by a range of health care providers including pharmacists and nurses[235,236] (Evidence A). Trained lay health educators (also known as community health workers) can deliver

discrete areas of respiratory care such as asthma self-management education, with, in one study, increased symptom-free days and reduced healthcare utilization compared with usual care[259] and in another, comparable outcomes to those achieved by practice nurses based in primary care[260] (Evidence B). These findings suggest the need for additional studies to assess applicability in other settings and populations.

Box 3-13. Asthma information

Goal: To provide the person with asthma, their family and other carers with suitable information and training to manage their asthma in partnership with their health care providers	
Approach • 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.37) • Fully discuss expectations, fears and concerns • Develop shared goals	**Content** • Asthma diagnosis • Rationale for treatment, and differences between 'relievers' and 'controllers' • Potential side-effects of medications • Prevention of symptoms and flare-ups • How to recognize worsening asthma and what actions to take; how and when to seek medical attention • Management of comorbidities

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TRAINING IN GUIDED ASTHMA SELF-MANAGEMENT

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

The essential components of effective guided asthma self-management are:[129]

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

Self-management education that includes these three components dramatically reduces asthma morbidity in both adults[129] (Evidence A) and children[130] (Evidence A). Benefits include a one-third to two-thirds reduction in asthma-related hospitalizations, emergency department visits and unscheduled doctor or clinic visits, missed work/school days, and nocturnal wakening. 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.[129,261] Less intensive interventions that involve self-management education but not a written action plan are less effective,[262] and information alone is ineffective.[256]

Self-monitoring of symptoms and/or peak flow

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

- Short-term monitoring
  - Following an exacerbation, to monitor recovery.
  - Following a change in treatment, to help in assessing whether the patient has responded.
  - If symptoms appear excessive (for objective evidence of degree of lung function impairment).
  - To assist in identification of occupational or domestic triggers for worsening asthma control
- Long-term monitoring
  - For earlier detection of exacerbations, mainly in patients with poor perception of airflow limitation.[114]
  - For patients with a history of sudden severe exacerbations.
  - For patients' who have difficult-to-control or severe asthma

For patients carrying out peak-flow monitoring, use of a laterally compressed PEF chart (showing 2 months on a landscape format page) allows more accurate identification of worsening asthma than other charts.[125] One such chart is available for download from www.woolcock.org.au/moreinfo/. There is increasing interest in internet or phone-based monitoring of asthma. Based on existing studies, the main benefit is likely to be for more severe asthma[263] (Evidence B).

Written asthma action plans

Personal written asthma action plans show patients how to make short-term changes to their treatment in response to changes in their symptoms and/or PEF. They also describe how and when to access medical care.[264,265]

The benefits of self-management education for asthma morbidity are greater in adults when the action plans include both a step up in ICS and the addition of OCS, and for PEF-based plans, when they are based on personal best rather than percent predicted PEF[265] (Evidence A).

The efficacy of self-management education is similar regardless of whether patients self-adjust their medications according to an individual written plan or whether the medication adjustments are made by a doctor[262] (Evidence A). Thus patients who are unable to undertake guided self-management can still achieve benefit from a structured program of regular medical review.

Examples of written asthma action plan templates, including for patients with low literacy, can be found on several websites (e.g. Asthma UK, www.asthma.org.uk; Asthma Society of Canada, www.asthma.ca; Family Physician Airways Group of Canada, www.fpagc.com; National Asthma Council Australia, www.nationalasthma.org.au) and in research publications (e.g. [266,267]). Health care providers should become familiar with action plans that are relevant to their local health care system, treatment options, and cultural and literacy context. Details of the specific treatment adjustments that can be recommended for written asthma action plans are described in the next chapter (Box 4-2, p.77).

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Regular review by a health care provider

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

- Ask the patient if they have any questions and concerns
  - Discuss issues, and provide additional educational messages as necessary; if available, refer the patient to someone trained in asthma education.
- Assess asthma control
  - Review the patient's level of symptom control and risk factors (Box 2-2, p.29).
  - Ask about flare-ups to identify contributory factors and whether the patient's response was appropriate (e.g. was an action plan used?)
  - Review the patient's symptom or PEF diary if they keep one.
  - Assess comorbidities
- Assess treatment issues
  - Watch the patient use their inhaler, and correct and re-check technique if necessary (Box 3-11 p.56).
  - Assess medication adherence and ask about adherence barriers (Box 3-12, p.58)
  - Ask about adherence with other interventions, (e.g. smoking cessation)
  - Review the asthma action plan and update it if level of asthma control or treatment have changed[268]

A single page prompt to clinicians has been shown to improve the provision of preventive care to children with asthma during office visits.[269] Follow-up by tele-healthcare is unlikely to benefit in mild asthma but may be of benefit in those with severe disease at risk of hospital admission.[263]

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PART D. MANAGING ASTHMA WITH COMORBIDITIES AND IN SPECIAL POPULATIONS

KEY POINTS

- Identify and manage comorbidities such as rhinosinusitis, obesity and gastro-esophageal reflux disease. Comorbidities may contribute to respiratory symptoms and impaired quality of life, and some contribute to poor asthma control.
- For patients with dyspnea or wheezing on exertion:
  - Distinguish between exercise-induced bronchoconstriction (EIB) and symptoms that result from obesity or a lack of fitness, or are the result of alternative conditions such as upper airway dysfunction
  - Provide advice about preventing and managing EIB
  - Prescribe regular controller medication for patients with asthma symptoms outside of exercising, and for patients who have risk factors for exacerbations.
- Refer patients with difficult-to-treat or severe asthma to a specialist or severe asthma service, after addressing common problems such as incorrect diagnosis, incorrect inhaler technique, ongoing environmental exposures, and poor adherence.

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MANAGING COMORBIDITIES

Several comorbidities are commonly present in patients with asthma, particularly those with difficult-to-treat or severe asthma. Active management of comorbidities is recommended because they may contribute to symptom burden, impair quality of life, and lead to medication interactions. Some comorbidities also contribute to poor asthma control.[270]

Obesity

Clinical features

Asthma is more difficult to control in obese patients.[271-274] This may be due to a different type of airway inflammation, contributory comorbidities such as obstructive sleep apnea and gastroesophageal reflux disease (GERD), mechanical factors, or other as yet undefined factors. In addition, lack of fitness and reduction in lung volume due to abdominal fat may contribute to dyspnea.

Diagnosis

Document body mass index (BMI) for all patients with asthma. Because of other potential contributors to dyspnea and wheeze in obese patients, it is important to confirm the diagnosis of asthma with objective measurement of variable airflow limitation (Box 1-2, p.17). Asthma is more common in obese than non-obese patients,[46] but both over- and under-diagnosis of asthma occur in obesity.[42,47]

Management

As for other patients with asthma, ICS are the mainstay of treatment in obese patients (Evidence B), although their response may be reduced.[274] 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).[275] Weight loss improves asthma control, lung function, health status and reduces medication needs in obese patients,[276,277] but the quality of some studies is poor. The most striking results have been observed after bariatric surgery,[278,279] but even 5–10% weight loss can lead to improved asthma control and quality of life.[275]

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,[270] 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.[270]

Diagnosis

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

Management

A review of proton pump inhibitors in patients with confirmed asthma, most of whom had a diagnosis of GERD, showed a significant but small benefit for morning PEF, but no significant benefit for other asthma outcomes.[280] 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.[281] In general, benefits of proton pump inhibitors in asthma appear to be limited to patients with both symptomatic reflux and night-time respiratory symptoms.[282] Other treatment options include motility agents, lifestyle changes and fundoplication. In summary, symptomatic reflux should be treated, but patients with poorly controlled asthma should not be treated with anti-reflux therapy unless they also have symptomatic reflux (Evidence A). Few data are available for children with asthma symptoms and symptoms of GERD.[283,284]

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Anxiety and depression

Clinical features

Psychiatric disorders, particularly depressive and anxiety disorders, are more prevalent among people with asthma.[285] Psychiatric comorbidity is also associated with worse asthma symptom control and medication adherence, and worse asthma-related quality of life.[286] Anxious and depressive symptoms have been associated with increased asthma-related exacerbations and emergency visits.[287] Panic attacks may be mistaken for asthma.

Diagnosis

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

Management

There have been few good quality pharmacological and non-pharmacological treatment trials for anxiety or depression in patients with asthma, and results are inconsistent. A Cochrane review of 15 randomized controlled trials of psychological interventions for adults with asthma included cognitive behavior therapy, psychoeducation, relaxation, and biofeedback.[288] Results for anxiety were conflicting, and none of the studies found significant treatment differences for depression. Drug treatments and cognitive behavior therapy[289] have been described as having some potential in

patients with asthma; however, current evidence is limited, with a small number of studies and methodological shortcomings.

Food allergy and anaphylaxis

Clinical features

Rarely, food allergy is a trigger for asthma symptoms (<2% of people with asthma). In patients with confirmed food-induced allergic reactions (anaphylaxis), co-existing asthma is a strong risk factor for more severe and even fatal reactions. Food-induced anaphylaxis often presents as life-threatening asthma.[88] 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.[290] 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.[291]

Diagnosis

In patients with confirmed food allergy, it is important to assess for asthma. Children with food allergy have a four-fold increased likelihood of having asthma compared with children without food allergy.[292] Refer patients with suspected food allergy or intolerance for specialist allergy assessment. This may include appropriate allergy testing such as skin prick testing and/or blood testing for specific IgE. On occasion, carefully supervised food challenges may be needed.

Management

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

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Rhinitis, sinusitis and nasal polyps

Clinical features

Evidence clearly supports a link between diseases of the upper and lower airways.[293] Most patients with asthma, either allergic or non-allergic, have concurrent rhinitis, and 10–40% of patients with allergic rhinitis have asthma.[294] Depending on sensitization and exposure, allergic rhinitis may be seasonal (e.g. ragweed or grass pollen), perennial (e.g. mite allergens), or intermittent (e.g. furred pets).[293]

Rhinitis is defined as irritation and inflammation of the mucous membranes of the nose. Allergic rhinitis may be accompanied by ocular symptoms (conjunctivitis). Rhinosinusitis is defined as inflammation of the nose and paranasal sinuses characterized by more than two symptoms including nasal blockage/obstruction and/or nasal discharge (anterior/posterior nasal drip).[295] Other symptoms may include facial pain/pressure and/or a reduction or loss of smell. Sinusitis rarely occurs in the absence of rhinitis.

Rhinosinusitis is defined as acute when symptoms last <12 weeks with complete resolution, and chronic when symptoms occur on most days for at least 12 weeks without complete resolution. Chronic rhinosinusitis is an inflammatory condition of the paranasal sinuses that encompasses two clinically distinct entities: chronic rhinosinusitis without nasal polyposis and chronic rhinosinusitis with nasal polyposis.[296] The heterogeneity of chronic rhinosinusitis may explain the wide variation in prevalence rates in the general population ranging from 1–10% without polyps and 4% with polyps. Chronic rhinosinusitis is associated with more severe asthma, especially in patients with nasal polyps.[297]

Diagnosis

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

Management

Evidence-based guidelines (Allergic Rhinitis in Asthma, ARIA)[298] recommend intranasal corticosteroids for treatment of allergic rhinitis. In population-based studies, treatment of rhinitis with intranasal corticosteroids is associated with less need for asthma-related hospitalization and emergency department visits.[299] However, few placebo-controlled studies have systematically evaluated the effect of proper treatment and management of chronic rhinosinusitis on asthma control. A recent placebo-controlled trial of nasal mometasone in adults and children with chronic rhinosinusitis and poorly-controlled asthma showed no benefit for asthma outcomes, suggesting that, while chronic rhinosinusitis can contribute to respiratory symptoms, e.g. chronic cough, its treatment in patients with asthma should be targeted at the symptoms of rhinosinusitis rather than to improve asthma control.[300]

MANAGING ASTHMA IN SPECIAL POPULATIONS OR SETTINGS

This section includes brief advice about managing asthma in special populations or settings in which the usual treatment approach may need to be modified. Also refer to the *Diagnosis of respiratory symptoms in special populations* section of Chapter 1 (p.21).

Settings with limited resources

Communities with limited resources are found not only in low and middle income countries (LMIC), but also in affluent nations. In these settings, in general, the GINA strategy may be followed for asthma management at the individual level (Box 3-3), as it offers options for low cost diagnostic procedures, and therapeutic interventions which have been shown to be effective and reduce costs among the underserved.[301,302] In dealing with asthma control at the population level (Box 3-3), it is critical to prioritize the most cost-effective approach to asthma treatment in primary health care, which includes the use of ICS and SABA;[303] these are listed as essential medications by the World Health Organization. For diagnosis of asthma and monitoring of treatment response, the World Health Organization also lists PEF meters as essential tools in the Package of Essential Non-communicable Diseases Interventions,[50] with pulse oximeters also recommended when resources permit, for assessment of severity of acute asthma. It is possible to build capacity of primary health care teams, including nurses and other health professionals, for the development of an integrated approach to the most common diseases and symptoms, including asthma.[304]

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.[305] Exploratory and risk-taking behaviors such as smoking occur at a higher rate in adolescents with chronic diseases than in healthy adolescents.

Management

General principles for managing chronic disease in adolescents have been published by WHO.[306] Adolescents and their parent/carers should be encouraged in the transition towards asthma self-management by the adolescent. This may involve the transition from a pediatric to an adult health care facility. During consultations, the adolescent should be seen separately from the parent/carer so that sensitive issues such as smoking, adherence and mental health can be discussed privately, and confidentiality agreed. Information and self-management strategies should be tailored to the patient's stage of psychosocial development and desire for autonomy; adolescents are often focused on short-term rather than long-term outcomes. An empathic approach should be used to identify beliefs and behaviors that may be barriers to optimal treatment; for example, adolescents may be concerned about the impact of treatment on their physical or sexual capabilities. Medication regimens should be tailored to the adolescent's needs and lifestyle, and reviews arranged regularly so that the medication regimen can be adjusted for changing needs. Information about local youth-friendly resources and support services should be provided, where available.

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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 vocal cord dysfunction.[17]

Management

Guidelines for exercise-induced bronchoconstriction (EIB) have been published.[17] Pharmacotherapy can substantially reduce EIB. If the patient's only symptoms are during or after exercise, and no other risk factors for exacerbations are present, an as-needed strategy using inhaled SABA before exercise or to relieve symptoms that develop after exercise is sufficient[17] (Evidence A). However, with regular (more than once-daily) use, tolerance to the protective effects of inhaled beta$_2$-agonists against EIB develops. LTRA or chromones are alternative pre-exercise treatments[17] (Evidence A). Training and sufficient warm-up also reduce the incidence and severity of EIB[17] (Evidence A).

For patients with asthma symptoms unrelated to exercise, or with any risk factors for exacerbations, regular controller treatment with ICS or LTRA is recommended and generally results in the reduction of EIB[17] (Evidence A). Breakthrough EIB often indicates poorly controlled asthma, and stepping up controller treatment (after checking inhaler technique and adherence) generally results in the reduction of exercise-related symptoms. For patients who still experience EIB despite otherwise well-controlled asthma, SABA or LTRA may be taken prior to exercise or to relieve symptoms that develop after exercise (Evidence A).

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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, vocal cord dysfunction, and recurrent respiratory infections. Airway hyperresponsiveness is common in elite athletes, often without reported symptoms. Asthma in elite athletes is commonly characterized by less correlation between symptoms and pulmonary function; higher lung volumes and expiratory flows; less eosinophilic airway inflammation; more difficulty in controlling symptoms; and some improvement in airway dysfunction after cessation of training.

Management

Preventative measures to avoid high exposure to air pollutants, allergens (if sensitized) and chlorine levels in pools, particularly during training periods, should be discussed with the athlete. They should avoid training in extreme cold or pollution (Evidence C), and the effects of any therapeutic trials of asthma medications should be documented. Adequate anti-inflammatory therapy, especially ICS, is advised; minimization of use of beta$_2$-agonists will help to avoid the development of tolerance.[17] Information on treatment of exercise-induced asthma in athletes can be found in a Joint Task Force Report prepared by the European Respiratory Society, the European Academy of Allergy and Clinical Immunology, and GA(2)LEN[307] and the World Anti-Doping Agency website (www.wada-ama.org).

Pregnancy

Clinical features

Asthma control often changes during pregnancy; in approximately one-third of women asthma symptoms worsen, in one-third they improve, and in the remaining one-third they remain unchanged.[308] Exacerbations are common in pregnancy, particularly in the second trimester.[92] Exacerbations and poor asthma control during pregnancy may be due to mechanical or hormonal changes, or to cessation or reduction of asthma medications due to concerns by the mother

and/or the health care provider. Pregnant women appear to be particularly susceptible to the effects of viral respiratory infections,[309] 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).[92] If asthma is well controlled throughout pregnancy there is little or no increased risk of adverse maternal or fetal complications.[35]

Management

Although there is a general concern about any medication use in pregnancy, the advantages of actively treating asthma in pregnancy markedly outweigh any potential risks of usual controller and reliever medications[35] (Evidence A). For this reason, using medications to achieve good symptom control and prevent exacerbations is justified even when their safety in pregnancy has not been unequivocally proven. Use of ICS, beta$_2$-agonists, montelukast or theophylline is not associated with an increased incidence of fetal abnormalities.[310] ICS prevent exacerbations of asthma during pregnancy[35,311,312] (Evidence A), and cessation of ICS during pregnancy is a significant risk factor for exacerbations[92] (Evidence A). One study reported that monthly FENO-guided treatment in pregnancy was associated with fewer exacerbations and better fetal outcomes than an ACQ-based algorithm;[313] however, given the design of the control algorithm, the results cannot be compared with current treatment recommendations. On balance, given the evidence in pregnancy for adverse outcomes from exacerbations[35] (Evidence A) and for safety of usual doses of ICS and LABA[310] (Evidence A), a low priority should be placed on stepping down treatment (however guided) until after delivery (Evidence D).

Despite lack of evidence for adverse effects of asthma treatment in pregnancy, many women and doctors remain concerned.[314] Pregnant patients with asthma should be advised that poorly controlled asthma, and exacerbations, provide a much greater risk to their baby than do current asthma treatments. Educational resources about asthma management during pregnancy (e.g. [315]) may provide additional reassurance. During pregnancy, monthly monitoring of asthma is recommended.[315] It is feasible for this to be achieved by pharmacist-clinician collaboration, with monthly telephone monitoring of asthma symptom control.[316]

Respiratory infections should be monitored and managed appropriately during pregnancy.[309] During acute asthma exacerbations, pregnant women may be less likely to be treated appropriately than non-pregnant patients.[92] To avoid fetal hypoxia, it is important to aggressively treat acute exacerbations during pregnancy with SABA, oxygen and early administration of systemic corticosteroids.

During labor and delivery, usual controller medications should be taken, with reliever if needed. Acute exacerbations during labor and delivery are uncommon, but bronchoconstriction may be induced by hyperventilation during labor, and should be managed with SABA. Neonatal hypoglycemia may be seen, especially in preterm babies, when high doses of beta-agonists have been given within the last 48 hours prior to delivery. If high doses of SABA have been given during labor and delivery, blood glucose levels should be monitored in the baby (especially if preterm) for the first 24 hours.[317]

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Occupational asthma

Clinical features

In the occupational setting, rhinitis often precedes the development of asthma (see p9 regarding diagnosis of occupational asthma). Once a patient has become sensitized to an occupational allergen, the level of exposure necessary to induce symptoms may be extremely low; resulting exacerbations become increasingly severe, and with continued exposure, persistent symptoms and irreversible airflow limitation may result.[31]

Management

Detailed information is available in evidence-based guidelines about management of occupational asthma.[31] 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.[31] Cost-effective minimization of latex

sensitization can be achieved by using non-powdered low-allergen gloves instead of powdered latex gloves.[31] 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.[318-320] 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.[319]

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.[318,319] 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 cataracts, are more common in the elderly than in younger adults.[318] Clearance of theophylline is also reduced.[318] 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,[319,321] and inhaler technique should be checked at each visit. Older patients may have difficulties with complex medication regimens, and prescribing of multiple inhaler devices should be avoided if possible. Large print versions may be needed for written information such as asthma action plans. Patients with cognitive impairment may require a carer to help them use their asthma medications. For diagnosis and initial management of patients with asthma-COPD overlap, see Chapter 5, p.89.

