Global Strategy for Asthma Management and Prevention (2022 update)

The reader acknowledges that this report is intended as an evidence-based asthma management strategy, for the use of health professionals and policy-makers. It is based, to the best of our knowledge, on current best evidence and medical knowledge and practice at the date of publication. When assessing and treating patients, health professionals are strongly advised to use their own professional judgment, and to take into account local and 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, 2022. Available from: www.ginasthma.org

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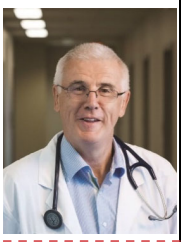
Preface

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.

The Global Initiative for Asthma was established in 1993 by the National Heart, Lung, and Blood Institute and the World Health Organization, with the aim of increasing awareness about asthma and providing a mechanism to translate scientific evidence into improved asthma care worldwide. 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. GINA"s flagship publication, the Global Strategy for Asthma Management and Prevention ('GINA report'), first published in 1995,[1] has been updated annually since 2002, with pivotal changes in 2006, 2014 and 2019. The main GINA report contains recommendations for clinical practice and brief supporting evidence, while additional resources and supporting material are provided online at www.ginasthma.org. Publications and resources based on the GINA reports have been translated into many languages. GINA is independent of industry. Its work is supported only by income generated from the sale and licensing of its resources.

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, we recognize 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 2015. Through their tireless contributions, Dr Hurd and Dr Lenfant fostered and facilitated the development of GINA. In 2016, we were delighted to welcome Ms Rebecca Decker, BS, MSJ, as the Program Director (now Executive Director) for GINA, and we appreciate the commitment and skills that she has brought to this demanding role. The members of the GINA Committees are solely responsible for the statements and conclusions presented in this publication. They receive no honoraria or reimbursement of expenses for their many hours of work in reviewing evidence or attending meetings. The GINA Advocates and Assembly, dedicated asthma care experts from many countries, work with the Science Committee, the Board of Directors and the Dissemination and Implementation Committee to promote international collaboration and dissemination of information about asthma.



We share the sadness that the global asthma community feels at the loss of Mark FitzGerald (18 June 1955–18 January 2022). In his 25 years of work with GINA, Mark was a compassionate leader and strong advocate for improving asthma diagnosis and management. Mark's guidance will be missed dearly but his research, legacy, and commitment to helping the world breathe better remain a guiding force. In Mark's honor, GINA is establishing a scholarship for junior researchers from low- or middle-income countries.

In spite of all of the above efforts, and the availability of effective therapies, international data provide ongoing evidence for suboptimal asthma control in many countries. The majority of the burden of asthma morbidity and mortality occurs in low- and middle-income countries, and is avoidable. 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, effective quality-assured medications, and to develop means to implement and evaluate effective asthma management programs.

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

Helen K Reddel, MBBS PhD
Chair, GINA Science Committee

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

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Ghent, Belgium¶

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

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 normally meets twice yearly in conjunction with the American Thoracic Society (ATS) and European Respiratory Society (ERS) international conferences, to review asthma-related scientific literature. During COVID-19, meetings of the Science Committee were held online each month. Statements of interest for Committee members are found on the GINA website www.ginasthma.org.

PROCESSES FOR UPDATES AND REVISIONS OF THE GINA REPORT

Literature search

A PubMed search is performed twice a year, each covering the previous 18 months, using filters established by the Science Committee. The search terms include asthma, all ages, only items with abstracts, clinical trial or meta-analysis or systematic review, and human. The search is not limited to specific PICOT questions (Population, Intervention, Comparison, Outcomes, Time). The 'clinical trial' publication type includes not only conventional randomized controlled trials, but also pragmatic, real-life and observational studies. Systematic reviews include, but are not limited to, those conducted using GRADE methodology[2] including, where relevant, guidelines documents published by other international organizations. The respiratory community is also invited to submit any other fully published peer-reviewed publications that they believe should be considered, providing the full paper is submitted in (or translated into) English; however, because of the comprehensive process for literature review, such *ad hoc* submissions have rarely resulted in substantial changes to the report.

Systematic reviews

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

Literature screening and review

Each article identified by the literature search, after removal of duplicates and those already reviewed, is pre-screened in Covidence for relevance and major quality issues by the Editorial Assistant (a medical librarian) and by at least two non-conflicted members of the Science Committee. Each publication selected from screening is allocated to be reviewed for quality and for relevance to the GINA strategy by at least two members of the Science Committee, neither of whom may be an author (or co-author) or declare a conflict of interest in relation to the publication. Articles that have been accepted for publication and are online in advance of print are eligible for full text review provided the approved/corrected copy-edited proof is available. All members receive a copy of all of the abstracts and full text publication, and non-conflicted members have the opportunity to provide comments during the pre-meeting review period. Members evaluate the abstract and the full text publication, and answer written questions in a review template about whether the scientific data impact on GINA recommendations, and if so, what specific changes should be made. In 2020, the CASP checklist was

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provided in the review template to assist in evaluation of systematic reviews. A list of all publications reviewed by the Committee is posted on the GINA website (www.ginasthma.org).

Discussion and decisions during Science Committee meetings

Each publication that is assessed by at least one reviewer to potentially impact on the GINA report is discussed in a Science Committee meeting (virtual or face-to-face). This process comprises three parts, as follows:

1. Quality and relevance of original research and systematic review publications. First, the Committee considers the relevance of the publication to the GINA report, the quality of the study, the reliability of the findings and the interpretation of the results, based on the responses from reviewers and discussion by members of the Committee. For systematic reviews, GRADE assessments, if available, are taken into account. However, for any systematic review, GINA members also independently consider the clinical relevance of the question addressed by the review, and the scientific and clinical validity of the included populations and study design. During this discussion, an author (or member with a conflict) may be requested to provide clarification or respond to questions relating to the study, but they may not otherwise take part in this discussion about the quality and relevance of the publication.

2. Decision about inclusion of the evidence. During this phase, the Committee decides whether the publication or its findings affect GINA recommendations or statements and should be included in the GINA report. These decisions to modify the report or its references are made by consensus by Committee members present and, again, any member with a conflict of interest is excluded from these decisions. If the chair is an author on a publication being reviewed, an alternative chair is appointed to lead the discussion in part 1 and the decision in part 2 for that publication.

3. Discussion about related changes to the GINA report. If the committee resolves to include the publication or its findings in the report, an author or conflicted member, if present, is permitted to take part in the subsequent discussions about and decisions on changes to the report, including the positioning of the study findings in the report and the way that they would be integrated with existing (or other new) components of the GINA management strategy. These discussions may take place immediately, or over the course of the year as new evidence emerges or as other changes to the report are agreed and implemented. The above conflict of interest considerations also apply to members of the GINA Board who ex-officio attend GINA Science Committee meetings.

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 (p.12), which was developed by the National Heart Lung and Blood Institute. From 2019, GINA has included in Evidence Level A strong observational evidence that provides a consistent pattern of findings in the population for which the recommendation is made and has also described the values and preferences that were taken into account in making major new recommendations. The table was updated in 2021 to avoid ambiguity about the positioning of observational data and systematic reviews.

New therapies and indications

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

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

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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), systematic reviews, observational evidence. Rich body of data.	Evidence is from endpoints of well designed RCTs, systematic reviews of relevant studies or observational studies that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	Randomized controlled trials and systematic reviews. Limited body of data.	Evidence is from endpoints of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs or systematic reviews of such RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomized trials or observational studies.	Evidence is from non-randomized trials or observational studies.
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.

For existing therapies with evidence for new regimens or in different populations than are covered by existing regulatory labels, the Science Committee and Board agreed in May 2018, in the context of new evidence for use of long-term low dose macrolides in moderate-severe asthma, that the Committee may, where relevant, consider making recommendations that are not necessarily covered by regulatory indications in any country at the time, provided the Committee is satisfied with the available evidence around safety and efficacy/effectiveness. The same approach was again taken in 2019 with recommendations for mild asthma about treatment with as-needed inhaled corticosteroid (ICS)-formoterol and taking ICS whenever SABA is taken rather than regularly.