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Surgery and asthma

Clinical features

There is no evidence of increased peri-operative risk for the general asthma population.[322] However, there is an increased risk for patients with COPD,[322] 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.[323]

Management

For elective surgery, meticulous attention should be paid pre-operatively to achieving good asthma control, as detailed elsewhere in this chapter, especially for patients with more severe asthma, uncontrolled symptoms, exacerbation history, or fixed airflow limitation[323] (Evidence B). For patients requiring emergency surgery, the risks of proceeding without first achieving good asthma control should be weighed against the need for immediate surgery. Patients taking long-term high-dose ICS or who have received OCS for more than 2 weeks during the previous 6 months should receive hydrocortisone peri-operatively as they are at risk of adrenal crisis in the context of surgery[324] (Evidence B). More immediate intra-operative issues relating to asthma management are reviewed in detail elsewhere.[323] For all patients, maintaining regular controller therapy throughout the peri-operative period is important.

Aspirin-exacerbated respiratory disease

Clinical features

The clinical picture and course of aspirin-exacerbated respiratory disease (AERD, previously called aspirin-induced asthma) are well established.[325] It starts with nasal congestion and anosmia, and progresses to chronic rhinosinusitis with nasal polyps that re-grow rapidly after surgery. Asthma and hypersensitivity to aspirin develop subsequently. Following ingestion of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), an acute asthma attack develops within minutes to 1–2 hours. It is usually accompanied by rhinorrhea, nasal obstruction, conjunctival irritation, and scarlet flush of the head and neck, and may sometimes progress to severe bronchospasm, shock, loss of consciousness, and respiratory arrest.[326,327] AERD is more likely to be associated with low lung function and severe asthma,[328,329] and with increased need for emergency care.[329]The prevalence of AERD is 7% in general adult asthma populations, and 15% in severe asthma.[329,330]

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[331,332] 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.[331,332] Bronchial (inhalational) and nasal challenges with lysine aspirin are safer than oral challenges and may be safely performed in allergy centers.[332,333]

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. celocoxib,or etoricoxib), or paracetamol (acetaminophen), may be considered[334,335] with appropriate health care provider supervision and observation for at least 2 hours after administration[336] (Evidence B). ICS are the mainstay of asthma therapy in AERD, but OCS are sometimes required; LTRA may also be useful[327,336] (Evidence B). An additional option is desensitization, which may be conducted under specialist care in a clinic or hospital.[337] Desensitization to aspirin followed by daily aspirin treatment can significantly improve overall symptoms and quality of life, decrease formation of nasal polyps and sinus infections, reduce the need for OCS and sinus surgery, and improve nasal and asthma scores.[332,338]

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Difficult-to-treat and severe asthma

Although the majority of patients can achieve the goal of well controlled asthma, some patients' asthma will not be well controlled even with optimal therapy.[110] The term '*difficult-to-treat' asthma* is used for patients in whom ongoing factors such as comorbidities, poor adherence, and allergen exposure interfere with achieving good asthma control. *'Treatment-resistant' or 'refractory' asthma* refers to patients with a confirmed diagnosis of asthma, whose symptoms or exacerbations remain poorly controlled despite high-dose ICS plus a second controller such as LABA (and/or systemic corticosteroids) and management of comorbidities, or whose asthma control deteriorates when this treatment is stepped down. *Severe asthma* includes patients with refractory asthma, and those in whom response to treatment of comorbidities is incomplete.[126]

Diagnosis

Factors that should be assessed and addressed in patients with uncontrolled asthma, before assuming that they have severe asthma, are shown in Box 2-4 (p.34). 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.[339] Strategies for confirming the diagnosis of asthma in patients already taking controller treatment are shown in Box 1-4 (p.22).

Box 3-14. Investigation and management of severe asthma

Investigations in severe asthma
• **Confirmation of the diagnosis of asthma**: upper airway dysfunction, concurrent COPD, and recurrent respiratory infections must be considered as alternative diagnoses or as contributors to persistent symptoms (Box 1-3, p.20).[126] • **Investigation for comorbidities**, including chronic sinusitis, obesity, GERD, AERD, obstructive sleep apnea and psychological or psychiatric disorders, that may worsen asthma control or contribute to symptoms. The ability to improve severe asthma by treating comorbidities remains unconfirmed (see '*Managing comorbidities*', p.62).[126] • **Checking of inhaler technique and medication adherence**: incorrect inhaler use[82] and poor adherence[340] are the most common reasons for failure to achieve good asthma control (see Box 3-11 p.56, Box 3-12 p.58), and they are also found in severe asthma. In difficult-to-treat asthma, adherence and health outcomes may be improved with a comprehensive adherence-promoting intervention.[341] • **Investigation for persistent environmental exposure to tobacco smoke, allergens or toxic substances**: these triggers, if present at home or workplace should be addressed and removed whenever possible (see Box 3-8 p.50 and Appendix Chapter 6).
Management of severe asthma
Very few patients are completely resistant to corticosteroids, so ICS remain the mainstay of therapy for difficult-to-treat asthma. Additional therapeutic options include: • **Optimization of ICS/LABA dose**: some patients may respond to higher doses of ICS than are routinely recommended for general use[342] (Evidence B). However, this carries the risk of systemic side-effects;[339] after some months dose optimization should be pursued by stepping down slowly at 3–6 month intervals; see Box 3-7 (p.49) (Evidence D). • **Oral corticosteroids**: some patients with severe asthma may benefit from low dose maintenance OCS treatment[339] (Evidence D), but the potential long-term side-effects should be taken into account.[205] Patients should be monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).[206] • **Add-on treatments without phenotyping**: In patients selected for uncontrolled symptoms and persistent airflow limitation despite moderate-high dose ICS and LABA, add-on treatment with the long-acting muscarinic antagonist bronchodilator, tiotropium, showed improved lung function and increased time to first exacerbation.[343] Other add-on controller medications such as theophylline and LTRAs, although suggested for severe asthma, appear in the small number of available studies to be of limited benefit. • **Sputum-guided treatment**: in centers with specific expertise in inducing and analyzing sputum, adjusting treatment for severe asthma on the basis of sputum eosinophils may allow corticosteroid dose and/or exacerbation frequency to be reduced[147] (Evidence A). • **Phenotype-guided add-on treatment**: patients with severe asthma, uncontrolled on Step 4 treatment, may benefit from phenotyping into categories such as severe allergic, aspirin-exacerbated or eosinophilic asthma.[6,7,143,339] Patients ≥6 years with severe allergic asthma with elevated IgE levels may benefit from omalizumab (anti-IgE) therapy[199,200] (Evidence A), those ≥12 years with severe eosinophilic asthma may benefit from anti-IL5 therapy (mepolizumab, reslizumab) (Evidence B), and LTRAs may be helpful for patients found to be aspirin sensitive[336] (Evidence B). • **Non-pharmacological interventions***:* bronchial thermoplasty may be helpful in selected patients with severe asthma (Evidence B),[104] but more studies are needed to identify its efficacy and long-term safety in broader severe asthma populations[126] (see p.51). Carefully controlled trials are important as a large placebo effect has been seen in studies to date.[104] High-altitude treatment[339] (Evidence C) or psychological interventions[344] (Evidence C) may be helpful in some patients. The place of these therapies and strategies in severe asthma has not been established.[126]

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Clinical features

Many people with severe or difficult-to-treat asthma experience frequent or persistent asthma symptoms, frequent exacerbations, persistent loss of lung function, substantial impairment of quality of life, and troublesome comorbidities such as anxiety and depression.[126,345] There is substantial heterogeneity in the clinical and inflammatory features of severe asthma, with several studies identifying clusters of patients with features such as early-onset severe allergic asthma; late onset non-atopic steroid-dependent asthma with fixed airways obstruction; frequent exacerbators; and older obese women with late onset asthma.[6,7,143,339,346] To date, only a few specific targetable biological pathways have been identified,[8,151,152] but this is an area of active research. In patients with adult-onset asthma, smoking history is an independent risk factor for progression to severe asthma.[347]

Management

Referral of patients with severe asthma to a health care provider with expertise in asthma management may be helpful for investigation and treatment. Additional investigations that should be considered for patients suspected of having severe asthma, and additional therapies or strategies that may assist in their management, are shown in Box 3-14.

When potential reasons for a lack of treatment response have been considered and addressed, a compromise level of asthma control may need to be accepted and discussed with the patient to avoid futile over-treatment (with its attendant cost and potential side-effects) (Evidence D). The objective is then to minimize exacerbations and the need for emergency medical interventions while achieving as high a level of symptom control as is feasible.[126] This should be achieved with as little disruption of activities and as few daily symptoms and side-effects as possible. [126]

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Chapter 4.

Management of worsening asthma and exacerbations

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KEY POINTS

- Exacerbations represent an acute or sub-acute worsening in symptoms and lung function from the patient's usual status, or in some cases, the initial presentation of asthma. The terms 'episodes', 'attacks' and 'acute severe asthma' are also often used, but they have variable meanings. The term 'flare-up' is preferred for use in discussions with patients.
- Patients who are at increased risk of asthma-related death should be identified, and flagged for more frequent review.
- The management of worsening asthma and exacerbations is part of a continuum, from self-management by the patient with a written asthma action plan, through to management of more severe symptoms in primary care, the emergency department and in hospital.
- All patients should be provided with a written asthma action plan appropriate for their level of asthma control and health literacy, so they know how to recognize and respond to worsening asthma.
  - The action plan should include when and how to change reliever and controller medications, use oral corticosteroids, and access medical care if symptoms fail to respond to treatment.
  - Patients who deteriorate quickly should be advised to go to an acute care facility or see their doctor immediately.
  - The action plan can be based on changes in symptoms or (only in adults) peak expiratory flow.
- For patients presenting with an exacerbation to a primary care or acute care facility:
  - Assessment of exacerbation severity should be based on the degree of dyspnea, respiratory rate, pulse rate, oxygen saturation and lung function, while starting short-acting beta$_2$-agonist (SABA) and oxygen therapy.
  - Immediate transfer should be arranged 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. While transferring the patient, inhaled SABA therapy, ipratropium bromide, controlled oxygen and systemic corticosteroids should be given.
  - Treatment should be started with repeated administration of SABA (in most patients, by pressurized metered dose inhaler and spacer), early introduction of oral corticosteroids, and controlled flow oxygen if available. Response of symptoms, oxygen saturation and lung function should be reviewed after 1 hour.
  - Ipratropium bromide treatment is recommended only for severe exacerbations.
  - Intravenous magnesium sulfate should be considered for patients with severe exacerbations not responding to initial treatment.
  - Chest X-ray is not routinely recommended.
  - Decisions about hospitalization should be based on clinical status, lung function, response to treatment, recent and past history of exacerbations, and ability to manage at home.
  - Before the patient goes home, ongoing treatment should be arranged. This should include starting controller treatment or stepping up the dose of existing controller treatment for 2–4 weeks, and reducing reliever medication to as-needed use.
- Antibiotics should not be routinely prescribed for asthma exacerbations.
- Arrange early follow-up after any exacerbation, regardless of where it was managed.
  - Review the patient's symptom control and risk factors for further exacerbations.
  - For most patients, prescribe regular controller therapy to reduce the risk of further exacerbations. Continue increased controller doses for 2–4 weeks.
  - Check inhaler technique and adherence.

For management of asthma exacerbations in children 5 years and younger, see Chapter 6, p.115.

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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.[15] Exacerbations may occur in patients with a pre-existing diagnosis of asthma or, occasionally, as the first presentation of asthma. Exacerbations usually occur in response to exposure to an external agent (e.g. viral upper respiratory tract infection, pollen or pollution) and/or poor adherence with controller medication; however, a subset of patients present more acutely and without exposure to known risk factors.[348] Severe exacerbations can occur in patients with mild or well-controlled asthma.[10,159]

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.[349,350] The term '*flare-up*' is simpler, and conveys the sense that asthma is present even when symptoms are absent. The term '*attack*' is used by many patients and health care providers but with widely varying meanings, and it may not be perceived as including gradual worsening.[349,350] In pediatric literature, the term 'episode' is commonly used, but understanding of this term by parent/carers is not known.

Identifying patients at risk of asthma-related death

In addition to factors known to increase the risk of asthma exacerbations (Box 2-2, p.29), some features are specifically associated with an increase in the risk of asthma-related death (Box 4-1). The presence of one or more of these risk factors should be quickly identifiable in the clinical notes, and these patients should be encouraged to seek urgent medical care early in the course of an exacerbation.

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

- A history of near-fatal asthma requiring intubation and mechanical ventilation[351]
- Hospitalization[351] or emergency care visit for asthma in the past year
- Currently using or having recently stopped using oral corticosteroids (a marker of event severity)[351]
- Not currently using inhaled corticosteroids[81,351]
- Over-use of SABAs, especially use of more than one canister of salbutamol (or equivalent) monthly[93,352]
- A history of psychiatric disease or psychosocial problems,[85]
- Poor adherence with asthma medications and/or poor adherence with (or lack of) a written asthma action plan[85]
- Food allergy in a patient with asthma[291,353]

DIAGNOSIS OF EXACERBATIONS

Exacerbations represent a change in symptoms and lung function from the patient's usual status.[15] The decrease in expiratory airflow can be quantified by lung function measurements such as peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV_1),[354] 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.[355]

A minority of patients may perceive symptoms poorly and experience a significant decline in lung function without a perceptible change in symptoms.[114,115,123] This situation especially affects patients with a history of near-fatal asthma and also appears to be more common in males.

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

SELF-MANAGEMENT OF EXACERBATIONS WITH A WRITTEN ASTHMA ACTION PLAN

All patients with asthma should be provided with guided self-management education as described in Chapter 3 (p.56), including monitoring of symptoms and/or lung function, a written asthma action plan, and regular review by a health professional.[129] (For children 5 years and younger, see Chapter 6, p.115.)

Treatment options for written asthma action plans

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

The criteria for initiating an increase in controller medication will vary from patient to patient. For patients taking conventional maintenance ICS-containing treatment, this should generally be increased when there is a clinically important change from the patient's usual level of asthma control, for example, if asthma symptoms are interfering with normal activities, or PEF has fallen by >20% for more than 2 days.[265]

Inhaled short-acting beta$_2$-agonists

Repeated dosing with inhaled short-acting beta$_2$-agonist (SABA) bronchodilators provides temporary relief until the cause of the worsening symptoms passes or increased controller treatment has had time to take effect. The need for repeated doses over more than 1–2 days signals the need to review, and possibly increase, controller treatment if this has not already been done. This is particularly important if there has been a lack of response to increased use of beta$_2$-agonist therapy. Although the rapid-acting long-acting beta$_2$-agonist formoterol has been studied in the emergency department management of acute asthma,[356] its use in a separate inhaler is no longer recommended in asthma, in order to avoid the possibility of it being used without concomitant inhaled corticosteroids (ICS).

Inhaled corticosteroids

In a systematic review of self-management studies, action plans in which the ICS dose was at least doubled were associated with improved asthma outcomes and reduced health care utilization.[265] In placebo-controlled trials, temporarily doubling the dose of ICS was not effective[357] (Evidence A); however, the delay before increasing the ICS dose (mean 5–7 days[358,359]) may have contributed. Only one small study of doubling ICS has been carried out in children.[360] There is emerging evidence in adults[361] and young children[362] that higher ICS doses might help prevent worsening asthma progressing to a severe exacerbation. Patients who quadrupled their ICS dose (to average of 2000mcg/day BDP equivalent) after their PEF fell were significantly less likely to require OCS.[363] In adult patients with an acute deterioration, high-dose ICS for 7–14 days (500–1600mcg BDP-HFA equivalent) had an equivalent effect to a short course of OCS[361] (Evidence A).

Combination low dose ICS (budesonide or beclometasone) with rapid-onset LABA (formoterol)

The combination of rapid-onset LABA (formoterol) and low dose ICS (budesonide or beclometasone) in a single inhaler as both the controller and the reliever medication is effective in improving asthma control,[146] and in at-risk patients, reduces exacerbations requiring OCS, and hospitalizations[174-177] (Evidence A). The combination ICS/formoterol inhaler may be taken up to a maximum total formoterol dose of 72 mcg in a day (Evidence A). The benefit of this regimen in preventing exacerbations appears to be due to intervention at a *very early stage* of worsening asthma.[177] This regimen is also effective in reducing exacerbations in children aged 4–11 years,[364] (Evidence B), but it is not approved for this age group in many countries. This approach should not be attempted with other combination controller therapies with a slower-onset LABA, or if evidence of efficacy and safety with this regimen is lacking.

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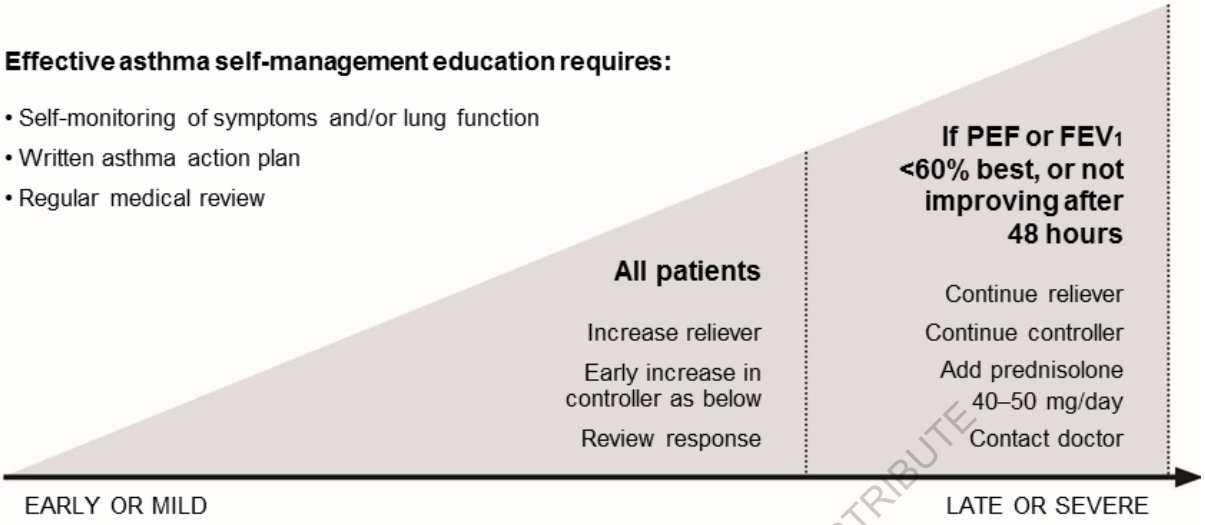
Box 4-2. Self-management of worsening asthma in adults and adolescents with a written asthma action plan



Medication	Short-term change (1-2 weeks) for worsening asthma	Evidence Level
Increase usual reliever:		
Short-acting beta2-agonist (SABA)	Increase frequency of SABA use For pMDI, add spacer	A A
Low dose ICS/formoterol *	Increase frequency of reliever use (maximum formoterol total 72 mcg/day)	A
Increase usual controller:		
Maintenance and reliever ICS/formoterol *	Continue maintenance ICS/formoterol and increase reliever ICS/formoterol as needed* (maximum formoterol total 72 mcg/day)	A
Maintenance ICS with SABA as reliever	At least double ICS; consider increasing ICS to high dose (maximum 2000 mcg/day BDP equivalent)	B
Maintenance ICS/formoterol with SABA as reliever	Quadruple maintenance ICS/formoterol (maximum formoterol 72 mcg/day)	B
Maintenance ICS/other LABA, with SABA as reliever	Step up to higher dose formulation of ICS/other LABA, or consider adding a separate ICS inhaler (to maximum total 2000 mcg/day BDP equivalent)	D
Add oral corticosteroids (OCS) and contact doctor		
OCS (prednisone or prednisolone)	Add OCS for severe exacerbations (e.g. PEF or FEV_1 <60% personal best or predicted), or patient not responding to treatment over 48 hours	A
	Adults: prednisolone 1 mg/kg/day (maximum 50 mg) usually for 5–7 days. *Children:* 1–2 mg/kg/day (maximum 40 mg) usually for 3–5 days.	D
	Tapering is not needed if OCS are prescribed for <2 weeks	B

BDP: beclometasone dipropionate; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; PEF: peak expiratory flow; SABA: short-acting $beta_2$-agonist. Options are listed in order of evidence.

*ICS/formoterol maintenance and reliever regimen: low dose budesonide or beclometasone with formoterol. This regimen is not approved for children <12 years in many countries.

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Other combination ICS/LABA controllers

For adults taking combination ICS/LABA as a fixed dose maintenance controller medication, the ICS dose may be increased by adding a separate ICS inhaler[361] (Evidence D). More research is needed to standardize this strategy.

Leukotriene receptor antagonists

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

Oral corticosteroids

For most patients, the written asthma action plan should provide instructions for when and how to commence OCS. Typically, a short course of OCS is used (e.g. 40–50 mg/day usually for 5–7 days,[361] Evidence B) for patients who:

- Fail to respond to an increase in reliever and controller medication for 2–3 days
- Deteriorate rapidly or who have a PEF or FEV_1 <60% of their personal best or predicted value
- Have a history of sudden severe exacerbations.

For children 6–11 years, the recommended dose of OCS is 1–2 mg/kg/day to a maximum of 40 mg/day (Evidence B), usually for 3–5 days. Patients should be advised about common side-effects, including sleep disturbance, increased appetite, reflux, and mood changes.[365] Patients should contact their doctor if they start taking OCS (Evidence D).

Reviewing response

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

Follow up after a self-managed exacerbation

After a self-managed exacerbation, patients should see their primary care health care provider for a semi-urgent review (e.g. within 1–2 weeks), for assessment of symptom control and additional risk factors for exacerbations (Box 2-2, p.29), and to identify the potential cause of the exacerbation. The written asthma action plan should be reviewed to see if it met the patient's needs. Maintenance controller treatment can generally be resumed at previous levels 2–4 weeks after the exacerbation (Evidence D), unless the history suggests that the exacerbation occurred on a background of long-term poorly controlled asthma. In this situation, provided inhaler technique and adherence have been checked, a step up in treatment is indicated (Box 3-5, p.43).

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MANAGEMENT OF ASTHMA EXACERBATIONS IN PRIMARY CARE

Assessing exacerbation severity

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

History

The history should include:

- Timing of onset and cause (if known) of the present exacerbation
- Severity of asthma symptoms, including any limiting exercise or disturbing sleep
- Any symptoms of anaphylaxis
- Any risk factors for asthma-related death (Box 4-1, p.75)
- All current reliever and controller medications, including doses and devices prescribed, adherence pattern, any recent dose changes, and response to current therapy.

Physical examination

The physical examination should assess:

- Signs of exacerbation severity (Box 4-3, p.80) 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, upper airway dysfunction, inhaled foreign body or pulmonary embolism).

Objective measurements

- Pulse oximetry. Saturation levels <90% in children or adults signal the need for aggressive therapy.
- PEF in patients older than 5 years (Box 4-3, p.80)

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Treating exacerbations in primary care

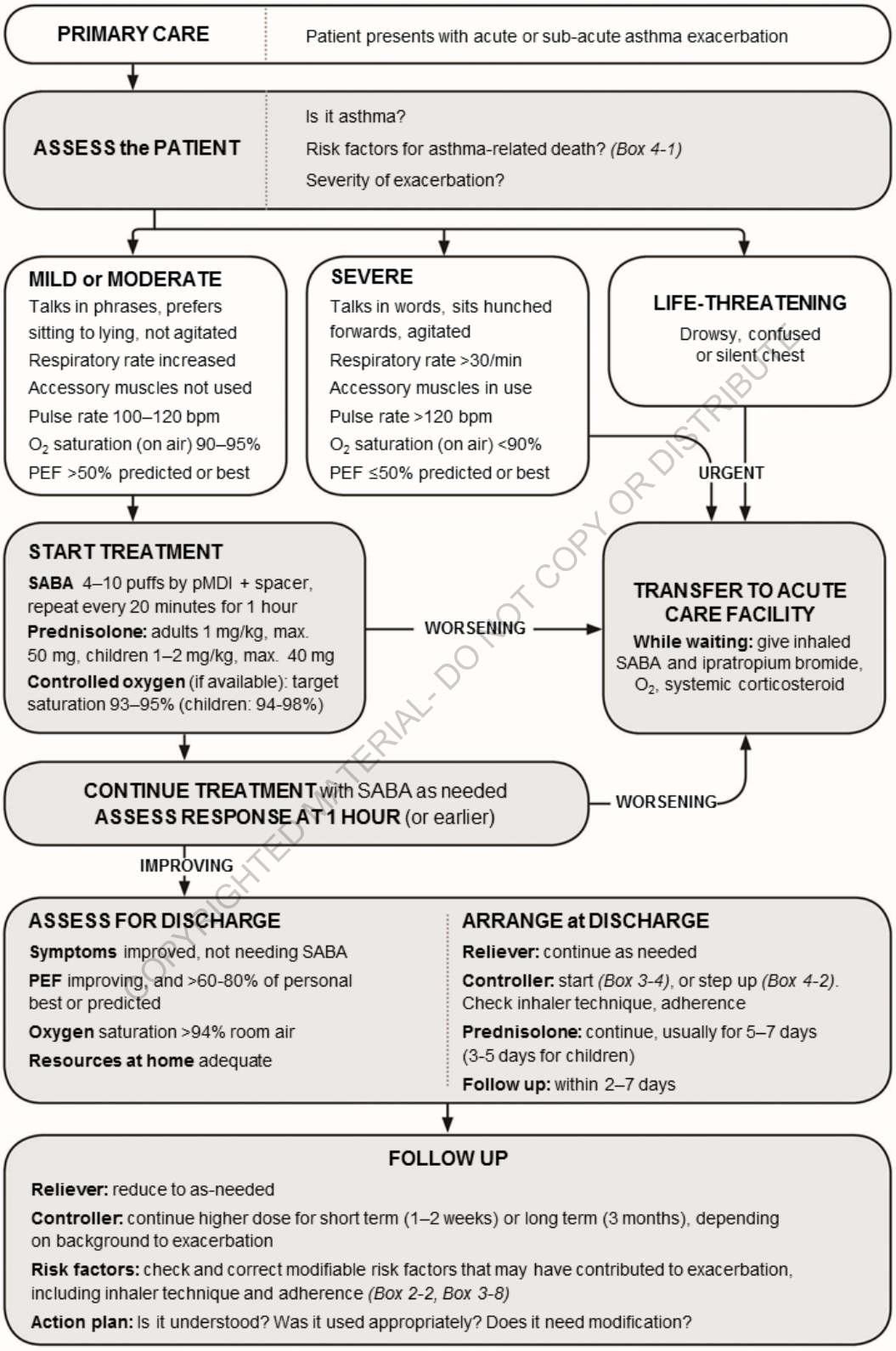
The main initial therapies include repetitive administration of short-acting inhaled bronchodilators, early introduction of systemic corticosteroids, and controlled flow oxygen supplementation.[354] The aim is to rapidly relieve airflow obstruction and hypoxemia, address the underlying inflammatory pathophysiology, and prevent relapse.

Inhaled short-acting beta$_2$-agonists

For mild to moderate exacerbations, repeated administration of inhaled SABA (up to 4–10 puffs every 20 minutes for the first hour) is usually the most effective and efficient way to achieve rapid reversal of airflow limitation[366] (Evidence A). After the first hour, the dose of SABA required varies from 4–10 puffs every 3–4 hours up to 6–10 puffs every 1–2 hours, or more often. No additional SABA is needed if there is a good response to initial treatment (e.g. PEF >60–80% of predicted or personal best for 3–4 hours).

Delivery of SABA via a pMDI and spacer or a DPI leads to a similar improvement in lung function as delivery via nebulizer[366,367] (Evidence A); however, patients with acute *severe* asthma were not included in these studies. The most cost-effective route of delivery is pMDI and spacer,[368] provided the patient can use this device. Because of the static charge on plastic spacers, they should be pre-washed with detergent and air-dried to be ready for immediate use; if a pre-treated spacer is not available, a new spacer should be primed with at least 20 puffs of salbutamol before use.[369]

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



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O_2: oxygen; PEF: peak expiratory flow; SABA: short-acting beta$_2$-agonist (doses are for salbutamol).

Controlled oxygen therapy (if available)

Oxygen therapy should be titrated against pulse oximetry (if available) to maintain oxygen saturation at 93–95% (94–98% for children 6–11 years). Controlled or titrated oxygen therapy gives better clinical outcomes than high-flow 100% oxygen therapy[370-372] (Evidence B). Oxygen should not be withheld if oximetry is not available, but the patient should be monitored for deterioration, somnolence or fatigue.

Systemic corticosteroids

OCS should be given promptly, especially if the patient is deteriorating, or had already increased their reliever and controller medications before presenting (Evidence B). The recommended dose for adults is 1 mg prednisolone/kg/day or equivalent up to a maximum of 50 mg/day, and 1–2 mg/kg/day for children 6–11 years up to a maximum of 40 mg/day). OCS should usually be continued for 5–7 days[373,374] (Evidence B). Patients should be advised about common side-effects, including sleep disturbance, increased appetite, reflux and mood changes.[365]

Controller medication

Patients already prescribed controller medication should be provided with advice about increasing the dose for the next 2–4 weeks, as summarized in Box 4-2 (p.77). Patients not currently taking controller medication should usually be commenced on regular ICS-containing therapy, as an exacerbation requiring medical care indicates that the patient is at increased risk of future exacerbations (Box 2-2, p.29).

Antibiotics (not recommended)

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

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Reviewing response

During treatment, patients should be closely monitored, and treatment titrated according to their response. Patients who present with signs of a severe or life-threatening exacerbation (Box 4-3, p.80), 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 as-needed reliever medication, OCS and, for most patients, regular controller treatment. Inhaler technique and adherence should be reviewed before discharge. A follow-up appointment should be arranged for about 2–7 days later, depending on the clinical and social context.

At the review visit the health care provider should assess the patient's level of symptom control and risk factors; explore the potential cause of the exacerbation; and review the written asthma action plan (or provide one if the patient does not already have one). Maintenance controller treatment can generally be resumed at previous levels 2–4 weeks after the exacerbation, unless the exacerbation was preceded by symptoms suggestive of chronically poorly controlled asthma. In this situation, provided inhaler technique and adherence have been checked, a step up in treatment (Box 3-5, p.43) is indicated.

MANAGEMENT OF ASTHMA EXACERBATIONS IN THE EMERGENCY DEPARTMENT

Severe exacerbations of asthma are life-threatening medical emergencies, which are most safely managed in an acute care setting e.g. emergency department (Box 4-4). Management of asthma in the intensive care unit is beyond the scope of this report and readers are referred to a recent comprehensive review.[375]

Assessment

History

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

- Time of onset and cause (if known) of the present exacerbation
- Severity of asthma symptoms, including any limiting exercise or disturbing sleep
- Any symptoms of anaphylaxis
- Risk factors for asthma-related death (Box 4-1, p.75)
- All current reliever and controller medications, including doses and devices prescribed, adherence pattern, any recent dose changes, and response to current therapy.

Physical examination

The physical examination should assess:

- Signs of exacerbation severity (Box 4-4), including vital signs (e.g. level of consciousness, temperature, pulse rate, respiratory rate, blood pressure, ability to complete sentences, use of accessory muscles)
- Complicating factors (e.g. anaphylaxis, pneumonia, atelectasis, pneumothorax or pneumomediastinum)
- Signs of alternative conditions that could explain acute breathlessness (e.g. cardiac failure, upper airway dysfunction, 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.[376,377] 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. This is especially useful in children if they are unable to perform PEF. In children, oxygen saturation is normally >95%, and saturation <92% is a predictor of the need for hospitalization[378] (Evidence C). Saturation levels <90% in children or adults signal the need for aggressive therapy. Subject to clinical urgency, saturation should be assessed before oxygen is commenced, or 5 minutes after oxygen is removed or when saturation stabilizes.
- *Arterial blood gas measurements are not routinely required*:[379] They should be considered for patients with a PEF or FEV_1 <50% predicted,[380] or for those who do not respond to initial treatment or are deteriorating. Supplemental controlled oxygen should be continued while blood gases are obtained. A PaO_2<60 mmHg (8 kPa) and normal or increased $PaCO_2$ (especially >45 mmHg, 6 kPa) indicate respiratory failure. Fatigue and somnolence suggest that pCO_2 may be increasing and airway intervention may be needed.
- *Chest X-ray (CXR) is not routinely recommended:* In adults, CXR should be considered if a complicating or alternative cardiopulmonary process is suspected (especially in older patients), or for patients who are not responding to treatment where a pneumothorax may be difficult to diagnose clinically.[381] Similarly, in children, routine CXR is not recommended unless there are physical signs suggestive of pneumothorax, parenchymal disease or an inhaled foreign body. Features associated with positive CXR findings in children include fever, no family history of asthma, and localized lung examination findings.[382]

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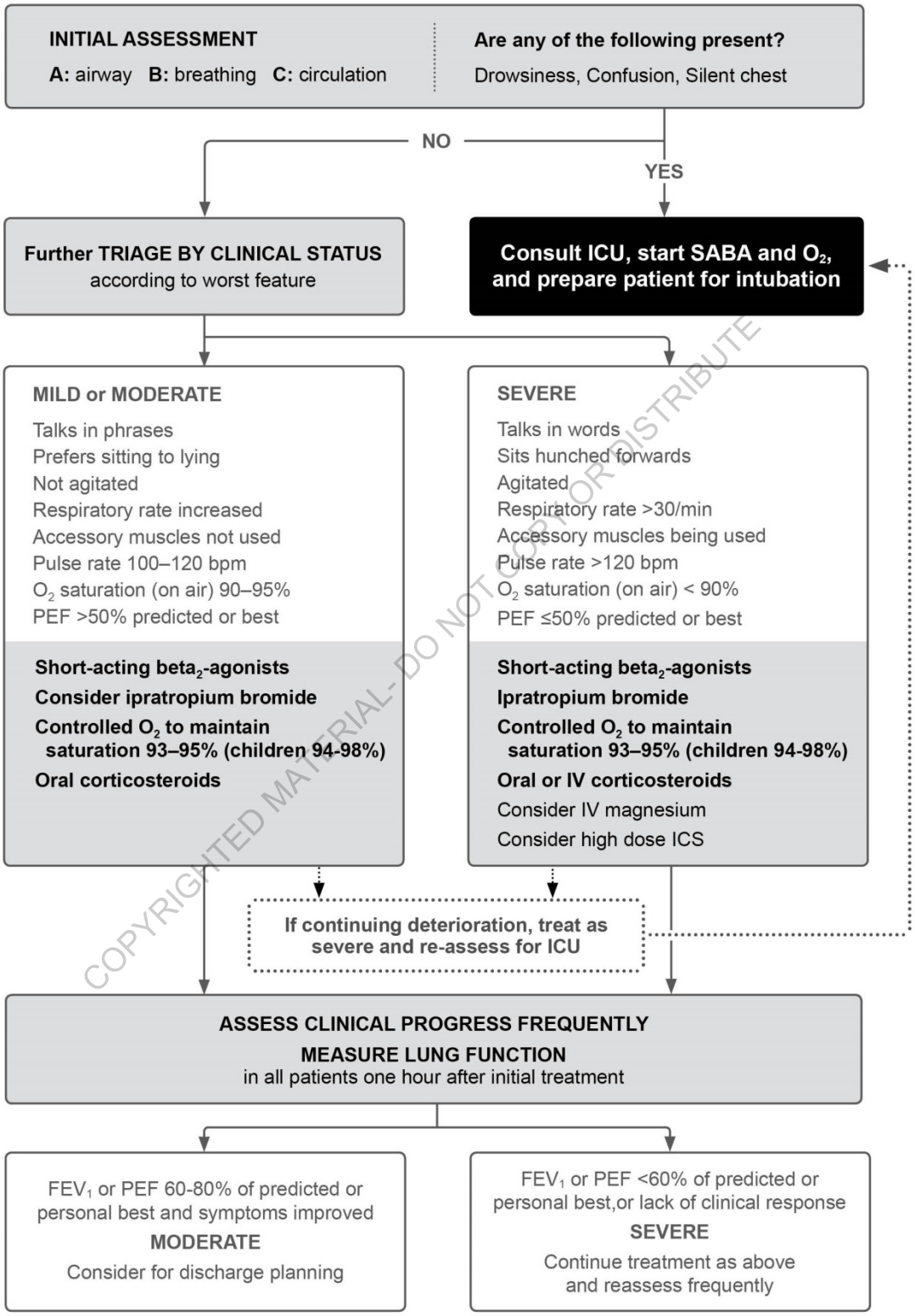
Box 4-4. Management of asthma exacerbations in acute care facility, e.g. emergency department



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ICS: inhaled corticosteroids; ICU: intensive care unit; IV: intravenous; O_2: oxygen; PEF; peak expiratory flow; FEV_1; forced expiratory volume in 1 second

Treatment in acute care settings such as the emergency department

The following treatments are usually administered concurrently to achieve rapid improvement.[383]

Oxygen

To achieve arterial oxygen saturation of 93–95% (94–98% for children 6–11 years), oxygen should be administered by nasal cannulae or mask. In severe exacerbations, controlled low flow oxygen therapy using pulse oximetry to maintain saturation at 93–95% is associated with better physiological outcomes than with high flow 100% oxygen therapy[370-372] (Evidence B). However, oxygen therapy should not be withheld if pulse oximetry is not available (Evidence D). Once the patient has stabilized, consider weaning them off oxygen using oximetry to guide the need for ongoing oxygen therapy.

Inhaled short-acting beta$_2$-agonists

Inhaled SABA therapy should be administered frequently for patients presenting with acute asthma. The most cost-effective and efficient delivery is by pMDI with a spacer[366,368] (Evidence A). Evidence is less robust in severe and near-fatal asthma. Systematic reviews of intermittent versus continuous nebulized SABA in acute asthma provide conflicting results. One found no significant differences in lung function or hospital admissions[384] but a later review with additional studies found reduced hospitalizations and better lung function with continuous compared with intermittent nebulization, particularly in patients with worse lung function.[385] An earlier study in hospitalized patients found that intermittent on-demand therapy led to a significantly shorter hospital stay, fewer nebulizations and fewer palpitations when compared with 4-hourly intermittent therapy.[386] A reasonable approach to inhaled SABA in exacerbations, therefore, would be to initially use continuous therapy, followed by intermittent on-demand therapy for hospitalized patients.

There is no evidence to support the routine use of intravenous beta$_2$-agonists in patients with severe asthma exacerbations[387] (Evidence A).

Epinephrine (for anaphylaxis)

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

Systemic corticosteroids

Systemic corticosteroids speed resolution of exacerbations and prevent relapse, and should be utilized in all but the mildest exacerbations in adults, adolescents and children 6–11 years.[388-390] (Evidence A). Where possible, systemic corticosteroids should be administered to the patient within 1 hour of presentation.[389,390] 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.[391,392] For children, a liquid formulation is preferred to tablets. OCS require at least 4 hours to produce a clinical improvement. Intravenous corticosteroids can be administered when patients are too dyspneic to swallow; if the patient is vomiting; or when patients require non-invasive ventilation or intubation. In patients discharged from the emergency department, an intramuscular corticosteroid may be helpful,[393] especially if there are concerns about adherence with oral therapy.[394]

Dosage: daily doses of OCS equivalent to 50 mg prednisolone as a single morning dose, or 200 mg hydrocortisone in divided doses, are adequate for most patients (Evidence B). For children, an OCS dose of 1–2 mg/kg up to a maximum of 40 mg/day is adequate.[395]

Duration: 5- and 7-day courses in adults have been found to be as effective as 10- and 14-day courses respectively,[373,374] and a 3–5-day course in children is usually considered sufficient (Evidence B). Oral dexamethasone

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for 2 days can also be used but there are concerns about metabolic side-effects if it is continued beyond 2 days.[396] 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[397] or over several weeks[398] (Evidence B).

Inhaled corticosteroids

Within the emergency department: high-dose ICS given within the first hour after presentation reduces the need for hospitalization in patients not receiving systemic corticosteroids[390] (Evidence A). When given in addition to systemic corticosteroids, evidence is conflicting[390] (Evidence B). Overall, ICS are well tolerated; however, cost is a significant factor, and the agent, dose and duration of treatment with ICS in the management of asthma in the emergency department remain unclear.