Since the GINA report represents a global strategy, the report does not refer to recommendations being 'off-label'. However, readers are advised that when assessing and treating patients, they should use their own professional judgment and should also take into account local and national guidelines and eligibility criteria, as well as licensed drug doses.

External review

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

LITERATURE REVIEWED FOR GINA 2022 UPDATE

The GINA report has been updated in 2022 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 systematic reviews identified a total of 3,864 publications, of which 3,054 duplicates/animal studies/non-asthma/pilot studies and protocols were removed. 810 publications underwent screening in Covidence by at least two reviewers, and 663 were screened out for relevance and/or quality. A total of 147 publications underwent full-text review by at least two members of the

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Science Committee (including 16 systematic reviews that had used GRADE methodology), and 76 publications were subsequently discussed at meetings of the Science Committee, which in 2021 were held virtually rather than face to face because of the COVID-19 pandemic. A list of key changes in GINA 2022 can be found starting on p.14, and a tracked changes copy of the report is archived on the GINA website at www.ginasthma.org/archived-reports/.

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FUTURE CHALLENGES

In spite of laudable efforts to improve asthma care over the past 30 years, and the availability of effective medications, many patients globally have not benefited from advances in asthma treatment and often lack even the rudiments of care. Many of the world's population live in areas with inadequate medical facilities and meager financial resources. 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.

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To improve asthma care and patient outcomes, evidence-based recommendations must also be disseminated and implemented nationally and locally and integrated into health systems and clinical practice. Implementation requires an evidence-based strategy involving professional groups and stakeholders and considering local cultural and socioeconomic conditions. 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 WHO, the Global Alliance against Chronic Respiratory Diseases (GARD). Through the work of GINA, and in cooperation with GARD, substantial progress toward better care for all patients with asthma should be achieved in the next decade.

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At the most fundamental level, patients in many areas do 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 access to and pricing of high quality asthma medications continues to be an issue of urgent need and a growing area of research interest.[3] The safest and most effective approach to asthma treatment in adolescents and adults, which also avoids the consequences of starting treatment with SABA alone, depends on access to ICS–formoterol across all asthma severity levels.[4] With budesonide-formoterol now on the World Health Organization (WHO) essential medicines list, the fundamental changes to treatment of mild asthma first included in the 2019 GINA report may provide a feasible solution to reduce the risk of severe exacerbations with very low dose treatment.

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The urgent need to ensure access to affordable, quality-assured inhaled asthma medications as part of universal health coverage must now be prioritized by all relevant stakeholders, particularly manufacturers of relevant inhalers. GINA is collaborating with the International Union Against Tuberculosis and Lung Diseases (IUATLD, 'The Union') to work towards a World Health Assembly Resolution on equitable access to affordable care, including inhaled medicines, for children, adolescents and adults with asthma.

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What's new in GINA 2022?

The GINA report has been updated in 2022 following the routine twice-yearly cumulative review of the literature by the GINA Scientific Committee. Full details of the changes can be found in the tracked version archived on the GINA website. In summary, the key changes are:

- ***GINA methodology***: the description of the methodology used in preparing annual updates of the GINA report has been expanded and clarified, including that relevant GRADE-based reviews are included when available, and that the GINA report undergoes extensive external review prior to publication.
- ***Guidance about asthma and COVID-19*** (p.17) has been updated. Further evidence confirms that patients with well-controlled mild to moderate asthma are not at increased risk of severe COVID-19, but the risk is higher in patients requiring oral corticosteroids (OCS) for their asthma and in hospitalized patients with severe asthma. Advice about aerosol-generating procedures has been updated. While use of an in-line filter minimizes the risk of transmission during spirometry, precautions are still needed since many patients cough *after* performing spirometry. Updated advice is provided about COVID-19 vaccinations (including boosters) and influenza vaccination.
- ***Diagnosis of asthma***: The flow-chart (Box 1-1, p.22) and text have been modified to emphasize that the approach to diagnostic testing is different depending on whether the patient is already on controller treatment, and to clarify the considerations for testing.
- ***Asthma diagnosis and management in low- and middle-income countries (LMICs)***: The majority of the burden of asthma morbidity and mortality is experienced in low- and middle-income countries, and most of this burden is avoidable. Additional detail has been included about diagnosis (p.30) and management (p.97) of asthma in low resource settings, where differential diagnoses often include endemic respiratory diseases and infections including tuberculosis and HIV/AIDS. Advice is provided about treatment options in LMIC. GINA strongly supports the current initiatives working towards a World Health Assembly resolution on equitable access to affordable care for asthma.
- ***Assessment of symptom control***: further details have been provided (p.34) about the rationale for the exclusion of use of as-needed ICS-formoterol >2 or ≤2 times per week from the assessment of symptom control. GINA is seeking relevant data to clarify this issue. In the meantime, the *average* frequency of use of as-needed ICS-formoterol should still be considered in treatment decisions. This reliever is already providing the patient with additional controller treatment, and higher use significantly reduces the risk of severe exacerbations.
- ***The definition of mild asthma***: The section on asthma severity (p.40) has been rewritten following extensive discussion. The current definition of asthma severity is based on the concept of 'difficulty to treat'. The definition of severe asthma is widely accepted, and relevant for use in clinical practice. However, the utility and relevance of the corresponding definition of mild asthma is much less clear. Patients and clinicians often assume that 'mild asthma' means no risk and no need for controller treatment, but up to 30% of asthma deaths are in people with infrequent symptoms. GINA proposes holding a stakeholder discussion, to obtain agreement about whether/how 'mild asthma' should be defined and used in future. In the meantime, GINA suggests that the term 'mild asthma' should generally be avoided in clinical practice where possible, but if used, it should be qualified with a reminder about the risks of severe exacerbations and the need for ICS-containing treatment.
- ***GINA treatment figure for adults and adolescents (Box 3-5A)***: The rationale for showing two treatment tracks in this figure (p.60) has been reinforced: Track 1, with as-needed ICS-formoterol as reliever across treatment steps, is preferred based on evidence for lower risk of exacerbation and similar or better symptom control compared with using SABA as reliever (p.53). The figure has been updated to include anti-thymic stromal lymphopoietin (anti-TSLP) as a new biologic therapy for severe asthma in Step 5, and to point to the severe asthma guide for more detail. About Step 5 options. The 'other controller options' have been clarified as those that either have specific indications or have less evidence for safety and/or efficacy than the treatments in Track 1 or Track 2.
- ***Steps 1–2: as-needed low-dose ICS-formoterol***: Additional evidence has been added, including a systematic review showing significant reduction in ED visits/hospitalizations with as-needed ICS-formoterol compared with daily ICS plus as-needed SABA; greater reduction in severe exacerbations in adults and adolescents previously taking

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SABA alone with as-needed ICS-formoterol compared with daily ICS plus as-needed SABA; similar findings in adolescents as adults; and additional safety data (p.63, p.65).