On discharge home: the majority of patients should be prescribed regular ongoing ICS treatment since the occurrence of a severe exacerbation is a risk factor for future exacerbations (Evidence B) (Box 2-2, p.29), and ICS-containing medications significantly reduce the risk of asthma-related death or hospitalization[162] (Evidence A). 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.[399] There was some evidence, however, that post-discharge ICS were as effective as systemic corticosteroids for milder exacerbations, but the confidence limits were wide.[399] (Evidence B). Cost may be a significant factor for patients in the use of high-dose ICS, and further studies are required to establish their role.[399]

Other treatments

Ipratropium bromide

For adults and children with moderate-severe exacerbations, treatment in the emergency department with both SABA and ipratropium, a short-acting anticholinergic, was associated with fewer hospitalizations and greater improvement in PEF and FEV_1 compared with SABA alone.[400,401] For children hospitalized for acute asthma, no benefits were seen from adding ipratropium to SABA, including no reduction in length of stay.[402]

Aminophylline and theophylline

Intravenous aminophylline and theophylline should not be used in the management of asthma exacerbations, in view of their poor efficacy and safety profile, and the greater effectiveness and relative safety of SABA.[403] 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.[403]

Magnesium

Intravenous magnesium sulfate is not recommended for routine use in asthma exacerbations; however, when administered as a single 2 g infusion over 20 minutes, it reduces hospital admissions in some patients, including adults with FEV_1 <25–30% predicted at presentation; adults and children who fail to respond to initial treatment and have persistent hypoxemia; and children whose FEV_1 fails to reach 60% predicted after 1 hour of care[404-406] (Evidence A). A large, randomized, controlled trial showed no benefit with the addition of intravenous or nebulized magnesium compared with placebo in the routine care of asthma exacerbations, but those with more severe exacerbations were excluded.[407] Nebulized salbutamol is most often administered in normal saline; however, it can also be administered in isotonic magnesium sulfate. While the overall efficacy of this practice is unclear, pooled data from three trials suggest possible improved pulmonary function in those with severe asthma exacerbations (FEV_1 <50% predicted)[408] (Evidence B).

Helium oxygen therapy

A systematic review of studies comparing helium-oxygen with air–oxygen suggests there is no role for this intervention in routine care (Evidence B), but it may be considered for patients who do not respond to standard therapy; however, availability, cost and technical issues should be considered.[409]

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Leukotriene receptor antagonists

There is limited evidence to support a role for oral or intravenous LTRAs in acute asthma. Small studies have demonstrated improvement in lung function[410,411] but the clinical role of these agents requires more study.

ICS/LABA combinations

The role of these medications in the emergency department or hospital is unclear. One study showed that high-dose budesonide/formoterol in patients in the emergency department, all of whom received prednisolone, had similar efficacy and safety profile to SABA.[412] Another study examined addition of salmeterol to OCS for hospitalized patients, but was not adequately powered to support a recommendation.[413]

Antibiotics (not recommended)

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

Sedatives

Sedation should be strictly avoided during exacerbations of asthma because of the respiratory depressant effect of anxiolytic and hypnotic drugs. An association between the use of these drugs and avoidable asthma deaths has been reported.[414,415]

Non-invasive ventilation (NIV)

The evidence regarding the role of NIV in asthma is weak. A systematic review identified five studies involving 206 participants with acute severe asthma treated with NIV or placebo.[416] Two studies found no difference in need for endotracheal intubation but one study identified fewer admissions in the NIV group. No deaths were reported in either study. Given the small size of the studies, no recommendation is offered. If NIV is tried, the patient should be monitored closely (Evidence D). It should not be attempted in agitated patients, and patients should not be sedated in order to receive NIV (Evidence D).

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Reviewing response

Clinical status and oxygen saturation should be re-assessed frequently, with further treatment titrated according to the patient's response (Box 4-4, p.83). 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.[417,418]

Consensus recommendations in another study were:[419]

- 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 4-1, p.75) 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:[420-422]

- 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.

Discharge planning

Prior to discharge from the emergency department or hospital to home, arrangements should be made for a follow-up appointment within one week, and strategies to improve asthma management including medications, inhaler skills and written asthma action plan, should be addressed (Box 4-5).[210]

Follow up after emergency department presentation or hospitalization for asthma

Following discharge, the patient should be reviewed by their health care provider regularly over subsequent weeks until good symptom control is achieved and personal best lung function is reached or surpassed. Incentives such as free transport and telephone reminders improve primary care follow up but have shown no effect on long-term outcomes.[210]

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

- The patient's understanding of the cause of their asthma exacerbation
- Modifiable risk factors for exacerbations (including, where relevant, smoking) (Box 3-8, p.50)
- The patient's understanding of the purposes and correct uses of medications
- The actions the patient needs to take to respond to worsening symptoms or peak flows.

After emergency department presentation, comprehensive intervention programs that include optimal controller management, inhaler technique, and elements of self-management education (self-monitoring, written action plan and regular review[129]) are cost effective and have shown significant improvement in asthma outcomes[210] (Evidence B).

Referral for expert advice should be considered for patients who have been hospitalized for asthma, or who repeatedly present to an acute care setting despite having a primary care provider. No recent studies are available, but earlier studies suggest that follow-up by a specialist is associated with fewer subsequent emergency department visits or hospitalizations and better asthma control.[210]

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

Medications
Oral corticosteroids (OCS) Prescribe at least a 5–7 day course of OCS for adults (prednisolone or equivalent 1 mg/kg/day to a maximum of 50 mg/day) and 3–5 days for children (1–2 mg/kg/day to a maximum of 40 mg). For patients considered at risk of poor adherence, intramuscular corticosteroids may be considered[393] (Evidence B). *Reliever medication* Transfer patients back to as-needed rather than regular reliever medication use, based on symptomatic and objective improvement. If ipratropium bromide was used in the emergency department or hospital, it may be quickly discontinued, as it is unlikely to provide ongoing benefit. *Inhaled corticosteroids (ICS)* Initiate ICS prior to discharge, if not previously prescribed (Box 3-4, p.42). Patients currently prescribed ICS-containing medication should generally have their treatment stepped up for 2–4 weeks (Box 4-2, p.77) and should be reminded about the importance of adherence with daily use.
Risk factors that contributed to the exacerbation
Identify factors that may have contributed to the exacerbation and implement strategies to reduce modifiable risk factors (Box 3-8, p.50). An exacerbation severe enough to require hospitalization may follow irritant or allergen exposure, inadequate long-term treatment, problems with adherence, and/or lack of a written asthma action plan, as well as unavoidable factors such as viral respiratory infections.
Self-management skills and written asthma action plan
• Review inhaler technique (Box 3-11, p.56). • Review technique with PEF meter if used. • Provide a written asthma action plan (Box 4-2, p.77) or review the patient's existing plan, either at discharge or as soon as possible afterwards. Patients discharged from the emergency department with an action plan and PEF meter have better outcomes than patients discharged without these resources.[423] • Evaluate the patient's response to the exacerbation. If it was inadequate, review the action plan and provide written guidance to assist if asthma worsens again.[423,424] • Review the patient's use of controller treatment before and during the exacerbation. Was it increased promptly and by how much? Were OCS added and if not, why not? Consider providing a short-course of OCS to be on hand for subsequent exacerbations.
Follow up appointment
A follow-up appointment within 2–7 days of discharge should be made with the patient's usual health care provider, to ensure that treatment is continued, that asthma symptoms are well controlled, and that the patient's lung function reaches their personal best (if known).

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

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Chapter 5.

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

A joint project of GINA and GOLD

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KEY POINTS

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

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OBJECTIVE

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

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

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

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

BACKGROUND TO DIAGNOSING ASTHMA, COPD AND ASTHMA-COPD OVERLAP

In children and young adults, the differential diagnosis in patients with respiratory symptoms is different from that in older adults. Once infectious disease and non-pulmonary conditions (e.g. congenital heart disease, vocal cord dysfunction) have been excluded, the most likely chronic airway disease in children is asthma. This is often accompanied by allergic rhinitis. In adults (usually after the age of 40 years) COPD becomes more common, and distinguishing asthma with chronic airflow limitation from COPD becomes problematic, particularly amongst smokers.[425-428]

A significant proportion of patients who present with chronic respiratory symptoms, particularly older patients, have diagnoses and/or features of both asthma and COPD, and are found to have chronic airflow limitation (i.e. that is not completely reversible after bronchodilatation).[429-433] Several diagnostic terms, most including the word 'overlap', have been applied to such patients, and the topic has been extensively reviewed.[41,428,430,434,435] However, there is no generally agreed term or defining features for this category of chronic airflow limitation, although a definition based upon consensus has been published for overlap in patients with existing COPD.[436]

In spite of these uncertainties, there is broad agreement that patients with features of both asthma and COPD experience frequent exacerbations,[41,430] have poor quality of life,[41,437] a more rapid decline in lung function and high mortality,[430] and consume a disproportionate amount of healthcare resources[41,438] than asthma or COPD alone. In these reports, the proportion of patients with features of both asthma and COPD is unclear and will have been influenced by the initial inclusion criteria used for the studies from which the data were drawn.

In epidemiological studies, reported prevalence rates for ACO have ranged between 15 and 55%, with variation by gender and age;[432,437,439] the wide range reflects the different criteria that have been used by different investigators for diagnosing asthma and COPD. Concurrent doctor-diagnosed asthma and COPD has been reported in between 15 and 20% of patients.[431,434,440,441]

This document has been developed and revised by the Science Committees of both GINA and GOLD, based on a detailed review of available literature and consensus. It provides an approach to identifying patients with asthma or COPD, and for distinguishing these from those with overlapping features of asthma and COPD, for which the descriptive term asthma-COPD overlap (ACO) is suggested. The term Asthma COPD Overlap Syndrome (ACOS) [430,434] is no longer advised, as this was often interpreted as implying a single disease.

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DEFINITIONS

Just as asthma and COPD are heterogeneous diseases, each with a range of underlying mechanisms, ACO also does not represent a single disease or a single phenotype. However, few studies have included broad populations, so the mechanisms underlying ACO are largely unknown, and a formal definition of ACO cannot be provided. Instead, this document presents features that identify and characterize typical asthma, typical COPD and asthma-COPD overlap, ascribing equal weight to features of asthma and of COPD. It is acknowledged that within this description of ACO will lie a number of phenotypes that may in due course be identified by more detailed characterization on the basis of clinical, pathophysiological and genetic identifiers.[442-444] The primary objective of this approach, based on *current* evidence, is to provide practical advice for clinicians, particularly those in primary care and non-pulmonary specialties, about diagnosis, safe initial treatment, and referral where necessary.

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

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

Asthma
Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. [GINA 2017][445]
COPD
Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. [GOLD 2017][39]
Asthma-COPD overlap (ACO) – not a definition, but a description for clinical use
Asthma-COPD overlap (ACO) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. Asthma-COPD overlap is therefore identified in clinical practice by the features that it shares with both asthma and COPD. This is not a definition, but a description for clinical use, as asthma-COPD overlap includes several different clinical phenotypes and there are likely to be several different underlying mechanisms.

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STEPWISE APPROACH TO DIAGNOSIS OF PATIENTS WITH RESPIRATORY SYMPTOMS

STEP 1: Does the patient have chronic airways disease?

A first step in diagnosing these conditions is to identify patients at risk of, or with significant likelihood of having chronic airways disease, and to exclude other potential causes of respiratory symptoms. This is based on a detailed medical history, physical examination, and other investigations.[48,427,446,447]

Clinical History

Features that prompt consideration of chronic airways disease include:

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

Physical examination

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

Radiology

- May be normal, particularly in early stages
- Abnormalities on chest X-ray or CT scan (performed for other reasons such as screening for lung cancer), including hyperinflation, airway wall thickening, air trapping, hyperlucency, bullae or other features of emphysema.

- May identify an alternative diagnosis, including bronchiectasis, evidence of lung infections such as tuberculosis, interstitial lung diseases or cardiac failure.

Screening questionnaires

Many screening questionnaires have been proposed to help the clinician identifying subjects at risk of chronic airways disease, based on the above risk factors and clinical features.[448-450] These questionnaires are usually context-specific, so they are not necessarily relevant to all countries (where risk factors and comorbid diseases differ), to all practice settings and uses (population screening *versus* primary or secondary care), or to all groups of patients (case-finding *versus* self-presenting with respiratory symptoms *versus* referred consultation). Examples of these questionnaires are provided on both the GINA and GOLD websites.

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

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

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

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

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

From Box 5-2b, count the number of checked boxes in each column. Having several (three or more) of the features listed for either asthma or for COPD, in the absence of those for the alternative diagnosis, provides a strong likelihood of a diagnosis of typical asthma or of typical COPD.[450]

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

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

In clinical practice, when a condition has no pathognomonic features, clinicians recognize that diagnoses are made on the weight of evidence, provided there are no features that clearly make the diagnosis untenable. Clinicians are able to provide an estimate of their level of certainty and factor it into their decision to treat. Doing so consciously may assist in the selection of treatment and, where there is significant doubt, it may direct therapy towards the safest option - namely, treatment for the condition that should not be missed and left untreated. The higher the level of certainty about the diagnosis of asthma or COPD, the more attention needs to be paid to the safety and efficacy of the initial treatment choices (see Step 4, p.90).

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Box 5-2a.Usual features of asthma, COPD and asthma-COPD overlap **Box 5-2b.Features that if present favor asthma or COPD**

Feature	Asthma	COPD	Asthma-COPD overlap	More likely to be asthma if several of …*	More likely to be COPD if several of…*
Age of onset	Usually childhood onset but can commence at any age.	Usually > 40 years of age	Usually age ≥40 years, but may have had symptoms in childhood or early adulthood	☐ Onset before age 20 years	☐ Onset after age 40 years
Pattern of respiratory symptoms	Symptoms may vary over time (day to day, or over longer periods), often limiting activity. Often triggered by exercise, emotions including laughter, dust or exposure to allergens	Chronic usually continuous symptoms, particularly during exercise, with 'better' and 'worse' days	Respiratory symptoms including exertional dyspnea are persistent but variability may be prominent	☐ Variation in symptoms over minutes, hours or days ☐ Symptoms worse during the night or early morning ☐ Symptoms triggered by exercise, emotions including laughter, dust or exposure to allergens	☐ Persistence of symptoms despite treatment ☐ Good and bad days but always daily symptoms and exertional dyspnea ☐ Chronic cough and sputum preceded onset of dyspnea, unrelated to triggers
Lung function	Current and/or historical variable airflow limitation, e.g. BD reversibility, AHR	FEV_1 may be improved by therapy, but post-BD $FEV_1/FVC < 0.7$ persists	Airflow limitation not fully reversible, but often with current or historical variability	☐ Record of variable airflow limitation (spirometry, peak flow)	☐ Record of persistent airflow limitation (post-bronchodilator $FEV_1/FVC < 0.7$)
Lung function between symptoms	May be normal between symptoms	Persistent airflow limitation	Persistent airflow limitation	☐ Lung function normal between symptoms	☐ Lung function abnormal between symptoms
Past history or family history	Many patients have allergies and a personal history of asthma in childhood, and/or family history of asthma	History of exposure to noxious particles and gases (mainly tobacco smoking and biomass fuels)	Frequently a history of doctor-diagnosed asthma (current or previous), allergies and a family history of asthma, and/or a history of noxious exposures	☐ Previous doctor diagnosis of asthma ☐ Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	☐ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema ☐ Heavy exposure to a risk factor: tobacco smoke, biomass fuels
Time course	Often improves spontaneously or with treatment, but may result in fixed airflow limitation	Generally, slowly progressive over years despite treatment	Symptoms are partly but significantly reduced by treatment. Progression is usual and treatment needs are high	☐ No worsening of symptoms over time. Symptoms vary either seasonally, or from year to year ☐ May improve spontaneously or have an immediate response to BD or to ICS over weeks	☐ Symptoms slowly worsening over time (progressive course over years) ☐ Rapid-acting bronchodilator treatment provides only limited relief.
Chest X-ray	Usually normal	Severe hyperinflation & other changes of COPD	Similar to COPD	☐ Normal	☐ Severe hyperinflation
Exacerbations	Exacerbations occur, but the risk of exacerbations can be considerably reduced by treatment	Exacerbations can be reduced by treatment. If present, comorbidities contribute to impairment	Exacerbations may be more common than in COPD but are reduced by treatment. Comorbidities can contribute to impairment		
Airway inflammation	Eosinophils and/or neutrophils	Neutrophils ± eosinophils in sputum, lymphocytes in airways, may have systemic inflammation	Eosinophils and/or neutrophils in sputum.		

Syndromic diagnosis of airways disease: how to use Box 5-2b

Shaded columns list features that, when present, best identify patients with typical asthma and COPD. For a patient, count the number of check boxes in each column. If three or more boxes are checked for either asthma or COPD, the patient is likely to have that disease. If there are similar numbers of checked boxes in each column, the diagnosis of ACO should be considered. See Step 2 for more details.

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STEP 3. Spirometry

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

Measurement of peak expiratory flow (PEF), although not an alternative to spirometry, if performed repeatedly on the same meter over a period of 1–2 weeks may help to confirm the diagnosis of asthma by demonstrating excessive variability (Box 1-2, p.17), but a normal PEF does not rule out either asthma or COPD. A high level of variability in lung function may also be found in ACO.

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

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

Spirometric variable	Asthma	COPD	Asthma-COPD overlap
Normal FEV_1/FVC pre- or post BD	Compatible with diagnosis	Not compatible with diagnosis	Not compatible unless other evidence of chronic airflow limitation
Post-BD FEV_1/FVC <0.7	Indicates airflow limitation but may improve spontaneously or on treatment	Required for diagnosis (GOLD criteria)	Usually present
Post-BD FEV_1 ≥80% predicted	Compatible with diagnosis (good asthma control or interval between symptoms)	Compatible with GOLD classification of mild airflow limitation if post-BD FEV_1/FVC <0.7	Compatible with diagnosis of mild ACO
Post-BD FEV_1 <80% predicted	Compatible with diagnosis. Risk factor for asthma exacerbations	An indicator of severity of airflow limitation and risk of future events (e.g. mortality and COPD exacerbations)	An indicator of severity of airflow limitation and risk of future events (e.g. mortality and exacerbations)
Post-BD increase in FEV_1 ≥12% and 200 ml from baseline (reversible airflow limitation).	Usual at some time in course of asthma, but may not be present when well-controlled or on controllers	Common and more likely when FEV_1 is low	Common and more likely when FEV_1 is low
Post-BD increase in FEV_1 >12% and 400ml from baseline (marked reversibility)	High probability of asthma	Unusual in COPD. Consider ACO	Compatible with diagnosis of ACO

ACO: asthma-COPD overlap; BD: bronchodilator; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung Disease.

STEP 4: Commence initial therapy

If the syndromic assessment favors asthma as a single diagnosis

Commence treatment as described in the GINA strategy report.[451] Pharmacotherapy is based on ICS, with add-on treatment if needed, e.g. add-on long-acting beta$_2$-agonist (LABA) and/or long-acting muscarinic antagonist (LAMA).

If the syndromic assessment favors COPD as a single disease

Commence treatment as in the current GOLD strategy report.[39] Pharmacotherapy starts with symptomatic treatment with bronchodilators (LABA and/or LAMA) or combination therapy, but not ICS alone (as monotherapy).

If the differential diagnosis is equally balanced between asthma and COPD (i.e. asthma-COPD overlap)

If the syndromic assessment suggests ACO, the recommended default position is to start treatment for asthma (Box 5-4, p.90) until further investigations have been performed. This approach recognizes the pivotal role of ICS in preventing morbidity and even death in patients with uncontrolled asthma symptoms, for whom even seemingly 'mild' symptoms (compared to those of moderate or severe COPD) might indicate significant risk of a life-threatening attack.[434]

- Pharmacotherapy for ACO includes an ICS (in a low or moderate dose (see Box 3-6, p.44), depending on level of symptoms and risk of adverse effects, including pneumonia).
- Usually also add a LABA and/or LAMA, or continue these together with ICS if already prescribed.

However, if there are features of asthma, do not treat with a LABA without ICS (often called LABA monotherapy).