- ***Treatment figure for children 6-11 years (Box 3-5B)***: the figure (p.61) has been updated to explain the 'other controller options' and to add anti-IL4R (dupilumab) to the Step 5 options for this age-group based on a randomized controlled trial. Maintenance OCS should be considered only as a last resort.
- ***Chromone pressurized metered dose inhalers have been discontinued globally***: These medications have had little place in management of asthma in recent years, because of their lack of efficacy compared with even low-dose inhaled corticosteroids, and the burdensome requirements for inhaler maintenance (p.68).
- ***LAMAs should not be used as monotherapy (i.e. without ICS) in asthma***: Just as LABA monotherapy is not safe in asthma, there is an increased risk of severe exacerbations in patients receiving LAMA without any ICS (p.65).
- ***Adding LAMA to ICS-LABA for adults and adolescents (Step 5)***: A meta-analysis of studies adding LAMA to ICS-LABA confirmed a modest increase in lung function, and a modest overall reduction in severe exacerbations, but without clinically important benefits for symptoms or quality of life. Evidence does not support adding LAMA for patients with persistent dyspnea. Patients with exacerbations despite ICS-LABA should receive at least medium dose ICS-LABA before considering add-on LAMA (p.71).
- ***GINA Guide and decision tree for difficult-to-treat and severe asthma in adults and adolescents***: The GINA Pocket Guide for assessment and management of difficult-to-treat and severe asthma in adults and adolescents, has been revised and increased to full letter size. The decision tree itself, which is included in the GINA report as Boxes 3-16 A–D (starting p.108), has been updated to include anti-TSLP as a new class of biologic therapy for this age-group. Additional treatment options (as below) are included for patients with no evidence of Type 2 inflammation on repeated testing.
- ***Investigations for patients with elevated blood eosinophils***: For patients with difficult-to-treat asthma and blood eosinophils ≥300/µl, investigate for non-asthma causes including testing for Strongyloides before considering biologic therapy; Strongyloides infection is often asymptomatic (p.115). For patients with hypereosinophilia (e.g. blood eosinophils ≥1500/µl), causes such as eosinophilic granulomatosis with polyangiitis (EGPA) should be considered, and anti-IL4R is preferably avoided as such patients were excluded from the Phase III studies (p.115).
- ***Add-on anti-thymic stromal lymphopoietin (anti-TSLP) for adults and adolescents:*** Tezepelumab is an add-on biologic therapy for patients aged ≥12 years with severe asthma, with the greatest benefit in reduction of severe exacerbations in those with high blood eosinophils or high FeNO (p.120 and decision tree p.110). A trial of anti-TSLP has been added to the options for consideration in patients ≥12 years who have no evidence of Type 2 inflammation on repeated testing, , but there is insufficient evidence in those taking maintenance OCS (Box 3-16B, p.109).
- ***Add-on anti-IL4R for adults and adolescents:*** for patients ≥12 years who have no evidence of Type 2 inflammation on repeated testing and require maintenance OCS, a trial of anti-IL4R has been added to the options for consideration (Box 3-16B, p.109).
- ***Add-on anti-IgE in pregnancy***: Evidence about treatment of severe asthma in pregnancy is scarce, and the risks of biologic therapy in pregnancy need to be balanced against the risks for mother and baby from uncontrolled asthma. A registry study found no increased risk of congenital malformations with use of omalizumab in pregnancy (p.118).
- ***Add-on anti-IL4R for children ≥6 years***: add-on dupilumab by SC injection has been approved for children ≥6 years with severe eosinophilic/Type 2 asthma (Box 3-5B, p.61 and Step 5, p.71).
- ***Add-on anti-IgE, anti-IL5/5R, anti-IL4R***: results of systematic reviews and meta-analyses in patients with eosinophilic/Type 2 severe asthma have been included
- ***Consider maintenance OCS as last resort***: Because of the risk of serious long-term adverse effects, maintenance OCS should be considered only as a last resort in any age-group if other treatments have been optimized and no alternative is available.

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- ***Written asthma action plans***: The term 'written' has been clarified as including printed, digital or pictorial plans. Give patients documented instructions about how to change their reliever and controller medications when their asthma worsens, and when to seek medical advice, rather than only verbal instructions (p.126).
- ***Management of wheezing episodes in pre-school children***: In children ≤5 years with intermittent viral wheezing and no or few interval respiratory symptoms, consideration of intermittent short course ICS has been added to the treatment figure (Box 6-5, p.165) for consistency with the existing text. Because of the risk of side-effects; this treatment should only be considered if the physician is confident that it will be used appropriately.
- ***Management of acute asthma in healthcare settings***: At present, salbutamol (albuterol) is the usual bronchodilator in acute asthma management. Several emergency department studies of formoterol and one study of budesonide-formoterol have shown similar safety and efficacy as salbutamol (p.134); more primary care and emergency department studies with ICS-formoterol are needed.
- ***Other changes*** include the following:
  - Use of e-cigarettes is associated with an increased risk of respiratory symptoms and asthma exacerbations (p.80)
  - Air filters can reduce fine particle exposure, but there is no consistent effect on asthma outcomes (p.84)
  - Updated evidence about the association between air pollution and urgent health care utilization for asthma (p.84)
  - Electronic inhaler monitoring can identify poor adherence in patients with difficult-to-treat asthma (p.88)
  - In patients with uncontrolled symptoms despite medium to high-dose ICS-containing treatment, higher blood eosinophils and higher FeNO are associated with greater risk of severe exacerbations (p.115)
  - A reminder that patients admitted to hospital for an asthma exacerbation should continue on, or be prescribed, ICS-containing therapy (p.137).

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Topics to be addressed in future GINA reports:

Review of these topics was delayed during 2021 due to the COVID-19 pandemic.

- Evidence included in the European Respiratory Society guidelines for diagnosis of asthma in adults/adolescents and in children will be reviewed during 2022 when the final full publication is available.
- Recommendations about the definition of mild asthma, and references to mild asthma, will be updated following the proposed stakeholder discussion described on p.40.
- GINA is seeking evidence relevant to the assessment of symptom control in patients whose reliever is ICS-formoterol
- Evidence on subcutaneous allergen immunotherapy (SCIT) and sublingual immunotherapy (SLIT) for patients with asthma is under review.
- Chapter 6, diagnosis, assessment and management of asthma in children 5 years and younger, is under review.
- A pocket guide on management of severe asthma in children 6–11 years is in development.
- The use of digital tools and communication in asthma management
- Advice about COVID-19 will be updated on the GINA website in a timely manner as relevant new information becomes available.

NOTE: minor edits 30 June 2022

- Page 118: in the eligibility criteria for anti-IL4R (dupilumab), the example of blood eosinophil count for dupilumab treatment has been updated to "≥150 to ≤1500 cells/μL", for consistency with the example in the decision tree. The dupilumab regimens for children have been clarified as "with dose and frequency depending on weight". As for all medications, particularly biologic therapies for severe asthma, clinicians should check local regulatory and payer criteria since they may vary from the examples given. Footnotes have been added in the section on biologic therapies to further emphasize this.

Advice on asthma management during the COVID-19 pandemic

COVID-19 and asthma

People with asthma do not appear to be at increased risk of acquiring COVID-19, and systematic reviews have not shown an increased risk of severe COVID-19 in people with well-controlled mild to moderate asthma. Overall, studies to date indicate that people with well-controlled asthma are not at increased risk of COVID-19-related death,[5,6] and in one meta-analysis, mortality appeared to be lower than in people without asthma. However, the risk of COVID-19 death was increased in people who had recently needed oral corticosteroids (OCS) for their asthma,[5] and in hospitalized patients with severe asthma. Therefore, it is important to continue good asthma management (as described in the GINA report), with strategies to maintain good symptom control, reduce the risk of severe exacerbations and minimize the need for OCS. In one study of hospitalized patients aged ≥50 years with COVID-19, mortality was lower among those with asthma who were using inhaled corticosteroid (ICS) than in patients without an underlying respiratory condition.[7]

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

Advise patients with asthma to continue taking their prescribed asthma medications, particularly inhaled corticosteroid (ICS)-containing medications, and oral corticosteroids (OCS) if prescribed

It is important for patients to continue taking their prescribed asthma medications as usual during the COVID-19 pandemic. This includes ICS-containing medications (alone or in combination with a long-acting beta$_2$-agonist [LABA]), and add-on therapy including biologic therapy for severe asthma. Stopping ICS often leads to potentially dangerous worsening of asthma. See Chapter 3B (p.50) for information about asthma medications and regimens and non-pharmacologic strategies, and Chapter 3C (p.87) for guided asthma self-management education and skills training.