For all patients with chronic airflow limitation

Provide advice, as described in the GINA and GOLD reports, about:

- Treatment of modifiable risk factors including advice about smoking cessation
- Treatment of comorbidities
- Non-pharmacological strategies including physical activity, and, for COPD or asthma-COPD overlap, pulmonary rehabilitation and vaccinations
- Appropriate self-management strategies
- Regular follow-up

In a majority of patients, the initial management of asthma and COPD can be satisfactorily carried out at primary care level. However, both the GINA and GOLD strategy reports make provision for referral for further diagnostic procedures at relevant points in patient management (see Step 5). This may be particularly important for patients with suspected ACO, given that it is associated with worse outcomes and greater health care utilization.

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STEP 5: Referral for specialized investigations (if necessary)

Referral for expert advice and further diagnostic evaluation is necessary in the following contexts:

- Patients with persistent symptoms and/or exacerbations despite treatment.
- Diagnostic uncertainty, especially if an alternative diagnosis (e.g. bronchiectasis, post-tuberculous scarring, bronchiolitis, pulmonary fibrosis, pulmonary hypertension, cardiovascular diseases and other causes of respiratory symptoms) needs to be excluded.
- Patients with suspected asthma or COPD in whom atypical or additional symptoms or signs (e.g. haemoptysis, significant weight loss, night sweats, fever, signs of bronchiectasis or other structural lung disease) suggest an additional pulmonary diagnosis. This should prompt early referral, without necessarily waiting for a trial of treatment for asthma or COPD.
- When chronic airways disease is suspected but syndromic features of both asthma and COPD are few.
- Patients with comorbidities that may interfere with the assessment and management of their airways disease.
- Referral may also be appropriate for issues arising during on-going management of asthma, COPD or ACO, as outlined in the GINA and GOLD strategy reports.[39,451]

Box 5-4. Summary of syndromic approach to diseases of chronic airflow limitation for clinical practice

STEP 1 DIAGNOSE CHRONIC AIRWAYS DISEASE
Do symptoms suggest chronic airways disease?

Yes → STEP 2 | No → Consider other diseases first

STEP 2 SYNDROMIC DIAGNOSIS IN ADULTS
(i) Assemble the features for asthma and for COPD that best describe the patient.
(ii) Compare number of features in favour of each diagnosis and select a diagnosis

Feature: if present suggests	ASTHMA	COPD
Age of onset	❑ Before age 20 years	❑ After age 40 years
Pattern of symptoms	❑ Variation over minutes, hours or days ❑ Worse during the night or early morning ❑ Triggered by exercise, emotions including laughter, dust or exposure to allergens	❑ Persistent despite treatment ❑ Good and bad days but always daily symptoms and exertional dyspnea ❑ Chronic cough & sputum preceded onset of dyspnea, unrelated to triggers
Lung function	❑ Record of variable airflow limitation (spirometry or peak flow)	❑ Record of persistent airflow limitation ($FEV_1/FVC < 0.7$ post-BD)
Lung function between symptoms	❑ Normal	❑ Abnormal
Past history or family history	❑ Previous doctor diagnosis of asthma ❑ Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	❑ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema ❑ Heavy exposure to riskfactor: tobacco smoke, biomass fuels
Time course	❑ No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year ❑ May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks	❑ Symptoms slowly worsening over time (progressive course over years) ❑ Rapid-acting bronchodilator treatment provides only limited relief
Chest X-ray	❑ Normal	❑ Severe hyperinflation

NOTE: • These features best distinguish between asthma and COPD. • Several positive features (3 or more) for either asthma or COPD suggest that diagnosis. • If there are a similar number for both asthma and COPD, consider diagnosis of asthma-COPD overlap (ACO)

DIAGNOSIS	Asthma	Some features of asthma	Features of both	Some features of COPD	COPD
CONFIDENCE IN DIAGNOSIS	Asthma	Possible Asthma	Could be ACO	Possibly COPD	COPD

STEP 3 PERFORM SPIROMETRY
Marked reversible airflow limitation (pre-post bronchodilator) or other proof of variable airflow limitation → $FEV_1/FVC < 0.7$ post-BD

STEP 4 INITIAL TREATMENT*

Asthma drugs No LABA monotherapy	Asthma drugs No LABA monotherapy	ICS and consider LABA +/or LAMA	COPD drugs	COPD drugs

*Consult GINA and GOLD documents for recommended treatments.

STEP 5 SPECIALISED INVESTIGATIONS or REFER IF:
- Persistent symptoms and/or exacerbations despite treatment.
- Diagnostic uncertainty (e.g. suspected pulmonary hypertension, cardiovascular diseases and other causes of respiratory symptoms).
- Suspected asthma or COPD with atypical or additional symptoms or signs (e.g. haemoptysis, weight loss, night sweats, fever, signs of bronchiectasis or other structural lung disease).
- Few features of either asthma or COPD.
- Comorbidities present.
- Reasons for referral for either diagnosis as outlined in the GINA and GOLD strategy reports.

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Box 5-5 (p.98) summarizes specialized investigations that are sometimes used to distinguish asthma and COPD.

Box 5-5. Specialized investigations sometimes used in distinguishing asthma and COPD

	Asthma	COPD
Lung function tests		
DLCO	Normal (or slightly elevated).	Often reduced.
Arterial blood gases	Normal between exacerbations	May be chronically abnormal between exacerbations in more severe forms of COPD
Airway hyperresponsiveness (AHR)	Not useful on its own in distinguishing asthma from COPD, but higher levels of AHR favor asthma	
Imaging		
High resolution CT Scan	Usually normal but air trapping and increased bronchial wall thickness may be observed.	Low attenuation areas denoting either air trapping or emphysematous change can be quantitated; bronchial wall thickening and features of pulmonary hypertension may be seen.
Inflammatory biomarkers		
Test for atopy (specific IgE and/or skin prick tests)	Modestly increases probability of asthma; not essential for diagnosis	Conforms to background prevalence; does not rule out COPD
FENO	A high level (>50 ppb) in non-smokers supports a diagnosis of eosinophilic airway inflammation	Usually normal. Low in current smokers.
Blood eosinophilia	Supports diagnosis of eosinophilic asthma	May be present including during exacerbations
Sputum inflammatory cell analysis	Role in differential diagnosis is not established in large populations	

DLCO: diffusing capacity of the lungs for carbon monoxide; FENO: fractional concentration of exhaled nitric oxide; IgE: immunoglobulin E

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FUTURE RESEARCH

Our understanding of asthma-COPD overlap is at a very preliminary stage, as most research has involved participants from existing studies which had specific inclusion and exclusion criteria (such as a physician diagnosis of asthma and/or COPD), a wide range of criteria have been used in existing studies for identifying ACO, and patients who do not have 'classical' features of asthma or of COPD, or who have features of both, have generally been excluded from studies of most therapeutic interventions for airways disease.[452,453]

There is an urgent need for more research on this topic, in order to guide better recognition and appropriate treatment. This should include study of clinical and physiological characteristics, biomarkers, outcomes and underlying mechanisms, starting with broad populations of patients with respiratory symptoms or with chronic airflow limitation, rather than starting with populations with existing diagnoses of asthma or COPD. The present chapter provides interim advice, largely based on consensus, for the perspective of clinicians, particularly those in primary care and non-pulmonary specialties. Further research is needed to inform evidence-based definitions and a more detailed classification of patients who present overlapping features of asthma and COPD, and to encourage the development of specific interventions for clinical use.

Chapter 6.

Diagnosis and management of asthma in children 5 years and younger

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PART A. DIAGNOSIS

KEY POINTS

- Recurrent wheezing occurs in a large proportion of children 5 years and younger, typically with viral upper respiratory tract infections. Deciding when this is the initial presentation of asthma is difficult.
- Previous classifications of wheezing phenotypes (episodic wheeze and multiple-trigger wheeze; or transient wheeze, persistent wheeze and late-onset wheeze) do not appear to identify stable phenotypes, and their clinical usefulness is uncertain.
- A diagnosis of asthma in young children with a history of wheezing is more likely if they have:
    - Wheezing or coughing that occurs with exercise, laughing or crying in the absence of an apparent respiratory infection
    - A history of other allergic disease (eczema or allergic rhinitis) or asthma in first-degree relatives
    - Clinical improvement during 2–3 months of controller treatment, and worsening after cessation.

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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.[454] Asthma often begins in early childhood; in up to half of people with asthma, symptoms commence during childhood.[455] Onset of asthma is earlier in males than females.[456-458] Atopy is present in the majority of children with asthma who are over 3 years old, and allergen-specific sensitization is one of the most important risk factors for the development of asthma.[459] However, no intervention has yet been shown to prevent the development of asthma, or modify its long-term natural course.

Viral-induced wheezing

Recurrent wheezing occurs in a large proportion of children aged 5 years or younger. It is typically associated with upper respiratory tract infections (URTI), which occur in this age group around 6–8 times per year.[460] Some viral infections (respiratory syncytial virus and rhinovirus) are associated with recurrent wheeze throughout childhood. However, wheezing in this age group is a highly heterogeneous condition, and not all wheezing in this age group indicates asthma. Many young children may wheeze with viral infections. Therefore, deciding when wheezing with a respiratory infection is truly an initial or recurrent clinical presentation of childhood asthma is difficult.[458,461]

Wheezing phenotypes

In the past, two main classifications of wheezing (called ‘wheezing phenotypes’) were proposed.

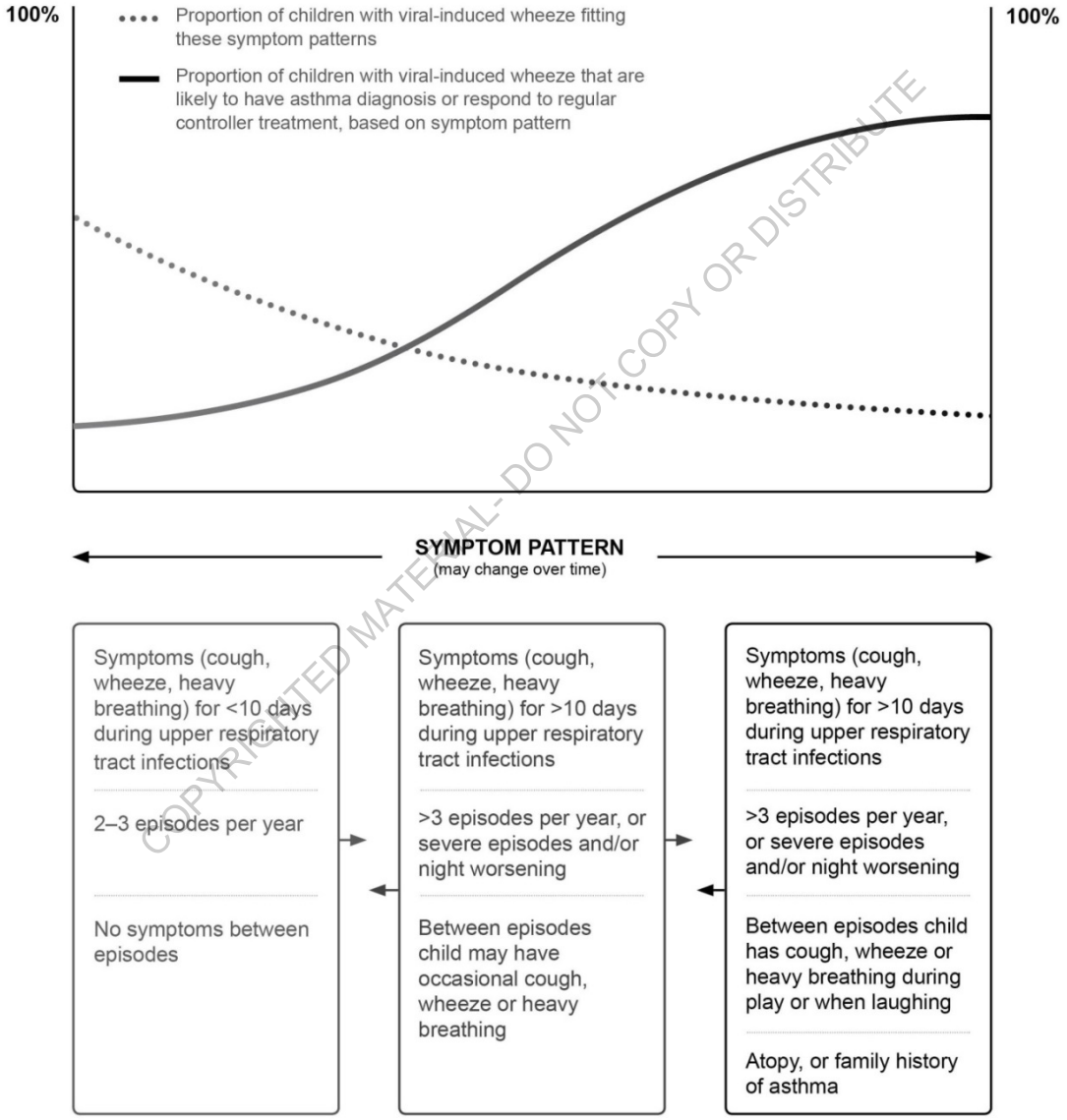
- *Symptom-based classification*:[462] this was based on whether the child had only *episodic wheeze* (wheezing during discrete time periods, often in association with URTI, with symptoms absent between episodes) or *multiple-trigger wheeze* (episodic wheezing with symptoms also occurring between these episodes, e.g. during sleep or with triggers such as activity, laughing, or crying).
- *Time trend-based classification*: this system was based on analysis of data from a cohort study.[458] 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).

However, prospective allocation of individual children to these phenotypes has been unreliable in ‘real-life’ clinical situations, and the clinical usefulness of these systems remains a subject of active investigation.[463,464 465,466]

CLINICAL DIAGNOSIS OF ASTHMA

It may be difficult to make a confident diagnosis of asthma in children 5 years and younger, because episodic respiratory symptoms such as wheezing and cough are also common in children without asthma, particularly in those 0–2 years old.[467,468] Furthermore, it is not possible to routinely assess airflow limitation in this age group. A probability-based approach, based on the pattern of symptoms during and between viral respiratory infections,[469] may be helpful for discussion with parents/carers (Box 6-1). This approach allows individual decisions to be made about whether to give a trial of controller treatment. It is important to make decisions for each child individually, to avoid either over- or under-treatment.

Box 6-1. Probability of asthma diagnosis or response to asthma treatment in children 5 years and younger



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This schematic figure shows the probability of an asthma diagnosis[470,471] or response to asthma treatment[472,473] in children aged 5 years or younger who have viral-induced cough, wheeze or heavy breathing, based on the pattern of symptoms. Many young children wheeze with viral infections, and deciding when a child should be given controller treatment is difficult. The frequency and severity of wheezing episodes and the temporal pattern of symptoms (only with

viral colds or also in response to other triggers) should be taken into account. Any controller treatment should be viewed as a treatment trial, with follow up scheduled after 2–3 months to review the response. Review is also important since the pattern of symptoms tends to change over time in a large proportion of children.

A diagnosis of asthma in young children is therefore based largely on symptom patterns combined with a careful clinical assessment of family history and physical findings. A positive family history of allergic disorders or the presence of atopy or allergic sensitization provide additional predictive support, as early allergic sensitization increases the likelihood that a wheezing child will develop persistent asthma.[459]

Symptoms suggestive of asthma in children 5 years and younger

As shown in Box 6-2, an asthma diagnosis in children 5 years and younger can often be based on:

- Symptom patterns (wheeze, cough, breathlessness (typically manifested by activity limitation), and nocturnal symptoms or awakenings)
- Presence of risk factors for development of asthma
- Therapeutic response to controller treatment.

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Box 6-2. Features suggesting a diagnosis of asthma in children 5 years and younger

Feature	Characteristics suggesting asthma
Cough	Recurrent or persistent non-productive cough that may be worse at night or accompanied by some wheezing and breathing difficulties Cough occurring with exercise, laughing, crying or exposure to tobacco smoke in the absence of an apparent respiratory infection
Wheezing	Recurrent wheezing, including during sleep or with triggers such as activity, laughing, crying or exposure to tobacco smoke or air pollution
Difficult or heavy breathing or shortness of breath	Occurring with exercise, laughing, or crying
Reduced activity	Not running, playing or laughing at the same intensity as other children; tires earlier during walks (wants to be carried)
Past or family history	Other allergic disease (atopic dermatitis or allergic rhinitis) Asthma in first-degree relatives
Therapeutic trial with low dose inhaled corticosteroid (Box 6-5, p.111) and as-needed SABA	Clinical improvement during 2–3 months of controller treatment and worsening when treatment is stopped

SABA: short-acting beta$_2$-agonist

Wheeze

Wheeze is the most common symptom associated with asthma in children 5 years and younger. Wheezing occurs in several different patterns, but a wheeze that occurs recurrently, during sleep, or with triggers such as activity, laughing, or crying, is consistent with a diagnosis of asthma. Clinician confirmation is important, as parents may describe any noisy breathing as ‘wheezing’.[474] Some cultures do not have a word for wheeze.

Wheezing may be interpreted differently based on:

- Who observes it (e.g. parent/carer versus the health care provider)
- When it is reported (e.g. retrospectively versus in real time)

- The environmental context (e.g. developed countries versus areas with a high prevalence of parasites that involve the lung)
- The cultural context (e.g. the relative importance of certain symptoms can differ between cultures, as can the diagnosis and treatment of respiratory tract diseases in general).

Cough

Cough due to asthma is non-productive, recurrent and/or persistent, and is usually accompanied by some wheezing episodes and breathing difficulties. Allergic rhinitis may be associated with cough in the absence of asthma. A nocturnal cough (when the child is asleep) or a cough that occurs with exercise, laughing or crying, in the absence of an apparent respiratory infection, supports a diagnosis of asthma. The common cold and other respiratory illnesses are also associated with coughing. Prolonged cough in infancy, and cough without cold symptoms, are associated with later parent-reported physician-diagnosed asthma, independent of infant wheeze. Characteristics of cough in infancy may be early markers of asthma susceptibility, particularly among children with maternal asthma.[475]

Breathlessness

Parents may also use terms such as ‘difficult breathing’, ‘heavy breathing’, or ‘shortness of breath’. Breathlessness that occurs during exercise and is recurrent increases the likelihood of the diagnosis of asthma. In infants and toddlers, crying and laughing are equivalent to exercise in older children.

Activity and social behavior

Physical activity is an important cause of asthma symptoms in young children. Young children with poorly controlled asthma often abstain from strenuous play or exercise to avoid symptoms, but many parents are unaware of such changes in their children’s lifestyle. Engaging in play is important for a child’s normal social and physical development. For this reason, careful review of the child’s daily activities, including their willingness to walk and play, is important when assessing a potential asthma diagnosis in a young child. Parents may report irritability, tiredness and mood changes in their child as the main problems when asthma is not well controlled.

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TESTS TO ASSIST IN DIAGNOSIS

While no tests diagnose asthma with certainty in children 5 years and younger, the following are useful adjuncts.

Therapeutic trial

A trial of treatment for at least 2–3 months with as-needed short-acting beta$_2$-agonist (SABA) and regular low dose inhaled corticosteroids (ICS) may provide some guidance about the diagnosis of asthma (Evidence D). Response should be evaluated by symptom control (daytime and night-time), and the frequency of wheezing episodes and exacerbations. Marked clinical improvement during treatment, and deterioration when treatment is stopped, support a diagnosis of asthma. Due to the variable nature of asthma in young children, a therapeutic trial may need to be repeated in order to be certain of the diagnosis.

Tests for atopy

Sensitization to allergens can be assessed using either skin prick testing or allergen-specific immunoglobulin E. Skin-prick testing is less reliable for confirming atopy in infants. Atopy is present in the majority of children with asthma once they are over 3 years of age; however, absence of atopy does not rule out a diagnosis of asthma.

Chest X-ray

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 4–5 years of age, children are often capable of performing reproducible spirometry if coached by an experienced technician and with visual incentives.

Exhaled nitric oxide

Fractional concentration of exhaled nitric oxide (FENO) can be measured in young children with tidal breathing, and normal reference values have been published for children aged 1–5 years.[476] FENO testing is becoming more widely available. An elevated FENO, recorded >4 weeks from any URTI in pre-school children with recurrent coughing and wheezing, may predict physician-diagnosed asthma by school age.[477]

Risk profiles

A number of risk profile tools to identify wheezing children aged 5 years and younger who are at high risk of developing persistent asthma symptoms have been evaluated for use in clinical practice.[466] The Asthma Predictive Index (API), based on the Tucson Children's Respiratory Study, is designed for use in children with four or more wheezing episodes in a year.[478] One study showed that children with a positive API have a 4–10-fold greater chance of developing asthma between the ages of 6–13 years than those with a negative API, and 95% of children with a negative API remained free of asthma.[478] The applicability and validation of the API in other contexts needs more study.

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DIFFERENTIAL DIAGNOSIS

A definite diagnosis of asthma in this young age group is challenging but has important clinical consequences. It is particularly important in this age group to consider and exclude alternative causes that can lead to symptoms of wheeze, cough, and breathlessness before confirming an asthma diagnosis (Box 6-3).[467]

Key indications for referral of a child 5 years or younger for further diagnostic investigations

Any of the following features suggest an alternative diagnosis and indicate the need for further investigations:

- Failure to thrive
- Neonatal or very early onset of symptoms (especially if associated with failure to thrive)
- Vomiting associated with respiratory symptoms
- Continuous wheezing
- Failure to respond to asthma controller medications
- No association of symptoms with typical triggers, such as viral URTI
- Focal lung or cardiovascular signs, or finger clubbing
- Hypoxemia outside context of viral illness

Box 6-3. Common differential diagnoses of asthma in children 5 years and younger

Condition	Typical features
Recurrent viral respiratory tract infections	Mainly cough, runny congested nose for <10 days; wheeze usually mild; no symptoms between infections
Gastroesophageal reflux	Cough when feeding; recurrent chest infections; vomits easily especially after large feeds; poor response to asthma medications
Foreign body aspiration	Episode of abrupt, severe cough and/or stridor during eating or play; recurrent chest infections and cough; focal lung signs
Tracheomalacia	Noisy breathing when crying or eating, or during upper airway infections (noisy inspiration if extrathoracic or expiration if intrathoracic); harsh cough; inspiratory or expiratory retraction; symptoms often present since birth; poor response to asthma medications
Tuberculosis	Persistent noisy respirations and cough; fever unresponsive to normal antibiotics; enlarged lymph nodes; poor response to bronchodilators or inhaled corticosteroids; contact with someone who has tuberculosis
Congenital heart disease	Cardiac murmur; cyanosis when eating; failure to thrive; tachycardia; tachypnea or hepatomegaly; poor response to asthma medications
Cystic fibrosis	Cough starting shortly after birth; recurrent chest infections; failure to thrive (malabsorption); loose greasy bulky stools
Primary ciliary dyskinesia	Cough and recurrent, mild chest infections; chronic ear infections and purulent nasal discharge; poor response to asthma medications; situs inversus occurs in about 50% of children with this condition
Vascular ring	Respirations often persistently noisy; poor response to asthma medications
Bronchopulmonary dysplasia	Infant born prematurely; very low birth weight; needed prolonged mechanical ventilation or supplemental oxygen; difficulty with breathing present from birth
Immune deficiency	Recurrent fever and infections (including non-respiratory); failure to thrive

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PART B. ASSESSMENT AND MANAGEMENT

KEY POINTS

- The goals of asthma management in young children are similar to those in older patients:
  - To achieve good control of symptoms and maintain normal activity levels
  - To minimize the risk of asthma flare-ups, impaired lung development and medication side-effects.
- Wheezing episodes in young children should be treated initially with inhaled short-acting beta$_2$-agonists, regardless of whether the diagnosis of asthma has been made.
- A trial of controller therapy should be given if the symptom pattern suggests asthma and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe.
- Response to treatment should be reviewed before deciding whether to continue it. If no response is observed, consider alternative diagnoses.
- The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered dose inhaler and spacer, with face mask for <4 years and mouthpiece for most 4–5 year olds.
- Review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children.

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GOALS OF ASTHMA MANAGEMENT

As with other age groups, the goals of asthma management in young children are:

- To achieve good control of symptoms and maintain normal activity levels
- To minimize future risk; that is to reduce the risk of flare-ups, maintain lung function and lung development as close to normal as possible, and minimize medication side-effects.

Maintaining normal activity levels is particularly important in young children because engaging in play is important for their normal social and physical development. It is important to also elicit the goals of the parent/carer, as these may differ from conventional medical goals.

The goals of asthma management are achieved through a partnership between the parent/carer and the health professional team, with a cycle of:

- *Assess* (diagnosis, symptom control, risk factors, inhaler technique, adherence, parent preference)
- *Adjust treatment* (medications, non-pharmacological strategies, and treatment of modifiable risk factors)
- *Review response* including medication effectiveness and side-effects.

This is carried out in combination with:

- Education of parent/carer, and child (depending on the child's age)
- Skills training for effective use of inhaler devices and encouragement of good adherence
- Monitoring of symptoms by parent/carer
- A written 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.[15,56] It has two components (Box 6-4): the child's asthma status over the previous four weeks (symptom control), and how asthma may affect them in the future (future risk). In young children, as in older patients, it is recommended that both symptom control and future risk should be monitored (Evidence D). In young children, lung function testing is not

feasible for monitoring asthma control. The rationale for monitoring both domains of asthma control is described on p29 ('*Assessing future risk of adverse outcomes*', p.31).

Assessing asthma symptom control

Defining satisfactory symptom control in children 5 years and younger is problematic. Health care providers are almost entirely dependent on the reports of family members and carers, who may be unaware either of how often the child has experienced asthma symptoms, or that their respiratory symptoms represent uncontrolled asthma. No objective measures to assess symptom control have been validated for children <4 years, although the Childhood Asthma Control Test has been developed for children aged 4–11 years.[71]

Box 6-4 shows a working schema for assessing asthma control in children ≤5 years, based on current expert opinion. It incorporates assessment of symptoms; the child's level of activity and their need for reliever/rescue treatment; and assessment of risk factors for adverse outcomes (Evidence D).

Box 6-4. GINA assessment of asthma control in children 5 years and younger

A. Symptom control		**Level of asthma symptom control**		
In the past 4 weeks, has the child had:		**Well controlled**	**Partly controlled**	**Uncontrolled**
• Daytime asthma symptoms for more than a few minutes, more than once a week?	Yes☐ No☐	None of these	1–2 of these	3–4 of these
• Any activity limitation due to asthma? (Runs/plays less than other children, tires easily during walks/playing?)	Yes☐ No☐			
• Reliever medication needed* more than once a week?	Yes☐ No☐			
• Any night waking or night coughing due to asthma?	Yes☐ No☐			
B. Future risk for poor asthma outcomes				
Risk factors for asthma exacerbations within the next few months • Uncontrolled asthma symptoms • One or more severe exacerbation in previous year • The start of the child's usual 'flare-up' season (especially if autumn/fall) • Exposures: tobacco smoke; indoor or outdoor air pollution; indoor allergens (e.g. house dust mite, cockroach, pets, mold), especially in combination with viral infection[479] • Major psychological or socio-economic problems for child or family • Poor adherence with controller medication, or incorrect inhaler technique				
Risk factors for fixed 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 • Local: moderate/high-dose or potent ICS; incorrect inhaler technique; failure to protect skin or eyes when using ICS by nebulizer or spacer with face mask				

ICS = inhaled corticosteroids; OCS = oral corticosteroids * Excludes reliever taken before exercise

This GINA asthma symptom control classification corresponds to 'current control' in GINA pediatric report 2009.[480] Before stepping up treatment, ensure that the child's symptoms are due to asthma, and that the child has good inhaler technique and good adherence to existing treatment.

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Assessing future risk of adverse outcomes

The relationship between symptom control and future risk of adverse outcomes such as exacerbations (Box 6-4, p.107) has not been sufficiently studied in young children. Although exacerbations may occur in children after months of apparently good symptom control, the risk is greater if current symptom control is poor.

The future risk of harm due to excessive doses of inhaled or systemic corticosteroids must also be avoided. This can be minimized by ensuring that the prescribed treatment is appropriate and reduced to the lowest dose that maintains satisfactory symptom control and minimizes exacerbations. The child's height should be measured and recorded at least yearly, as growth velocity may be lower in the first 1-2 years of ICS treatment,[102] and poorly-controlled asthma can affect growth.[101] The minimum effective dose of ICS to maintain good asthma control should be used. If decreased growth velocity is seen, other factors should be considered, including poorly-controlled asthma, frequent use of oral corticosteroids, and poor nutrition, and referral should be considered.

If ICS is delivered through a face-mask or nebulizer, the skin on the nose and around the mouth should be cleaned shortly after inhalation in order to avoid local side-effects such as steroid rash (reddening and atrophy).

MEDICATIONS FOR SYMPTOM CONTROL AND RISK REDUCTION

Choosing medications for children 5 years and younger

Good control of asthma can be achieved in a majority of young children with a pharmacological intervention strategy.[481] This should be developed in a partnership between the family/carer and the health care provider. As with older children and adults, medications comprise only one component of asthma management in young children; other key components include education, skills training for inhaler devices and adherence, non-pharmacological strategies including environmental control where appropriate, regular monitoring, and clinical review (see later sections in this chapter).

When recommending treatment for a young child, both general and individual questions apply (Box 3-3, p.39).

- What is the 'preferred' medication option at each treatment step to control asthma symptoms and minimize future risk? These decisions are based on data for efficacy, effectiveness and safety from clinical trials, and on observational data.
- How does this particular child differ from the 'average' child with asthma, in terms of:
  - Response to previous treatment
  - Parental preference (goals, beliefs and concerns about medications)
  - Practical issues (cost, inhaler technique and adherence)?

The following treatment recommendations for children of 5 years of age or younger are based on the available evidence and on expert opinion. Evidence is limited, as most clinical trials in this age group have not characterized participants with respect to their symptom pattern, and different studies have used different outcomes and different definitions of exacerbations.

A stepwise treatment approach is recommended (Box 6-5, p.111), based on symptom patterns, risk of exacerbations and side-effects, and response to initial treatment. Generally, treatment includes the daily, long-term use of controller medications to keep asthma well-controlled, and reliever medications for as-needed symptom relief. The choice of inhaler device is also an important consideration (Box 6-7, p.114).

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Which children should be prescribed regular controller treatment?

Intermittent or episodic wheezing of any severity may represent an isolated viral-induced wheezing episode, an episode of seasonal or allergen-induced asthma, or unrecognized uncontrolled asthma. The *initial* treatment of wheezing is identical for all of these – a SABA every 4–6 hours as needed for one or more days until symptoms disappear. Further treatment of the acute wheezing episodes themselves is described below (see *Acute asthma exacerbations in children 5 years and younger*). However, uncertainty surrounds the addition of other drugs in these children, especially when the nature of the episode is unclear. In general, the following principles apply.

- *If the symptom pattern suggests a diagnosis of asthma* (Box 6-2, p.102) and respiratory symptoms are uncontrolled (Box 6-4, p.107) and/or wheezing episodes are frequent (e.g. three or more episodes in a season), regular controller treatment should be initiated (Step 2, Box 6-5, p.111) and the response evaluated (Evidence D). Regular controller treatment may also be indicated in a child with less frequent, but more severe episodes of viral-induced wheeze (Evidence D).
- *If the diagnosis of asthma is in doubt*, and inhaled SABA therapy needs to be repeated frequently, e.g. more than every 6–8 weeks, a trial of regular controller treatment should be considered to confirm whether the symptoms are due to asthma (Evidence D).

It is important to discuss the decision to prescribe controller treatment and the choice of treatment with the child's parents or carers. They should be aware of both the relative benefits and risks of the treatments, and the importance of maintaining normal activity levels for their child's normal physical and social development. Although effects of ICS on growth velocity are seen in pre-pubertal children in the first 1-2 years of treatment, this is not progressive or cumulative, and the one study that examined long-term outcomes showed a difference of only 0.7% in adult height.[102,482] Poorly-controlled asthma itself adversely affects adult height.[101] For more detail see Appendix Chapter 5B.

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Treatment steps to control asthma symptoms and minimize future risk for children 5 years and younger

Asthma treatment in young children follows a stepwise approach (Box 6-5), with medication adjusted up or down to achieve good symptom control and minimize future risk of exacerbations and medication side-effects. The need for controller treatment should be re-assessed regularly. More details about asthma medications for children 0–5 years are provided in Appendix Chapter 5, Part C.

Before considering a step-up of controller treatment

If symptom control is poor and/or exacerbations persist despite 3 months of adequate controller therapy, check the following *before any step up in treatment is considered*.

- Confirm that the symptoms are due to asthma rather than a concomitant or alternative condition (Box 6-3, p.105). Refer for expert assessment if the diagnosis is in doubt.
- Check and correct inhaler technique.
- Confirm good adherence with the prescribed dose.
- Enquire about risk factors such as allergen or tobacco smoke exposure (Box 6-4, p.107).

***STEP 1*: As-needed inhaled short-acting beta$_2$-agonist (SABA)**

Preferred option: as-needed inhaled short-acting beta$_2$-agonist (SABA)

All children who experience wheezing episodes should be provided with inhaled SABA for relief of symptoms (Evidence D), although it is not effective in all children. See Box 6-7 (p.114) for choice of inhaler device.

Other options

Oral bronchodilator therapy is not recommended due to its slower onset of action and higher rate of side-effects compared with inhaled SABA (Evidence D). For children with intermittent viral-induced wheeze and no interval symptoms in whom inhaled SABA medication is not sufficient, intermittent ICS may be considered[362,483,484] (see *Management of worsening asthma and exacerbations*, p.115), but because of the risk of side-effects, this should only be considered if the physician is confident that the treatment will be used appropriately.

STEP 2: Initial controller treatment plus as-needed SABA

Preferred option: regular daily low dose ICS plus as-needed SABA

Regular daily, low dose ICS (Box 6-6, p.112) is recommended as the preferred initial treatment to control asthma in children 5 years and younger (Evidence A).[485-487] This initial treatment should be given for at least 3 months to establish its effectiveness in achieving good asthma control.

Other options

In young children with persistent asthma, regular treatment with a leukotriene receptor antagonist (LTRA) modestly reduces symptoms and need for oral corticosteroids compared with placebo.[488] For young children with recurrent viral-induced wheezing, a recent Cochrane review concluded that neither regular nor intermittent LTRA reduces oral corticosteroid-requiring exacerbations (Evidence A).[489] For pre-school children with frequent viral-induced wheezing and with interval asthma symptoms, as-needed (prn)[490] or episodic ICS[491] may be considered but a trial of regular ICS should be undertaken first.

***STEP 3*: Additional controller treatment, plus as-needed SABA**

If 3 months of initial therapy with a low dose ICS fails to control symptoms, or if exacerbations persist, check the following *before any step up in treatment is considered*.

- Confirm that the symptoms are due to asthma rather than a concomitant or alternative condition (Box 6-3, p.105).
- Check and correct inhaler technique.
- Confirm good adherence with the prescribed dose.
- Enquire about risk factors such as allergen or tobacco smoke exposure (Box 6-4, p.107).

Preferred option: moderate dose ICS (double the 'low' daily dose)

Doubling the initial low dose of ICS may be the best option (Evidence C). Assess response after 3 months.

Other options

Addition of a LTRA to low dose ICS may be considered, based on data from older children (Evidence D).

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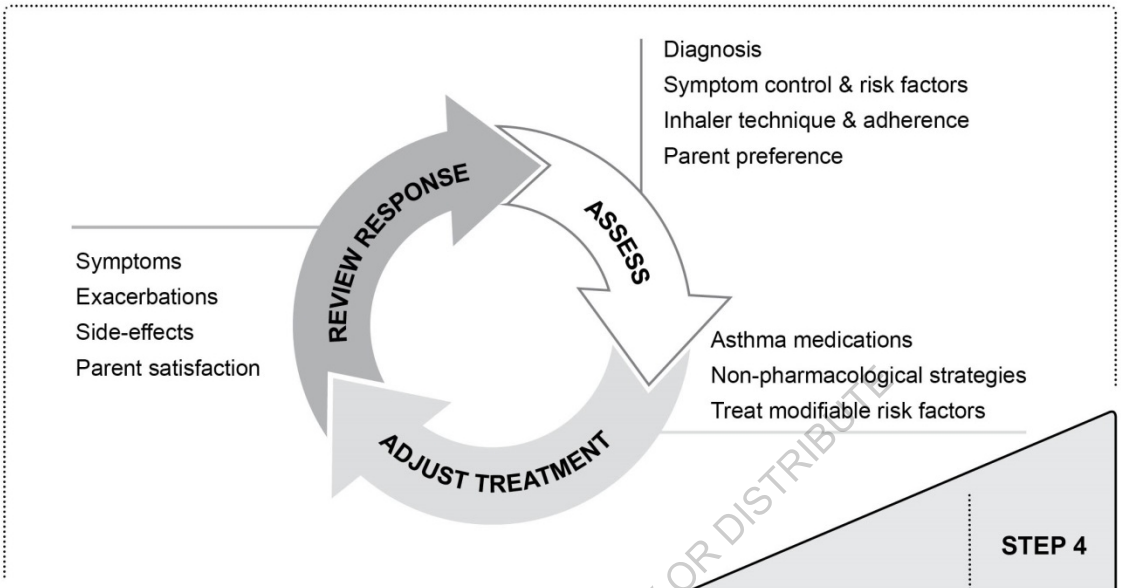
Box 6-5. Stepwise approach to long-term management of asthma in children 5 years and younger



	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE		**Daily low dose ICS**	**Double 'low dose' ICS**	Continue controller & refer for specialist assessment
Other controller options		*Leukotriene receptor antagonist (LTRA)* *Intermittent ICS*	*Low dose ICS + LTRA*	*Add LTRA* *Inc. ICS frequency* *Add intermitt ICS*
RELIEVER	As-needed short-acting beta$_2$-agonist (all children)			

CONSIDER THIS STEP FOR CHILDREN WITH:	Infrequent viral wheezing and no or few interval symptoms *(Box 6-2)*	Symptom pattern consistent with asthma *(Box 6-2)* and asthma symptoms not well-controlled *(Box 6-4)*, or ≥3 exacerbations per year	Asthma diagnosis, and not well-controlled on low dose ICS	Not well-controlled on double ICS
		Symptom pattern not consistent with asthma *(Box 6-2)* but wheezing episodes occur frequently, e.g. every 6–8 weeks. Give diagnostic trial for 3 months.	First check diagnosis, inhaler skills, adherence, exposures	

KEY ISSUES

ALL CHILDREN

- **Assess** symptom control, future risk (Box 6-4), comorbidities
- **Self-management:** education, inhaler skills, written asthma action plan, adherence
- **Regular review:** assess response, adverse events, establish minimal effective treatment
- (Where relevant): environmental control for smoke, allergens, indoor/outdoor air pollution

ICS: inhaled corticosteroid; intermitt.: intermittent; LTRA: leukotriene receptor antagonist. See Box 6-6 for definition of 'low dose' ICS in children 5 years and younger.

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***STEP 4*: Continue controller treatment and refer for expert assessment**

Preferred option: refer the child for expert advice and further investigation (Evidence D).

If doubling the initial dose of ICS fails to achieve and maintain good asthma control, carefully assess inhaler technique and medication adherence as these are common problems in this age group. In addition, assess and address control of environmental factors where relevant, and reconsider the asthma diagnosis. The child should be referred for expert assessment if symptom control remains poor and/or flare-ups persist, or if side-effects of treatment are observed or suspected.

Other options

The best treatment for this population has not been established. If the diagnosis of asthma has been confirmed, options to consider, preferably with specialist advice, are:

- Further increase the dose of ICS (perhaps combined with more frequent dosing) for a few weeks until the control of the child's asthma improves (Evidence D).
- Add a LTRA, theophylline, or a low dose of oral corticosteroid (for a few weeks only) until asthma control improves (Evidence D).
- Add intermittent ICS to the regular daily ICS if exacerbations are the main problem (Evidence D).

The need for additional controller treatment should be re-evaluated at each visit and maintained for as short a period as possible, taking into account potential risks and benefits. Treatment goals and their feasibility should be re-considered and discussed with the child's family/carer; it may become necessary to accept a degree of persisting asthma symptoms to avoid excessive and harmful medication doses.

There are insufficient data about the efficacy and safety of inhaled combination ICS/long-acting beta$_2$-agonist (LABA) products in this age group to recommend their use.

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Box 6-6. Low daily doses of inhaled corticosteroids for children 5 years and younger

Drug	Low daily dose (mcg)
Beclomethasone dipropionate (HFA)	100
Budesonide pMDI + spacer	200
Budesonide nebulized	500
Fluticasone propionate (HFA)	100
Ciclesonide	160
Mometasone furoate	Not studied below age 4 years
Triamcinolone acetonide	Not studied in this age group

HFA: hydrofluoralkane propellant; pMDI: pressurized metered dose inhaler

This is not a table of clinical equivalence. A low daily dose is defined as the dose that has not been associated with clinically adverse effects in trials that included measures of safety.