For a small proportion of patients with severe asthma, long-term OCS may sometimes be needed, and it is very dangerous to stop these suddenly. See Chapter 3E (p.104) for advice about investigation and management of difficult-to-treat and severe asthma, including addition of biologic therapy for minimizing use of OCS.

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

Make sure that all patients have a written asthma action plan

A written action plan (printed, digital or pictorial) tells the patient how to recognize worsening asthma, how to increase their reliever and controller medications, and when to seek medical help. A short course of OCS may be needed during severe asthma flare-ups (exacerbations). See Box 4-2 (p.130) for more information about specific action plan options for increasing both controller and reliever medications, depending on the patient's usual therapeutic regimen.

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

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

Nebulizers can transmit respiratory viral particles for at least 1 meter. Use of nebulizers for delivering bronchodilator therapy is mainly restricted to management of life-threatening asthma in acute care settings. Instead, to deliver short-acting beta$_2$-agonist for acute asthma in adults and children, use a pressurized metered-dose inhaler and spacer, with a mouthpiece or tightly fitting face mask, if required. Check the manufacturer's instructions about whether a spacer can be autoclaved. If not (as is the case for many types of spacers), or if in doubt, spacers should be restricted to single patient

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Commented [A1]: Added 2022: Hou H, Xu J, Li Y, Wang Y, Yang H. The association of asthma with COVID-19 mortality: an updated meta-analysis based on adjusted effect estimates. J Allergy Clin Immunol Pract 2021;9(11):3944-3968.e5. (In eng). DOI: 10.1016/j.jaip.2021.08.016.

Commented [A2]: Added 2002: Shi T, Pan J, Katikireddi SV, et al. Risk of COVID-19 hospital admission among children aged 5-17 years with asthma in Scotland: a national incident cohort study. Lancet Respir Med 2022;10(2):191-198. (In eng). DOI: 10.1016/s2213-2600(21)00491-4.

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use. If use of a nebulizer is needed in settings where COVID-19 infection is possible, strict infection control procedures should be followed.

Remind patients not to share inhaler devices or spacers with family members, to avoid transmitting infection.

Avoid spirometry in patients with confirmed/suspected COVID-19

In healthcare facilities, follow local COVID-19 testing recommendations and infection control procedures if spirometry or peak flow measurement is needed. Use of an in-line filter minimizes the risk of transmission during spirometry, but many patients cough after performing spirometry; before performing spirometry, coach the patient to stay on the mouthpiece if they feel the need to cough.

The U.S. Centers for Disease Control and Prevention (CDC) recommendations are found here. If spirometry is not available due to local infection control restrictions, and information about lung function is needed, consider asking patients to monitor lung function at home.

Follow infection control recommendations if other aerosol-generating procedures are needed

Other aerosol-generating procedures include oxygen therapy (including with nasal prongs), sputum induction, manual ventilation, non-invasive ventilation and intubation. CDC recommendations are found here. Follow local health advice about hygiene strategies and use of personal protective equipment, as new information becomes available in your country or region.

The CDC website provides up-to-date information about COVID-19 for health professionals here, and for patients here.

The website of the World Health Organization (WHO) provides comprehensive advice for health professionals and health systems about prevention and management of COVID-19 here.

Asthma and COVID-19 vaccines

Many types of COVID-19 vaccines have been studied and are in use. New evidence about the vaccines, including in people with asthma, will emerge over time. In general, allergic reactions to the vaccines are rare. Patients with a history of severe allergic reaction to a COVID-19 vaccine ingredient (e.g. polyethylene glycol for Pfizer/BioNTech or Moderna, or polysorbate 80 for AstraZeneca or J&J/Janssen) should receive a different COVID-19 vaccine. However, people with anaphylaxis to foods, insect venom, or other medications can safely receive COVID-19 vaccines. More details from the U.S. Advisory Committee on Immunization Practices (ACIP) are here. As always, patients should speak to their healthcare provider if they have concerns. Follow local advice about monitoring patients after COVID-19 vaccination.

Usual vaccine precautions apply. For example, ask if the patient has a history of allergy to any components of the vaccine, and if the patient has a fever or another infection, delay vaccination until they are well.

At present, based on the benefits and risks, and with the above caution, GINA recommends people with asthma should be up to date with COVID-19 vaccination, including booster doses if available.

For people with severe asthma, GINA suggests that, if possible, the first dose of biologic therapy and COVID-19 vaccine should not be given on the same day, to allow adverse effects of either to be more easily distinguished.

Remind people with asthma to have an annual influenza vaccination (p.77). CDC (advice here) now advises that influenza vaccine and COVID-19 vaccine can be given on the same day.

Current advice from the CDC is that where there is substantial transmission of COVID-19, people will be better protected, even if they are fully vaccinated, if they wear a mask in indoor public settings. Further details are here.

Additional advice about management of asthma in the context of COVID-19 will be posted on the GINA website (www.ginasthma.org) as it becomes available.

Global Initiative for Asthma, April 30, 2022

Commented [A5]: Added 2022: Virant FS, Randolph C, Nanda A, et al. Pulmonary procedures during the COVD-19 pandemic: a Workgroup Report of the American Academy of Allergy, Asthma, and Immunology (AAAAI) Asthma Diagnosis and Treatment (ADT) Interest Section. J Allergy Clin Immunol Pract 2022 (In eng). DOI: 10.1016/j.jaip.2022.02.044.

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Moved up [3]: Remind people with asthma to have an annual influenza vaccination (p.76). A gap of 14 days between COVID-19 vaccination and any other vaccination including influenza is recommended by CDC (advice **Error! Hyperlink reference not valid.**), because of a lack of data on safety and effectiveness of COVID-19 vaccine administered at the same time as other vaccines. ¶

Moved up [2]: For people with severe asthma receiving biologic therapy, GINA suggests that biologic therapy and COVID-19 vaccine should not be given on the same day, to allow adverse effects of either to be more easily distinguished.¶

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Global Initiative for Asthma, April 26, 2021¶

Chapter 1.

Definition, description, and diagnosis of asthma

KEY POINTS

What is asthma?

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

How is asthma diagnosed?

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

DEFINITION OF ASTHMA

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

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

DESCRIPTION OF ASTHMA

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

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

Asthma phenotypes

Asthma is a heterogeneous disease, with different underlying disease processes. Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called 'asthma phenotypes'.[8-10] In patients with more severe asthma, some phenotype-guided treatments are available. However, no strong relationship has been found

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

Many clinical phenotypes of asthma have been identified.[8-10] Some of the most common are:

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

There are limited data about the natural history of asthma after diagnosis, but one longitudinal study showed that approximately 16% of adults with recently diagnosed asthma may experience clinical remission (no symptoms or asthma medication for at least 1 year) within 5 years.[11]

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

MAKING THE INITIAL DIAGNOSIS

Making the diagnosis of asthma in a patient not on controller treatment, as shown in Box 1-1 (p.22) 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.[12] The pattern of symptoms is important, as respiratory symptoms may be due to acute or chronic conditions other than asthma (see Box 1-3 (p.27). If possible, the evidence supporting a diagnosis of asthma (Box 1-2, p.23) 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.

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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:[12]

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

- Patients (especially adults) experience more than one of these types of symptoms.
- Symptoms are often worse at night or in the early morning.
- Symptoms vary over time and in intensity.
- Symptoms are triggered by viral infections (colds), exercise, allergen exposure, changes in weather, laughter, or irritants such as car exhaust fumes, smoke or strong smells.

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

- Isolated cough with no other respiratory symptoms (see p.28)
- Chronic production of sputum
- Shortness of breath associated with dizziness, light-headedness or peripheral tingling (paresthesia)
- Chest pain
- Exercise-induced dyspnea with noisy inspiration.

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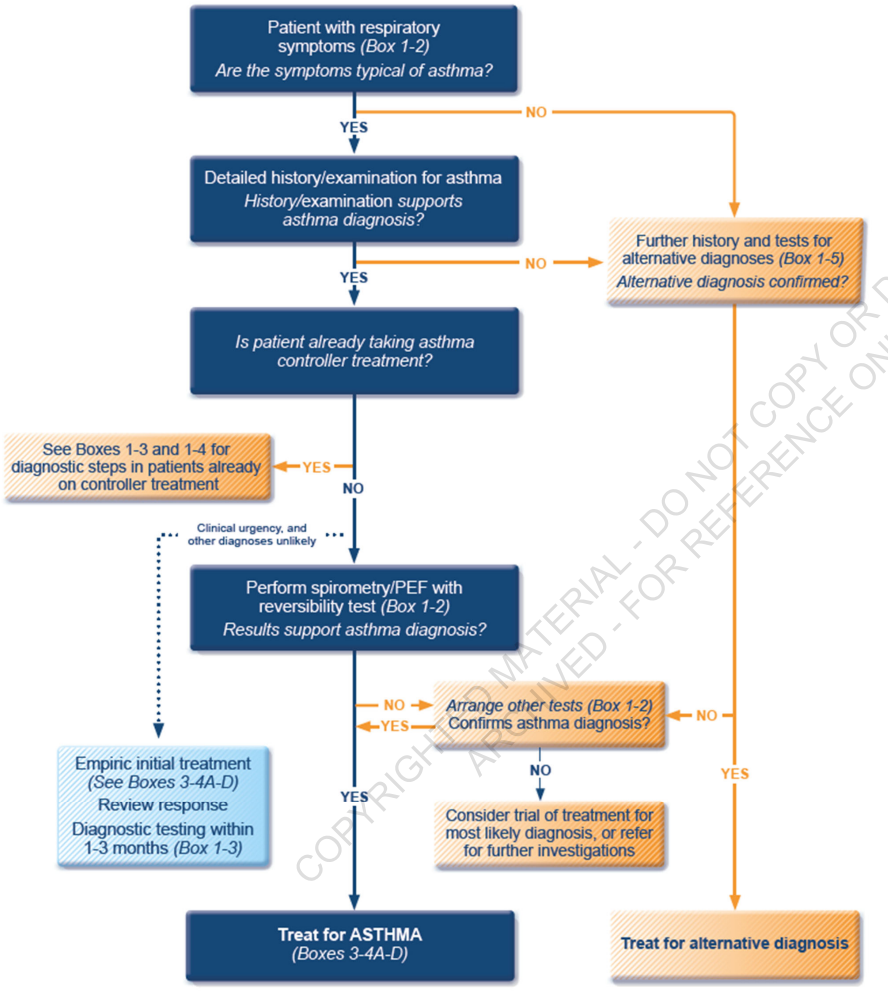
Box 1-1. Diagnostic flowchart for clinical practice



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

Bronchodilator responsiveness (reversibility) may be lost during severe exacerbations or viral infections, and in long-standing asthma, and it usually decreases with inhaled corticosteroid treatment. If bronchodilator responsiveness is not found at initial presentation, the next step depends on the availability of tests and the clinical urgency of need for treatment.

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

1. HISTORY OF VARIABLE RESPIRATORY SYMPTOMS	
Feature	*Symptoms or features that support the diagnosis of asthma*
Wheeze, shortness of breath, chest tightness and cough (Descriptors may vary between cultures and by age)	• 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	
Feature	*Considerations, definitions, criteria*
2.1 Documented* expiratory airflow limitation	At a time when FEV_1 is reduced, confirm that FEV_1/FVC is reduced compared with the lower limit of normal (it is usually >0.75–0.80 in adults, >0.90 in children[13])
AND	
2.2 Documented* excessive variability in lung function* (one or more of the following):	The greater the variations, or the more occasions excess variation is seen, the more confident the diagnosis. If initially negative, tests can be repeated during symptoms or in the early morning.
• Positive bronchodilator (BD) responsiveness (reversibility) test	*Adults*: increase in FEV_1 of >12% and >200 mL (greater confidence if increase is >15% and >400 mL). *Children*: increase in FEV_1 of >12% predicted Measure change 10–15 minutes after 200–400 mcg salbutamol (albuterol) or equivalent, compared with pre-BD readings. Positive test more likely if BD withheld before test: SABA ≥4 hours, twice-daily LABA 24 hours, once-daily LABA 36 hours
• 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 for adults)	Fall in FEV_1 from baseline of ≥20% with standard doses of methacholine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge
• Excessive variation in lung function between visits (good specificity but poor sensitivity)	*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 (SABA or rapid-acting LABA); FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; LABA: long-acting $beta_2$-agonist; PEF: peak expiratory flow (highest of three readings); SABA: short-acting $beta_2$-agonist. See Box 1-3 (p.26) for how to confirm the diagnosis in patients already taking controller treatment. *Daily diurnal PEF variability is calculated from twice daily PEF as (day's highest minus day's lowest) divided by (mean of day's highest and lowest), averaged over one week. †For PEF, use the same meter each time, as PEF may vary by up to 20% between different meters. BD responsiveness may be lost during severe exacerbations or viral infections,[14] and airflow limitation may become persistent over time. If 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.27), but other conditions that can mimic asthma (Box 1-5) should be considered, and the diagnosis confirmed as soon as possible.

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Why is it important to confirm the diagnosis of asthma?

This is important to avoid unnecessary treatment or over-treatment, and to avoid missing other important diagnoses. In adults with an asthma diagnosis in the last 5 years, one-third could not be confirmed as having asthma after repeated testing over 12 months and staged withdrawal of controller treatment. The diagnosis of asthma was less likely to be confirmed in patients who had not had lung function testing performed at the time of initial diagnosis. Some patients (2%) had serious cardiorespiratory conditions that had been misdiagnosed as asthma.[15]

History and family history

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

Physical examination

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

Lung function testing to document variable expiratory airflow limitation

Asthma is characterized by variable expiratory airflow limitation, i.e. expiratory lung function varies over time and in magnitude, to a greater extent than in healthy populations. In asthma, lung function may vary between completely normal and severely obstructed in the same patient. Poorly controlled asthma is associated with greater variability in lung function than well-controlled asthma.[14]

Lung function testing should be carried out by well-trained operators with well-maintained and regularly calibrated equipment,[16] with an inline filter to protect against transmission of infection. 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%.[17]

A reduced FEV_1 may be found with many other lung diseases (or poor spirometric technique), but a reduced ratio of FEV_1 to forced vital capacity (FEV_1/FVC), compared with the lower limit of normal, indicates expiratory airflow limitation. Many spirometers now include multi-ethnic age-specific predicted values.[13]

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'* (now called 'responsiveness')[16] 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,[18] or more sustained improvement over days or weeks after the introduction of effective controller treatment such as ICS.[18]

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

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Specific criteria for demonstrating excessive variability in expiratory lung function are listed in Box 1-2 (p.23). A decrease in lung function during a respiratory infection, while commonly seen in asthma, does not necessarily indicate that a person has asthma, as it may also be seen in otherwise healthy individuals or people with COPD.

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

How much variation in expiratory airflow is consistent with asthma?

There is overlap in bronchodilator reversibility and other measures of variation between health and disease.[19] 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.23). 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,[20] and 12.3% in healthy children,[21] 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 expiratory airflow limitation be documented?

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

If spirometry is not available, or variable expiratory 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 1-3 (p.27) describes how to confirm the diagnosis of asthma in a patient already taking controller treatment.

Other tests

Bronchial provocation tests

One option for documenting variable expiratory airflow limitation is to refer the patient for bronchial provocation testing to assess airway hyperresponsiveness. Challenge agents include inhaled methacholine,[22] histamine, exercise, [23] eucapnic voluntary hyperventilation or inhaled mannitol. These tests are moderately sensitive for a diagnosis of asthma but have limited specificity.[22,23] For example, airway hyperresponsiveness to inhaled methacholine has been described in patients with allergic rhinitis,[24] cystic fibrosis,[25] bronchopulmonary dysplasia[26] and COPD.[27] 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.23) and other clinical features (Box 1-3, p.26) must also be considered.