REVIEWING RESPONSE AND ADJUSTING TREATMENT

Assessment at every visit should include asthma symptom control and risk factors (Box 6-4, p.107), 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,[492-494] so the need for continued controller treatment should be regularly assessed (e.g. every 3–6 months) (Evidence D). If therapy is discontinued, schedule a follow-up visit 3–6 weeks later to check whether symptoms have recurred, as therapy may need to be 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/carer should be provided with a written asthma action plan detailing specific signs of worsening asthma, the medications that should be initiated to treat it, and when and how to contact medical care.

CHOICE OF INHALER DEVICE

Inhaled therapy constitutes the cornerstone of asthma treatment in children 5 years and younger. A pressurized metered dose inhaler (pMDI) with a valved spacer (with or without a face mask, depending on the child's age) is the preferred delivery system[495] (Box 6-7) (Evidence A). This recommendation is based on studies with beta$_2$-agonists. The spacer device should have documented efficacy in young children. The dose delivered may vary considerably between spacers, so consider this if changing from one spacer to another.

The only possible inhalation technique in young children is tidal breathing. The optimal number of breaths required to empty the spacer depends on the child's tidal volume, and the dead space and volume of the spacer. Generally 5–10 breaths will be sufficient per actuation. The way a spacer is used can markedly affect the amount of drug delivered:

- Spacer size may affect the amount of drug available for inhalation in a complex way depending on the drug prescribed and the pMDI used. Young children can use spacers of all sizes, but theoretically a lower volume spacer (<350 mL) is advantageous in very young children.
- A single pMDI actuation should be delivered at a time, with the inhaler shaken in between. Multiple actuations into the spacer before inhalation may markedly reduce the amount of drug inhaled.
- Delay between actuating the pMDI into the spacer and inhalation may reduce the amount of drug available. This varies between spacers, but to maximize drug delivery, inhalation should start as soon as possible after actuation. If a health care provider or a carer is giving the medication to the child, they should actuate the pMDI only when the child is ready and the spacer is in the child's mouth.
- If a face mask is used it must be fitted tightly around the child's mouth and nose, to avoid loss of drug.
- Ensure that the valve is moving while the child is breathing through the spacer.
- Static charge may accumulate on some plastic spacers, attracting drug particles and reducing lung delivery. This charge can be reduced by washing the spacer with detergent (without rinsing) and allowing it to air dry, but it may re-accumulate over time. Spacers made of anti-static materials or metals are less subject to this problem. If a patient or health care provider carries a new plastic spacer for emergency use, it should be regularly washed with detergent (e.g. monthly) to reduce static charge.

Nebulizers, the only viable alternative delivery systems in children, are reserved for the minority of children who cannot be taught effective use of a spacer device. If a nebulizer is used for delivery of ICS, it should be used with a mouthpiece to avoid the medication reaching the eyes.

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Box 6-7. Choosing an inhaler device for children 5 years and younger

Age	Preferred device	Alternate device
0–3 years	Pressurized metered-dose inhaler plus dedicated spacer with face mask	Nebulizer with face mask
4–5 years	Pressurized metered-dose inhaler plus dedicated spacer with mouthpiece	Pressurized metered-dose inhaler plus dedicated spacer with face mask or nebulizer with mouthpiece or face mask

ASTHMA SELF-MANAGEMENT EDUCATION FOR CARERS OF YOUNG CHILDREN

Asthma self-management education should be provided to family members and carers of wheezy children 5 years and younger when wheeze is suspected to be caused by asthma. An educational program should contain:

- A basic explanation about asthma and the factors that influence it
- Training about correct inhalation technique
- Information on the importance of the child's adherence to the prescribed medication regimen
- A written asthma action plan.

Crucial to a successful asthma education program are a partnership between patient/carer and health care providers, with a high level of agreement regarding the goals of treatment for the child, and intensive follow-up (Evidence D).[16]

Written asthma action plans

Asthma action plans should be provided for the family/carers of all children with asthma, including those aged 5 years and younger (Evidence D). Action plans, developed through collaboration between an asthma educator, the health care provider and the family, have been shown to be of value in older children,[496] although they have not been extensively studied in children of 5 years and younger. A written asthma action plan includes:

- A description of how the parent or carer can recognize when symptom control is deteriorating
- The medications to administer
- When and how to obtain medical care, including telephone numbers of services available for emergencies (e.g. doctors' offices, emergency rooms and hospitals, ambulance services and emergency pharmacies). Details of treatments that can be initiated at home are provided in the following section, *Part C: Management of worsening asthma and exacerbations in children 5 years and younger*.

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PART C. MANAGEMENT OF WORSENING ASTHMA AND EXACERBATIONS IN CHILDREN 5 YEARS AND YOUNGER

KEY POINTS

- Early symptoms of exacerbations in young children may include increased symptoms; increased coughing, especially at night; lethargy or reduced exercise tolerance; impaired daily activities including feeding; and a poor response to reliever medication.
- Give a written asthma action plan to parents/carers of young children with asthma so they can recognize a severe attack, start treatment, and identify when urgent hospital treatment is required.
  - Initial treatment at home is with inhaled short-acting beta$_2$-agonist (SABA), with review after 1 hour or earlier.
  - Parents/carers should seek urgent medical care if the child is acutely distressed, lethargic, fails to respond to initial bronchodilator therapy, or is worsening, especially in children <1 year of age.
  - Medical attention should be sought on the same day if inhaled SABA is needed more often than 3-hourly or for more than 24 hours.
  - There is only weak evidence to support parent-initiated oral corticosteroids.
- In children presenting to primary care or an acute care facility with an asthma exacerbation:
  - Assess severity of the exacerbation while initiating treatment with SABA (2–6 puffs every 20 minutes for first hour) and oxygen (to maintain saturation 94–98%).
  - Recommend immediate transfer to hospital if there is no response to inhaled SABA within 1–2 hours; if the child is unable to speak or drink or has subcostal retractions or cyanosis; if resources are lacking in the home; or if oxygen saturation is <92% on room air.
  - Give oral prednisone/prednisolone 1–2 mg/kg/day for up to 5 days, up to a maximum of 20 mg/day for 0–2 years, and 30 mg/day for 3–5 years.
- Children who have experienced an asthma exacerbation are at risk of further exacerbations. Follow up should be arranged within 1 week of an exacerbation to plan ongoing asthma management.

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DIAGNOSIS OF EXACERBATIONS

A flare-up or exacerbation of asthma in children 5 years and younger is defined as an acute or sub-acute deterioration in symptom control that is sufficient to cause distress or risk to health, and necessitates a visit to a health care provider or requires treatment with systemic corticosteroids. They are sometimes called ‘episodes’.

Early symptoms of an exacerbation may include any of the following:

- 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.[497]

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 carers to recognize worsening asthma and initiate treatment, recognize when it is severe, identify when urgent hospital treatment is necessary, and provide recommendations for follow up (Evidence D). The action plan should include specific information about medications and dosages and when and how to access medical care.

Need for urgent medical attention

Parents/carers should know that immediate medical attention should be sought if:

- The child is acutely distressed
- The child's symptoms are not relieved promptly by inhaled bronchodilator
- The period of relief after doses of SABA becomes progressively shorter
- A child younger than 1 year requires repeated inhaled SABA over several hours.

Initial treatment at home

Inhaled SABA via a mask or spacer, and review response

The parent/carer should initiate treatment with two puffs of inhaled SABA (200 mcg salbutamol or equivalent), given one puff at a time via a spacer device with or without a facemask (Evidence D). This may be repeated a further two times at 20 minute intervals, if needed. The child should be observed by the family/carer and, if improving, maintained in a restful and reassuring atmosphere for an hour or more. Medical attention should be sought urgently if any of the features listed above apply; or on the same day if more than 6 puffs of inhaled SABA are required for symptom relief within the first 2 hours, or if the child has not recovered after 24 hours.

Family/carer-initiated corticosteroids

Although practiced in some parts of the world, the evidence to support the initiation of oral corticosteroid (OCS) treatment by family/carers in the home management of asthma exacerbations in children is weak.[498-502] Because of the high potential for side-effects, especially if the treatment is continued inappropriately or is given frequently, family-administered OCS or high dose ICS should be considered only where the health care provider is confident that the medications will be used appropriately, and the child is closely monitored for side-effects (see p.119. Emergency treatment and initial pharmacotherapy).

Leukotriene receptor antagonists

In children aged 2–5 years with intermittent viral wheezing, one study found that a short course of an oral LTRA (for 7–20 days, commenced at the start of an URTI or the first sign of asthma symptoms) reduced symptoms, health care utilization and time off work for the carer.[503] In contrast another study found no significant effect on episode-free days (primary outcome), OCS use, health care utilization, quality of life or hospitalization in children with or without a positive Asthma Predictive Index (API). However, activity limitation and a symptom trouble score were significantly improved, particularly in children with a positive API.[504]

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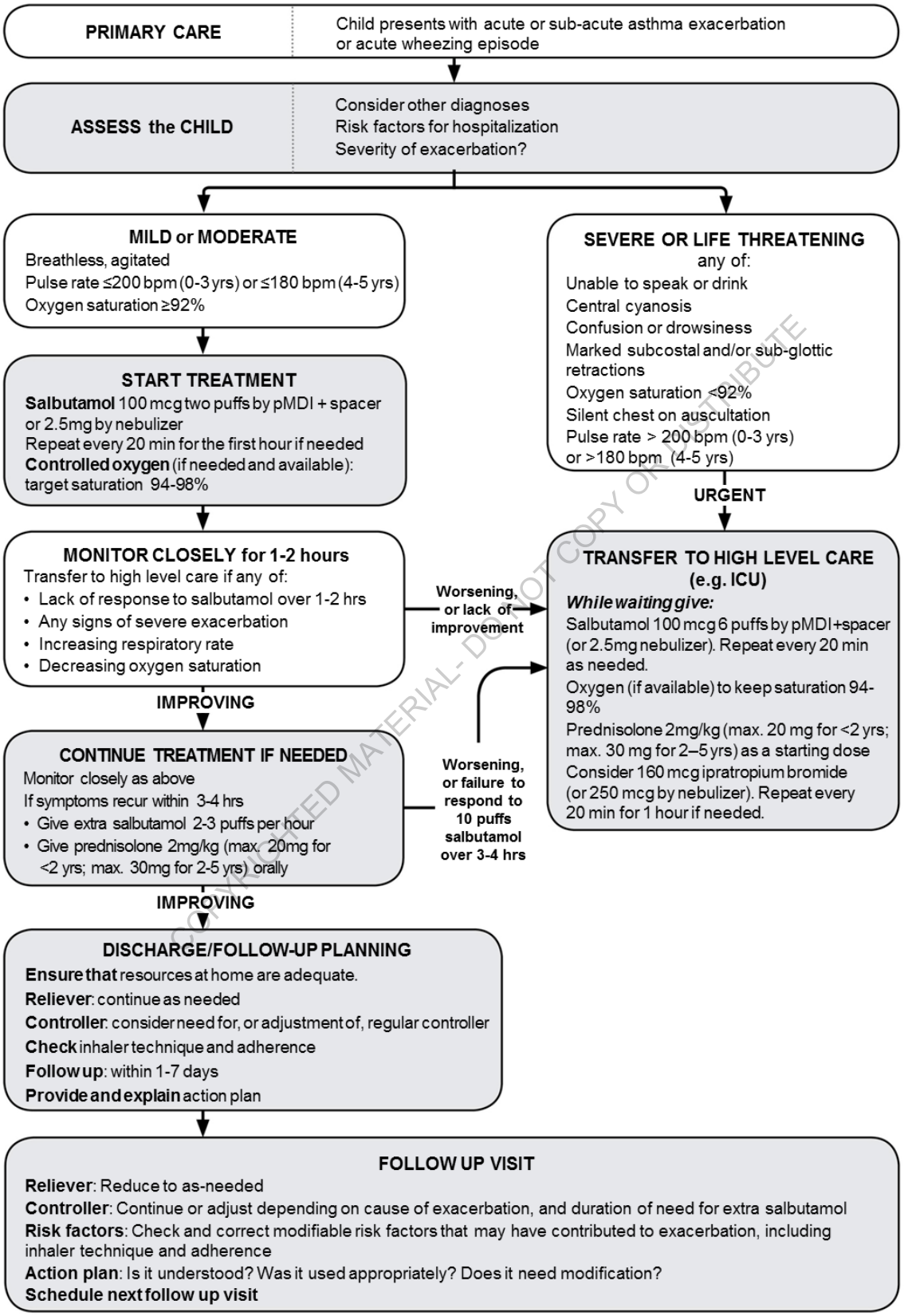
Box 6-8. Primary care management of acute asthma or wheezing in children 5 years and younger



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PRIMARY CARE OR HOSPITAL MANAGEMENT OF ACUTE ASTHMA EXACERBATIONS

Assessment of exacerbation severity

Conduct a brief history and examination concurrently with the initiation of therapy (Box 6-8, Box 6-9). The presence of any of the features of a severe exacerbation listed in Box 6-9 are an indication of the need for urgent treatment and immediate transfer to hospital (Evidence D). Oxygen saturation from pulse oximetry of <92% on presentation (before oxygen or bronchodilator treatment) is associated with high morbidity and likely need for hospitalization; saturation of 92–95% is also associated with higher risk.[378] Agitation, drowsiness and confusion are features of cerebral hypoxemia. A quiet chest on auscultation indicates minimal ventilation, insufficient to produce a wheeze.

Several clinical scoring systems such as PRAM (Preschool Respiratory Assessment Measure) and PASS (Pediatric Asthma Severity Score) have been developed for assessing the severity of acute asthma exacerbations in children.[505]

Box 6-9. Initial assessment of acute asthma exacerbations in children 5 years and younger

Symptoms	Mild	Severe*
Altered consciousness	No	Agitated, confused or drowsy
Oximetry on presentation (SaO_2)**	>95%	<92%
Speech†	Sentences	Words
Pulse rate	<100 beats/minute	>200 beats/minute (0–3 years)
		>180 beats/minute (4–5 years)
Central cyanosis	Absent	Likely to be present
Wheeze intensity	Variable	Chest may be quiet

*Any of these features indicates a severe asthma exacerbation. **Oximetry before treatment with oxygen or bronchodilator.
† The normal developmental capability of the child must be taken into account.

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Indications for immediate transfer to hospital

Children with features of a severe exacerbation that fail to resolve within 1–2 hours despite repeated dosing with inhaled SABA, with or without OCS, must be referred to hospital for observation and further treatment (Evidence D). Other indications are respiratory arrest or impending arrest; lack of supervision in the home or doctor's office; and recurrence of signs of a severe exacerbation within 48 hours (particularly if treatment with OCS has already been given). In addition, early medical attention should be sought for children less than 2 years of age as the risk of dehydration and respiratory fatigue is increased (Box 6-10).

Emergency treatment and initial pharmacotherapy

Oxygen

Treat hypoxemia urgently with oxygen by face mask to achieve and maintain percutaneous oxygen saturation 94–98% (Evidence A). To avoid hypoxemia during changes in treatment, children who are acutely distressed should be treated immediately with oxygen and SABA (2.5 mg of salbutamol or equivalent diluted in 3 mL of sterile normal saline) delivered by an oxygen-driven nebulizer (if available). This treatment should not be delayed, and may be given before the full assessment is completed.

Box 6-10. Indications for immediate transfer to hospital for children 5 years and younger

Immediate transfer to hospital is indicated if a child ≤5 years with asthma has ANY of the following*:*

• At initial or subsequent assessment
  o Child is unable to speak or drink
  o Cyanosis
  o Subcostal retraction
  o Oxygen saturation <92% when breathing room air
  o Silent chest on auscultation
• Lack of response to initial bronchodilator treatment
  o Lack of response to 6 puffs of inhaled SABA (2 separate puffs, repeated 3 times) over 1–2 hours
  o Persisting tachypnea* despite three administrations of inhaled SABA, even if the child shows other clinical signs of improvement
• Social environment that impairs delivery of acute treatment, or parent/carer unable to manage acute asthma at home

*Normal respiratory rates: <60 breaths/minute in children 0–2 months; <50 breaths/minute in children 2–12 months; <40 breaths/minute in children 1–5 years.

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Bronchodilator therapy

The initial dose of SABA may be given by a pMDI with spacer and mask or mouthpiece or an air-driven nebulizer; or, if oxygen saturation is low, by an oxygen-driven nebulizer (as described above). For most children, pMDI plus spacer is favored as it is more efficient than a nebulizer for bronchodilator delivery[495,506] (Evidence A). The initial dose of SABA is two puffs of salbutamol (100 mcg per puff) or equivalent, except in acute, severe asthma when six puffs should be given. When a nebulizer is used, a dose of 2.5 mg salbutamol solution is recommended. The frequency of dosing depends on the response observed over 1–2 hours (see below).

For children with moderate-severe exacerbations and a poor response to initial SABA, ipratropium bromide may be added, as 2 puffs of 80mcg (or 250mcg by nebulizer) every 20 minutes for 1 hour only.[401]

Magnesium sulfate

The role of magnesium sulfate is not yet established for children 5 years and younger, because there are few studies in this age group. Nebulized isotonic magnesium sulfate may be considered as an adjuvant to standard treatment with nebulized salbutamol and ipratropium in the first hour of treatment for children ≥2 years old with acute severe asthma (e.g. oxygen saturation <92%, Box 6-9, p.118), particularly those with symptoms lasting <6 hours.[507] Intravenous magnesium sulfate in a single dose of 40-50 mg/kg (maximum 2 g) by slow infusion (20–60 minutes) has also been used.

Assessment of response and additional bronchodilator treatment

Children with a severe asthma exacerbation must be observed for at least 1 hour after initiation of treatment, at which time further treatment can be planned.

- *If symptoms persist after initial bronchodilator*: a further 2–6 puffs of salbutamol (depending on severity) may be given 20 minutes after the first dose and repeated at 20-minute intervals for an hour. Failure to respond at 1 hour, or earlier deterioration, should prompt urgent admission to hospital and a short-course of oral corticosteroids (Evidence D).

- *If symptoms have improved by 1 hour but recur within 3–4 hours*: the child may be given more frequent doses of bronchodilator (2–3 puffs each hour), and oral corticosteroids should be given. The child may need to remain in the emergency room, or, if at home, should be observed by the family/carer and have ready access to emergency care. Children who fail to respond to 10 puffs of inhaled SABA within a 3–4 hour period should be referred to hospital (Evidence D).
- *If symptoms resolve rapidly after initial bronchodilator and do not recur for 1–2 hours*: no further treatment may be required. Further SABA may be given every 3–4 hours (up to a total of 10 puffs/24 hours) and, if symptoms persist beyond 1 day, other treatments including inhaled or oral corticosteroids are indicated (Evidence D), as outlined below.

Box 6-11.Initial management of asthma exacerbations in children 5 years and younger

Therapy	Dose and administration
Supplemental oxygen	24% delivered by face mask (usually 1 L/minute) to maintain oxygen saturation 94–98%
Short-acting beta$_2$-agonist (SABA)	2–6 puffs of salbutamol by spacer, or 2.5 mg of salbutamol by nebulizer, every 20 minutes for first hour*, then reassess severity. If symptoms persist or recur, give an additional 2–3 puffs per hour. Admit to hospital if >10 puffs required in 3–4 hours.
Systemic corticosteroids	Give initial dose of oral prednisolone (1–2 mg/kg up to a maximum 20 mg for children <2 years old; 30 mg for children 2–5 years) OR, intravenous methylprednisolone 1 mg/kg 6-hourly on day 1
Additional options in the first hour of treatment	
Ipratropium bromide	For children with moderate-severe exacerbations, 2 puffs of ipratropium bromide 80mcg (or 250mcg by nebulizer) every 20 minutes for 1 hour only
Magnesium sulfate	Consider nebulized isotonic magnesium sulfate (150mg) 3 doses in the first hour of treatment for children aged ≥2 years with severe exacerbation (Box 6-9, p.118)

*If inhalation is not possible an intravenous bolus of terbutaline 2 mcg/kg may be given over 5 minutes, followed by continuous infusion of 5 mcg/kg/hour[508] (Evidence C). The child should be closely monitored, and the dose should be adjusted according to clinical improvement and side-effects. See below for additional and ongoing treatment, including controller therapy.