Allergy tests

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

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anaphylaxis.[28] The presence of a positive skin test or positive sIgE, however, does not mean that the allergen is causing symptoms - the relevance of allergen exposure and its relation to symptoms must be confirmed by the patient's history.

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

The fractional concentration of exhaled nitric oxide (FeNO) is modestly associated with levels of sputum and blood eosinophils.[29] FeNO has not been established as useful for ruling in or ruling out a diagnosis of asthma, as defined on p.20, because while FeNO is higher in asthma that is characterized by Type 2 airway inflammation,[30] it is also elevated in non-asthma conditions (e.g. eosinophilic bronchitis, atopy, allergic rhinitis, eczema), and it is not elevated in some asthma phenotypes (e.g. neutrophilic asthma). FeNO is lower in smokers and during bronchoconstriction[31] and the early phases of allergic response;[32] it may be increased or decreased during viral respiratory infections.[31] See Chapter 3B, p.52 for discussion about FeNO in the context of decisions about initial asthma treatment.

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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.[15,33-36]

The process for confirming the diagnosis in patients already on controller treatment depends on the patient's symptoms and lung function (Box 1-3, p.26). In some patients, this may include a trial of either a lower or a higher dose of controller treatment. If the diagnosis of asthma cannot be confirmed, refer the patient for expert investigation and diagnosis. For some patients, it may be necessary to step down the controller treatment in order to confirm the diagnosis of asthma. The process is described in Box 1-4, p.27.

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

Current status	Steps to confirm the diagnosis of asthma
Variable respiratory symptoms and variable airflow limitation	Diagnosis of asthma is confirmed. Assess the level of asthma control (Box 2-2, p.36) and review controller treatment (Box 3-5, p.60).
Variable respiratory symptoms but no variable airflow limitation	Consider repeating spirometry after withholding BD (4 hrs for SABA, 24 hrs for twice-daily ICS-LABA, 36hrs for once-daily ICS-LABA) or during symptoms. Check between-visit variability of FEV_1, and bronchodilator responsiveness. If still normal, consider other diagnoses (Box 1-5, p.27). *If FEV_1 is >70% predicted*: consider stepping down controller treatment (see Box 1-5) and reassess in 2–4 weeks, then consider bronchial provocation test or repeating BD responsiveness. *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	Consider repeating BD responsiveness test again after withholding BD as above or during symptoms. If normal, consider alternative diagnoses (Box 1-5, p.27). Consider stepping down controller treatment (see Box 1-5): • *If symptoms emerge and lung function falls*: asthma is confirmed. Step up controller treatment to previous lowest 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 persistent airflow limitation	Consider stepping up controller treatment for 3 months (Box 3-5, p.60), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation. Consider asthma–COPD overlap (Chapter 5, p.141).

BD: bronchodilator; LABA: long-acting $beta_2$-agonist; SABA: short-acting $beta_2$-agonist. 'Variable airflow limitation' refers to expiratory airflow.

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Box 1-4. 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.36) 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.130) 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.74). 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.23).
- If symptoms increase and variable expiratory 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 expiratory 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

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DIFFERENTIAL DIAGNOSIS

The differential diagnosis in a patient with suspected asthma varies with age (Box 1-5). Any of these alternative diagnoses may also be found *together with* asthma.

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

Age	Symptoms	Condition
6–11 years	Sneezing, itching, blocked nose, throat-clearing	Chronic upper airway cough syndrome
	Sudden onset of symptoms, unilateral wheeze	Inhaled foreign body
	Recurrent infections, productive cough	Bronchiectasis
	Recurrent infections, productive cough, sinusitis	Primary ciliary dyskinesia
	Cardiac murmurs	Congenital heart disease
	Pre-term delivery, symptoms since birth	Bronchopulmonary dysplasia
	Excessive cough and mucus production, gastrointestinal symptoms	Cystic fibrosis

(continued next page)

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

Age	Symptoms	Condition
12–39 years	Sneezing, itching, blocked nose, throat-clearing	Chronic upper airway cough syndrome
	Dyspnea, inspiratory wheezing (stridor)	Inducible laryngeal obstruction
	Dizziness, paresthesia, sighing	Hyperventilation, dysfunctional breathing
	Productive cough, recurrent infections	Bronchiectasis
	Excessive cough and mucus production	Cystic fibrosis
	Cardiac murmurs	Congenital heart disease
	Shortness of breath, family history of early emphysema	$Alpha_1$-antitrypsin deficiency
	Sudden onset of symptoms	Inhaled foreign body
40+ years	Dyspnea, inspiratory wheezing (stridor)	Inducible laryngeal obstruction
	Dizziness, paresthesia, sighing	Hyperventilation, dysfunctional breathing
	Cough, sputum, dyspnea on exertion, smoking or noxious exposure	COPD*
	Productive cough, recurrent infections	Bronchiectasis
	Dyspnea with exertion, nocturnal symptoms, ankle edema	Cardiac failure
	Treatment with angiotensin converting enzyme (ACE) inhibitor	Medication-related cough
	Dyspnea with exertion, non-productive cough, finger clubbing	Parenchymal lung disease
	Sudden onset of dyspnea, chest pain	Pulmonary embolism
	Dyspnea, unresponsive to bronchodilators	Central airway obstruction
All ages	Chronic cough, hemoptysis, dyspnea; and/or fatigue, fever, (night) sweats, anorexia, weight loss	Tuberculosis

*For more detail, see Chapter 5 (p.141). Any of the above conditions may also contribute to respiratory symptoms in patients with confirmed asthma.

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HOW TO MAKE THE DIAGNOSIS OF ASTHMA IN OTHER CONTEXTS

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

Diagnoses to be considered are chronic upper airway cough syndrome (often called 'postnasal drip'), cough induced by angiotensin converting enzyme (ACE) inhibitors, gastroesophageal reflux, chronic sinusitis, and inducible laryngeal obstruction.[37,38] Patients with so-called 'cough-variant asthma' have persistent cough as their principal or only symptom, associated with airway hyperresponsiveness. It is often more problematic at night. Lung function may be normal, and for these patients, documentation of variability in lung function (Box 1-2, p.23) is important.[39] Cough-variant asthma must be distinguished from eosinophilic bronchitis in which patients have cough and sputum eosinophilia but normal spirometry and airway responsiveness.[39]

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Occupational asthma and work-exacerbated asthma

Asthma acquired in the workplace is frequently missed. Asthma may be induced or (more commonly) aggravated by exposure to allergens or other sensitizing agents at work, or sometimes from a single, massive exposure. Occupational rhinitis may precede asthma by up to a year and early diagnosis is essential, as persistent exposure is associated with worse outcomes.[40,41]

An estimated 5–20% of new cases of adult-onset asthma can be attributed to occupational exposure.[40] Adult-onset asthma requires a systematic inquiry about work history and exposures, including hobbies. Asking patients whether their symptoms improve when they are away from work (weekends or vacation) is an essential screening question.[42] 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.101) and in specific guidelines.[40]

Athletes

The diagnosis of asthma in athletes should be confirmed by lung function tests, usually with bronchial provocation testing.[43] Conditions that may either mimic or be associated with asthma, such as rhinitis, laryngeal disorders (e.g. inducible laryngeal obstruction[38]), dysfunctional breathing, cardiac conditions and over-training, must be excluded.[44]

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 with multimorbidity and in specific populations*, p.100).[45] 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,[46] due to poor perception of airflow limitation; acceptance of dyspnea as being 'normal' in old age; lack of fitness; and reduced physical activity. The presence of multimorbidity also complicates the diagnosis. In a large population based survey of asthma patients older than 65 years, factors associated with a history of asthma hospitalization included co-diagnosis of COPD, coronary artery disease, depression, diabetes mellitus, and difficulty accessing medications or clinical care because of cost.[47] 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.[48] Measurement of plasma brain natriuretic polypeptide (BNP) and assessment of cardiac function with echocardiography may also be helpful.[49] In older people with a history of smoking or biomass fuel exposure, COPD and overlapping asthma and COPD (asthma–COPD overlap) should be considered (Chapter 5, p.141).