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Additional treatment

When treatment in addition to SABA is required for an exacerbation, the options available for children in this age group include ICS; a short course of oral corticosteroid; and/or LTRA (see p.116). However, the clinical benefit of these interventions – particularly on endpoints such as hospitalizations and longer-term outcomes – has not been impressive.

Maintain current controller treatment (if prescribed)

Children who have been prescribed maintenance therapy with ICS, LTRA or both should continue to take the prescribed dose during and after an exacerbation (Evidence D).

Inhaled corticosteroids

For children not previously on ICS, an initial dose of ICS twice the low daily dose indicated in Box 6-6 (p.112) may be given and continued for a few weeks or months (Evidence D). Some studies have used high dose ICS (1600 mcg/day, preferably divided into four doses over the day and given for 5–10 days) as this may reduce the need for

OCS.[362,483,484,509,510] In one study of hospitalized pre-school children, adding nebulized budesonide to existing treatment (including OCS) reduced length of stay.[511] However, the potential for side-effects with high dose ICS should be taken into account, especially if used repeatedly, and the child should be monitored closely. For those children already on ICS, doubling the dose was not effective in a small study in older children,[360] and there are no studies in children 5 years and younger; this approach should be reserved mainly for individual cases, and should always involve regular follow up (Evidence D).

Oral corticosteroids

For children with severe exacerbations, a dose of OCS equivalent to prednisolone 1–2 mg/kg/day, with a maximum of 20 mg/day for children under 2 years of age and 30 mg/day for children aged 2–5 years, is currently recommended (Evidence A),[512] although several studies have failed to show any benefits when given earlier (e.g. by parents) during periods of worsening wheeze (Evidence D).[498-501,513,514] A 3–5 day course is sufficient in most children and can be stopped abruptly (Evidence D).

Regardless of whether the intervention is corticosteroids or LTRA, the severity of symptoms must be carefully monitored. The sooner therapy is started in relation to the onset of symptoms, the more likely it is that the impending exacerbation may be clinically attenuated or prevented.

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Discharge and follow up after an exacerbation

Before discharge, the condition of the child should be stable (e.g. he/she should be out of bed and able to eat and drink without problems).

Children who have recently had an asthma exacerbation are at risk of further episodes and require follow up. The purpose is to ensure complete recovery, to establish the cause of the exacerbation, and, when necessary, to establish appropriate maintenance treatment and adherence (Evidence D).

Prior to discharge from the emergency department or hospital, family/carers should receive the following advice and information (all are Evidence D).

- Instruction on recognition of signs of recurrence and worsening of asthma. The factors that precipitated the exacerbation should be identified, and strategies for future avoidance of these factors implemented.
- A written, individualized action plan, including details of accessible emergency services.
- Careful review of inhaler technique.
- Further treatment advice explaining that:
  - SABAs should be used on an as-needed basis, but the daily requirement should be recorded to ensure it is being decreased over time to pre-exacerbation levels
  - ICS has been initiated where appropriate (at twice the low initial dose in Box 6-6 (p.112) for the first month after discharge, then adjusted as needed) or continued, for those previously prescribed controller medication.
- A supply of SABA and, where applicable, the remainder of the course of oral corticosteroid, ICS or LTRA.
- A follow-up appointment within 2–7 days and another within 1–2 months, depending on the clinical, social and practical context of the exacerbation.

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Chapter 7.

Primary prevention of asthma

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KEY POINTS

- The development and persistence of asthma are driven by gene–environment interactions. For children, a 'window of opportunity' exists *in utero* and in early life, but intervention studies are limited.
- For intervention strategies that include allergen avoidance:
  - Strategies directed at a single allergen have not been effective
  - Multifaceted strategies may be effective, but the essential components have not been identified.
- Current recommendations, based on high quality evidence or consensus, include:
  - Avoid exposure to environmental tobacco smoke during pregnancy and the first year of life
  - Encourage vaginal delivery
  - Advise breast-feeding for its general health benefits (not necessarily for asthma prevention)
  - Where possible, avoid use of paracetamol (acetaminophen) and broad-spectrum antibiotics during the first year of life.

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FACTORS CONTRIBUTING TO THE DEVELOPMENT OF ASTHMA

Asthma is generally believed to be a heterogeneous disease whose inception and persistence is driven by gene–environment interactions. The most important of these interactions may occur in early life and even *in-utero*. There is consensus that a 'window of opportunity' exists during pregnancy and early in life when environmental factors may influence asthma development. Multiple environmental factors, both biological and sociological, may be important in the development of asthma. Data supporting the role of environmental risk factors for the development of asthma include a focus on: nutrition, allergens (both inhaled and ingested), pollutants (particularly environmental tobacco smoke), microbes, and psychosocial factors. Additional information about factors contributing to the development of asthma, including occupational asthma, is found in Appendix Chapter 2.

'Primary prevention' refers to preventing the onset of disease. This chapter focuses on primary prevention in children. See p.67 and review articles[31] for strategies for preventing occupational asthma.

FACTORS ASSOCIATED WITH INCREASED RISK OF ASTHMA IN CHILDREN

Nutrition

Maternal diet and weight gain during pregnancy

For some time, the mother's diet during pregnancy has been a focus of concern relating to the development of allergy and asthma in the child. There is no firm evidence that ingestion of any specific foods during pregnancy increases the risk for asthma. However, a recent study of a pre-birth cohort observed that maternal intake of foods commonly considered allergenic (peanut and milk) was associated with a *decrease* in allergy and asthma in the offspring.[515] 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.[516,517] 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.[518] No dietary changes during pregnancy are therefore recommended for prevention of allergies or asthma.

Data suggest that maternal obesity and weight gain during pregnancy pose an increased risk for asthma in children. A recent meta-analysis[519] showed that maternal obesity in pregnancy was associated with higher odds of ever asthma or wheeze or current asthma or wheeze; each 1 kg/m2 increase in maternal BMI was associated with a 2% to 3% increase in the odd of childhood asthma. High gestational weight gain was associated with higher odds of ever asthma or wheeze. However, no recommendations can be made at present, as unguided weight loss in pregnancy should not be encouraged.

Breast-feeding

Despite the existence of many studies reporting a beneficial effect of breast-feeding on asthma prevention, results are conflicting,[298] and caution should be taken in advising families that breast-feeding will prevent asthma.[520] Breast-feeding decreases wheezing episodes in early life; however, it may not prevent development of persistent asthma (Evidence D). Regardless of its effect on development of asthma, breast-feeding should be encouraged for all of its other positive benefits (Evidence A).

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 intake of vitamin D, and of vitamin E, was associated with lower risk of wheezing illnesses in children.[521] This was not confirmed in randomized controlled trials of vitamin D supplementation in pregnancy, although a significant effect was not ruled out.[522,523] Evidence is still inconclusive.

Delayed introduction of solids

Beginning in the 1990s, many national pediatric agencies and societies recommended delay of introduction of solid food, especially for children at a high risk for developing allergy. Current guidelines do not recommend strict avoidance of high-risk foods,[298] but carefully controlled, prospective studies are needed to conclusively resolve this controversy.

Probiotics

A meta-analysis provided insufficient evidence to recommend probiotics for the prevention of allergic disease (asthma, rhinitis, eczema or food allergy).[524]

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Inhalant allergens

Sensitization to indoor, inhaled aero-allergens is generally more important than sensitization to outdoor allergens for the presence of, and/or development of, asthma. While there appears to be a linear relationship between exposure and sensitization to house dust mite,[525,526] the relationship for animal allergen appears to be more complex.[298] Some studies have found that exposure to pet allergens is associated with increased risk of sensitization to these allergens,[527,528] and of asthma and wheezing.[529,530] By contrast, other studies have demonstrated a *decreased* risk of developing allergy with exposure to pets.[531,532] A review of over 22,000 school-age children from 11 birth cohorts in Europe found no correlation between pets in the homes early in life and higher or lower prevalence of asthma in children.[533] For children at risk of asthma, dampness, visible mold and mold odor in the home environment are associated with increased risk of developing asthma.[534] Overall, there are insufficient data to recommend efforts to either reduce or increase pre-natal or early-life exposure to common sensitizing allergens, including pets, for the prevention of allergies and asthma.

Birth cohort studies provide some evidence for consideration. A meta-analysis found that studies of interventions focused on reducing exposure to a single allergen did not significantly affect asthma development, but that multifaceted interventions such as in the Isle of Wight study,[535] the Canadian Asthma Primary Prevention Study,[536] and the Prevention of Asthma in Children study[537] were associated with lower risk of asthma diagnosis in children younger than 5 years.[538] Two multifaceted studies that followed children beyond 5 years of age demonstrated a significant protective effect both before and after the age of 5 years.[535,539] The Isle of Wight study has shown a continuing positive benefit for early-life intervention through to 18 years of age;[540] however, exactly which components of the intervention were important and which specific mechanistic changes were induced remain elusive.

Pollutants

Maternal smoking during pregnancy is the most direct route of pre-natal environmental tobacco smoke exposure.[541] A meta-analysis concluded that pre-natal smoking had its strongest effect on young children, whereas post-natal maternal smoking seemed relevant only to asthma development in older children.[542]

Exposure to outdoor pollutants, such as living near a main road, is associated with increased risk of asthma.[543,544]

Microbial effects

The 'hygiene hypothesis', and the more recently coined 'microflora hypothesis' and 'biodiversity hypothesis',[545] 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.[546] The risk of asthma is also reduced in children whose bedrooms have high levels of bacterial-derived lipopolysaccharide endotoxin.[547,548] Similarly, children in homes with ≥2 dogs or cats are less likely to be allergic than those in homes without dogs or cats.[532] 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 Caesarian section than those born vaginally.[549] This may relate to differences in the infant gut microbiota according to their mode of delivery.[550]

Medications and other factors

Antibiotic use during pregnancy and in infants and toddlers has been associated with the development of asthma later in life,[551-553] although not all studies have shown this association.[554] Intake of the analgesic, paracetamol (acetaminophen), may be associated with asthma in both children and adults,[555] although exposure during infancy may be confounded by use of paracetamol for respiratory tract infections.[555] Frequent use of paracetamol by pregnant women has been associated with asthma in their children.[556]

There is no evidence that vaccinations increase the risk of a child developing asthma.

Psychosocial factors

The social environment to which children are exposed may also contribute to the development and severity of asthma. Maternal distress that persists from birth through to early school age has been associated with an increased risk of the child developing asthma.[551]

ADVICE ABOUT PRIMARY PREVENTION OF ASTHMA

Based on the results of cohort and observational studies,[557] and a GRADE-based analysis for the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines,[298] parents enquiring about how to reduce the risk of their children developing asthma can be provided with the advice summarized in Box 7-1.

There is interest in investigating other strategies for prevention of asthma, based on known associations. For example, respiratory syncytial virus infection is associated with subsequent recurrent wheeze, and preventative treatment of premature infants with monthly injections of the monoclonal antibody, palivizumab, (prescribed for prophylaxis of respiratory syncytial virus) is associated with a reduction in recurrent wheezing in the first year of life.[558]

Possibly the most important factor is the need to provide a positive, supportive environment that decreases stress, and which encourages families to make choices with which they feel comfortable.

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

Parents enquiring about how to reduce the risk of their child developing asthma can be provided with the following advice:

- Children should not be exposed to environmental tobacco smoke during pregnancy or after birth
- Vaginal delivery should be encouraged where possible
- Breast-feeding is advised, for reasons other than prevention of allergy and asthma
- The use of broad-spectrum antibiotics during the first year of life should be discouraged.

Chapter 8.

Implementing asthma management strategies into health systems

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KEY POINTS

- In order to improve asthma care and patient outcomes, evidence-based recommendations must not only be developed, but also disseminated and implemented at a national and local level, and integrated into clinical practice.
- Recommendations for implementing asthma care strategies are based on many successful programs worldwide.
- Implementation requires an evidence-based strategy involving professional groups and stakeholders, and should take into account local cultural and socioeconomic conditions.
- Cost-effectiveness of implementation programs should be assessed so a decision can be made to pursue or modify them.
- Local adaptation and implementation of asthma care strategies is aided by the use of tools developed for this purpose.

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INTRODUCTION

Due to the exponential increase in medical research publications, practical syntheses are needed to guide policy makers and health care professionals in delivering evidence-based care. When asthma care is consistent with evidence-based recommendations, outcomes improve.[140,559,560] The *Global Strategy for Asthma Management and Prevention* is a resource document for health care professionals to establish the main goals of asthma treatment and the actions required to ensure their fulfilment, as well as to facilitate the achievement of standards for quality asthma care.

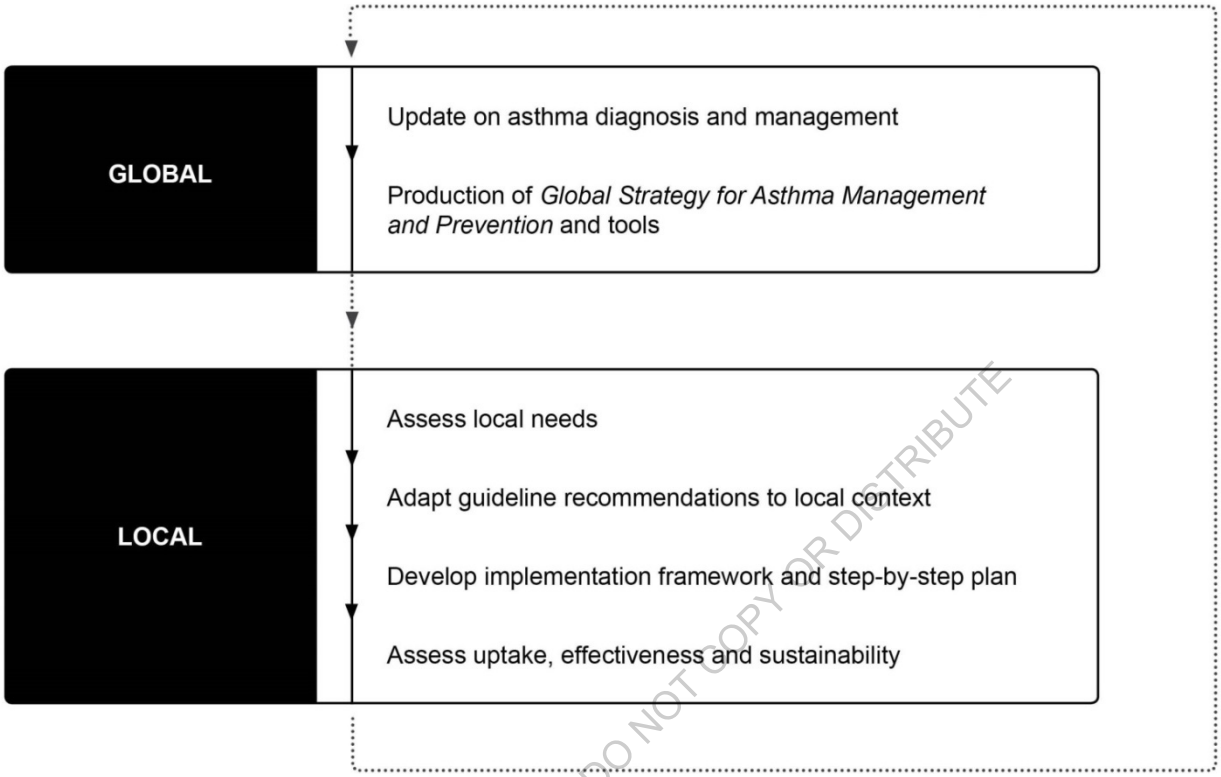
The recent adoption of rigorous methodologies such as GRADE[2] for the development of clinical practice recommendations, and the ADAPTE[561] and similar approaches for assisting the adaptation of recommendations for local country and regional conditions, has assisted in reducing biased opinion as the 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.[562] Further, there is generally very limited high quality evidence addressing the many decision nodes in comprehensive clinical practice guidelines, particularly in developing countries.

ADAPTING AND IMPLEMENTING ASTHMA CLINICAL PRACTICE GUIDELINES

Implementation of asthma management strategies may be carried out at a national, regional or local level.[563] Ideally, implementation should be a multidisciplinary effort involving many stakeholders, and using cost-effective methods of knowledge translation.[563-565] Each implementation initiative needs to consider the nature of the local health system and its resources (e.g. human, infrastructure, available treatments) (Box 8-1). Moreover, goals and implementation strategies will need to vary from country to country and within countries, based on economics, culture and the physical and social environment. Priority should be given to high-impact interventions.

Specific steps need to be followed before clinical practice recommendations can be embedded into local clinical practice and become the standard of care, particularly in low resource settings. The individual steps are summarized in Box 8-2, and a detailed description of the processes involved in each step can be found in the GINA Appendix Chapter 7, available online at www.ginasthma.org.

Box 8-1. Approach to implementation of the Global Strategy for Asthma Management and Prevention



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Box 8-2. Essential elements required to implement a health-related strategy

Steps in implementing an asthma strategy into a health system
1. Develop a multidisciplinary working group 2. Assess the current status of asthma care delivery, care gaps and current needs 3. Select the material to be implemented, agree on main goals, identify key recommendations for diagnosis and treatment, and adapt them to the local context or environment 4. Identify barriers to, and facilitators of, implementation 5. Select an implementation framework and its component strategies 6. Develop a step-by-step implementation plan: o Select target populations and evaluable outcomes o Identify local resources to support implementation o Set timelines o Distribute tasks to members o Evaluate outcomes 7. Continuously review progress and results to determine if the strategy requires modification

BARRIERS AND FACILITATORS

Many barriers to, and facilitators of, implementation procedures have been described.[565-568] Some of the barriers to implementation of evidence-based asthma management relate to the delivery of care, while others relate to patients' attitudes (see Box 8-3, and examples in Appendix Chapter 7, Box 7-1). Cultural and economic barriers can particularly affect the application of recommendations.

Box 8-3. Examples of barriers to the implementation of evidence-based recommendations

Health care providers	Patients
Insufficient knowledge of recommendations 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	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

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EXAMPLES OF HIGH IMPACT IMPLEMENTATION INTERVENTIONS

Ideally, interventions should be applied at the level of both the patient and the health care provider and, where relevant, the health system. Studies of the most effective means of medical education show that it may be difficult to induce changes in clinical practice. Examples of highly effective interventions are shown in Box 8-4.

Box 8-4 Examples of high-impact interventions in asthma management

- Optimized ICS use for patients with a recent hospital admission and/or severe asthma[569]
- Early treatment with ICS, guided self-management, reduction in exposure to tobacco smoke, improved access to asthma education[140]
- Self-inking stamp prompting assessment of asthma control and treatment strategies[570]
- Use of individualized written asthma action plans as part of self-management education[265]
- An evidence-based care process model for acute and chronic pediatric asthma management, implemented at multiple hospitals[571]

ICS: inhaled corticosteroids

EVALUATION OF THE IMPLEMENTATION PROCESS

An important part of the implementation process is to establish a means of evaluating the effectiveness of the program and any improvements in quality of care (see Appendix Chapter 7, Box A7-3). The Cochrane Effective Practice and Organization of Care Group (EPOC) offers suggestions on how to assess the effectiveness of interventions.[572]

Evaluation involves surveillance of traditional epidemiological parameters, such as morbidity and mortality, as well as specific audits of both process and outcome within different sectors of the health care system. Each country should determine its own minimum sets of data to audit health outcomes.

HOW CAN GINA HELP WITH IMPLEMENTATION?

GINA, through the work of its Dissemination and Implementation Committee, assists in the processes of adaptation and implementation of the recommendations in the *Global Strategy for Asthma Management and Prevention* report. The GINA report provides an annually-updated summary of evidence relevant to asthma diagnosis, management and prevention that may be used in the formulation and adaptation of local guidelines; where evidence is lacking, the GINA report provides approaches for consideration. A web-based implementation 'toolkit' will provide a template and guide to local adaptation and implementation of these recommendations, together with materials and advice from successful examples of asthma clinical practice guideline development and implementation in different settings.

Educational materials and tools based on the *Global Strategy for Asthma Management and Prevention* are available in several forms and can be found on the GINA Website (www.ginasthma.org).

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