Smokers and ex-smokers

Asthma and COPD may be difficult to distinguish in clinical practice, particularly in older patients and smokers and ex-smokers, and these conditions may overlap (asthma-COPD overlap). The *Global Strategy for Diagnosis, Management and Prevention of COPD (GOLD)*[50] 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.[51] Low diffusion capacity is more common in COPD than asthma. The history and pattern of symptoms and past records can help to distinguish these patients from those with long-standing asthma who have developed persistent airflow limitation (see Chapter 5, p.141). 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.[52]

Obese patients

While asthma is more common in obese than non-obese people,[53] respiratory symptoms associated with obesity can mimic asthma. In obese patients with dyspnea on exertion, it is important to confirm the diagnosis of asthma with objective measurement of variable expiratory airflow 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).[33] Another study found both over- and under-diagnosis of asthma in obese patients.[54]

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Low- and middle-income countries

As described above, asthma is a clinical diagnosis, based on the history of characteristic symptom patterns and evidence of variable expiratory airflow limitation. However, in low- and middle-income countries (LMICs), access to lung function testing is often very limited, and even when available, may be substantially underused (e.g. unaffordable for the patient or health system, too time-consuming in a busy clinic, or impractical because requiring repeated visits of indigent patients.

In addition, in LMICs, the differential diagnosis of asthma may include other endemic respiratory disease (e.g. tuberculosis, HIV/AIDS-associated lung diseases, and parasitic or fungal lung diseases), so clinicians tend to place greater reliance on clinical findings and often use a syndromic approach to diagnosis and initial management. This comes at the cost of precision, but is based on the assumption (valid in most LMICs) that under-diagnosis and under-treatment of asthma is more likely than the overdiagnosis and overtreatment often seen in high income countries.

Although acknowledging that poor access to lung function testing is a common barrier to asthma diagnosis in LMICs, GINA does not recommend that diagnosis should be solely based on syndromic clinical patterns. When spirometry is not available, the presence of variable expiratory airflow limitation (including reversible obstruction) can be confirmed by PEF (Box 1-2, p.23). The World Health Organization (WHO) Package of essential noncommunicable (PEN) disease interventions for primary care lists the PEF meter as an essential tool in the management of chronic respiratory diseases. WHO-PEN proposes use of PEF in support of a clinical diagnosis: a ≥20% improvement in PEF 15 minutes after giving 2 puffs of albuterol increases the likelihood of a diagnosis of asthma versus COPD and other diagnoses. GINA also suggests that improvement in symptoms and PEF after a 4-week therapeutic trial with anti-inflammatory therapy, with a 1-week course of OCS if necessary, can help to confirm the diagnosis of asthma (or prompt investigation for alternative diagnoses) before starting long-term controller treatment.

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

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

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Variable expiratory 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.**Error! Hyperlink reference not valid.** ¶
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.**Error! Hyperlink reference not valid.** ¶ ... [1]

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Chapter 2.

Assessment of asthma

KEY POINTS

Asthma control

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

Asthma severity

- The current definition of asthma severity is based on retrospective assessment, after at least 2–3 months of controller treatment, from the treatment required to control symptoms and exacerbations.
- This definition is clinically useful for severe asthma, as it identifies patients whose asthma is relatively refractory to conventional high dose ICS-LABA and who may benefit from additional treatment such as biologic therapy. It is important to distinguish between severe asthma and asthma that is uncontrolled due to modifiable factors such as incorrect inhaler technique and/or poor adherence.
- However, the clinical utility of the retrospective definition of 'mild asthma' is less clear. In particular, the term is often used in clinical practice to mean infrequent or mild symptoms, and patients often incorrectly assume that it means they are not at risk and do not need controller treatment.
- For these reasons, GINA suggest that the term 'mild asthma' should generally be avoided in clinical practice or, if used, qualified with a reminder that patients with infrequent symptoms can still have severe or fatal exacerbations, and that this risk is substantially reduced with ICS-containing treatment.
- GINA proposes holding a stakeholder discussion about the definition of mild asthma, to obtain agreement about the implications for clinical practice and clinical research of the changes in knowledge about asthma pathophysiology and treatment since the current definition of asthma severity was published.

How to assess a patient with asthma

- Assess symptom control from the frequency of daytime and night-time asthma symptoms, night waking and activity limitation and, for patients using short-acting beta$_2$ agonist (SABA) reliever, their frequency of SABA use. Other symptom control tools include Asthma Control Test and Asthma Control Questionnaire.
- Assess the patient's future risk for exacerbations, even when symptom control is good. Risk factors for exacerbations that are independent of symptom control include a history of ≥1 exacerbation in the previous year, socioeconomic problems, poor adherence, incorrect inhaler technique, low forced expiratory volume in 1 second (FEV_1), smoking, and blood eosinophilia.
- Also assess risk factors for persistent airflow limitation and medication side-effects, treatment issues such as inhaler technique and adherence, and comorbidities, and ask the patient about their asthma goals.
- Once the diagnosis of asthma has been made, the main role of lung function testing is in the assessment of future risk. It should be recorded at diagnosis, 3–6 months after starting treatment, and periodically thereafter.
- Investigate further if there are few symptoms but impaired lung function, or frequent symptoms and good lung function.

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, p.33). Lung function, particularly FEV_1 as a percentage of predicted, is an important part of the assessment of future risk.

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

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.[20,55] 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.[55]

Asthma control has two domains: symptom control and future risk of adverse outcomes (Box 2-2, p.36). 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.

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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.[55,56] If the term 'asthma control' is used with patients, the meaning should always be explained.

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

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

- Assess symptom control over the last 4 weeks (Box 2-2A).
- Identify any other risk factors for exacerbations, persistent airflow limitation or side-effects (Box 2-2B).
- Measure lung function at diagnosis/start of treatment, 3–6 months after starting controller treatment, then periodically, e.g. at least once every 1–2 years, but more often in at-risk patients and those with severe asthma.

2. Assess treatment issues

- Document the patient's current treatment step (Box 3-5, p.60).
- Watch inhaler technique (Box 3-12, p.88), assess adherence (Box 3-13, p.90) 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.

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3. Assess comorbidities

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

ASSESSING ASTHMA SYMPTOM CONTROL

Asthma symptoms such as wheeze, chest tightness, shortness of breath and cough typically vary in frequency and intensity, and contribute to the burden of asthma for the patient. Poor symptom control is also strongly associated with an increased risk of asthma exacerbations.[57-59]

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

To assess 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, for patients using a SABA reliever, frequency of its use for relief of symptoms. In general, do not include reliever taken before exercise, because some people take this routinely without knowing whether they need it.

Frequency of reliever use

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

However, if a patient who is prescribed as-needed ICS-formoterol as their reliever (Track 1 in Box 3-5A, p.60) uses it on average more than 2 days/week, this is already providing additional controller therapy, so further dose escalation may not be needed. Increasing use of as-needed ICS-formoterol is associated with a significantly lower risk of severe exacerbation in subsequent days or weeks compared with if the reliever is SABA, or compared with if the patient is using SABA alone.

For these reasons, use of ICS-formoterol reliever divided categorically as ≤2 versus >2 days/week is not included in the composite assessment of symptom control. However, the patient's *average* frequency of as-needed ICS-formoterol use over the past 4 weeks should be assessed, and taken into account when the patient's maintenance controller dose is reviewed. This issue will be reviewed again when further data are available.

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.[60,61] It can be used, together with a risk assessment (Box 2-2B), to guide treatment decisions (Box 3-5, p.60). Other examples are the Primary Care Asthma Control Screening Tool (PACS),[62] and the 30-second Asthma Test, which also includes time off work/school.[63]

Categorical symptom control tools: e.g. the consensus-based 'Royal College of Physicians (RCP) Three Questions' tool,[64] which asks about difficulty sleeping, daytime symptoms and activity limitation due to asthma in the previous month. The Asthma APGAR tool includes a patient-completed asthma control assessment covering 5 domains: activity limitations, daytime and nighttime symptom frequency (based on US criteria for frequency of night waking), triggers, adherence, and patient-perceived response to treatment. This assessment is linked to a care algorithm for identifying problems and adjusting treatment up or down. A study in the US showed that introduction of the Asthma APGAR tools for patients aged 5–45 in primary care improved rates of asthma control; reduced asthma-related urgent care, and hospital visits; and increased practices' adherence to asthma management guidelines.[65]

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

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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.[60]

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). The ACQ score is the average of 5, 6 or 7 items: all versions include five symptom questions; ACQ-6 includes SABA reliever use; and ACQ-7, pre-bronchodilator FEV_1. The authors stated that ACQ ≤0.75 indicated a high probability that asthma was well-controlled; 0.75–1.5 as a 'grey zone'; and ≥1.5 a high probability that asthma was poorly controlled, based on concepts of asthma control at the time; the authors later added that the crossover point between 'well-controlled' and 'not well-controlled' asthma was close to 1.00.[68] The minimum clinically important difference for all three versions of ACQ is 0.5.[69] GINA prefers ACQ-5 over ACQ-6 or 7 because the reliever question assumes regular rather than as-needed use of SABA, and ACQ has not been validated with ICS-formoterol as the reliever. If ACQ is used in adjustment of treatment, inclusion of FEV_1 in the composite score could lead to repeated step-up in ICS dose for patients with persistent airflow limitation.
- *Asthma Control Test (ACT)*:[61,70,71] Scores range from 5–25 (higher is better). Scores of 20–25 are classified as well-controlled; 16–19 as not well-controlled; and 5–15 as very poorly controlled asthma. The ACT has four symptom/reliever questions plus patient self-assessed control. The minimum clinically important difference is 3 points.[71]

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

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

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

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

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

- *Childhood Asthma Control Test* (c-ACT)[72] with separate sections for parent and child to complete
- *Asthma Control Questionnaire* (ACQ)[73,74]

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

- Test for Respiratory and Asthma Control in Kids (TRACK)[75-77]
- Composite Asthma Severity Index (CASI)[78]

The results of these various tests correlate to some extent with each other and with the GINA classification of symptom control. Box 2-3 (p.37) 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☐			
• SABA reliever for symptoms more than twice/week?*	Yes☐ No☐			
• Any activity limitation due to asthma?	Yes☐ No☐			

B. Risk factors for poor asthma outcomes

Assess risk factors at diagnosis and periodically, 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.

Having uncontrolled asthma symptoms is an important risk factor for exacerbations.[79]

Additional **potentially modifiable risk factors for flare-ups (exacerbations)**, even in patients with few symptoms† include:

- ***Medications***: high SABA use (≥3x200-dose canisters/year associated with increased risk of exacerbations;[123,80] increased mortality particularly if ≥1 canister per month[81,82]); inadequate ICS: not prescribed ICS; poor adherence;[83] incorrect inhaler technique[84]
- ***Other medical conditions***: obesity;[85,86] chronic rhinosinusitis;[86] GERD;[86] confirmed food allergy;[87] pregnancy[88]
- ***Exposures***: smoking;[89] e-cigarettes; allergen exposure if sensitized;[89] air pollution[90-92]
- ***Context***: major psychological or socioeconomic problems[93]
- ***Lung function***: low FEV_1, especially <60% predicted[89,94]; high BD responsiveness[86,95,96]
- ***Type 2 inflammatory markers***: higher blood eosinophils;[86,97,98] elevated FeNO (in adults with allergic asthma taking ICS)[99]

Having any of these risk factors increases the patient's risk of exacerbations *even if they have few asthma symptoms*

Other major independent risk factors for flare-ups (exacerbations)

- Ever intubated or in intensive care unit for asthma[100]
- ≥1 severe exacerbation in last 12 months[101,102]

Risk factors for developing persistent airflow limitation

- History: preterm birth, low birth weight and greater infant weight gain;[103] chronic mucus hypersecretion[104,105]
- Medications: lack of ICS treatment in patients who had a severe exacerbation[106]
- Exposures: tobacco smoke;[104] noxious chemicals; occupational exposures[40]
- Investigations: low initial FEV_1;[105] sputum or blood eosinophilia[105]

Risk factors for medication side-effects

- Systemic: frequent OCS; long-term, high dose and/or potent ICS; also taking P450 inhibitors[107]
- Local: high dose or potent ICS;[107,108] poor inhaler technique[109]

BD: bronchodilator; 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. *Based on SABA (as-needed ICS-formoterol reliever not included); excludes reliever taken before exercise. For children 6–11 years, also refer to Box 2-3, p.37. See Box 3-8, p.75 for specific risk reduction strategies. †'Independent' risk factors are those that are significant after adjustment for the level of symptom control.

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

Asthma symptom control	
Day symptoms	Ask: How often does the child have cough, wheeze, dyspnea or heavy breathing (number of times per week or day)? What triggers the symptoms? How are they handled?
Night symptoms	Cough, awakenings, tiredness during the day? (If the only symptom is cough, consider other diagnoses such as rhinitis or gastroesophageal reflux disease).
Reliever use	How often is reliever medication used? (check date on inhaler or last prescription) Distinguish between pre-exercise use (sports) and use for relief of symptoms.
Level of activity	What sports/hobbies/interests does the child have, at school and in their spare time? How does the child's level of activity compare with their peers or siblings? How many days is the child absent from school? Try to get an accurate picture of the child's day from the child without interruption from the parent/carer.
Risk factors for adverse outcomes	
Exacerbations	Ask: How do viral infections affect the child's asthma? Do symptoms interfere with school or sports? How long do the symptoms last? How many episodes have occurred since their last medical review? Any urgent doctor/emergency department visits? Is there a written action plan? Risk factors for exacerbations include a history of exacerbations, poor symptom control, poor adherence and poverty,[102] and persistent bronchodilator reversibility even if the child has few symptoms.[96]
Lung function	Check curves and technique. Main focus is on FEV_1 and FEV_1/FVC ratio. Plot these values as percent predicted to see trends over time.
Side-effects	Check the child's height at least yearly, as poorly controlled asthma can affect growth,[110] and growth velocity may be lower in the first 1-2 years of ICS treatment.[111] Ask about frequency and dose of ICS and OCS.
Treatment factors	
Inhaler technique	Ask the child to show how they use their inhaler. Compare with a device-specific checklist.
Adherence	Is there any controller medication in the home at present? On how many days does the child use their controller in a week (e.g. 0, 2, 4, 7 days)? Is it easier to remember to use it in the morning or evening? Where is inhaler kept – is it in plain view to reduce forgetting? Check date on inhaler.
Goals/concerns	Does the child or their parent/carer have any concerns about their asthma (e.g. fear of medication, side-effects, interference with activity)? What are the child's/parent's/carer's goals for treatment?
Comorbidities	
Allergic rhinitis	Itching, sneezing, nasal obstruction? Can the child breathe through their nose? What medications are being taken for nasal symptoms?
Eczema	Sleep disturbance, topical corticosteroids?
Food allergy	Is the child allergic to any foods? (confirmed food allergy is a risk factor for asthma-related death[87])
Obesity	Check age-adjusted BMI. Ask about diet and physical activity.
Other investigations (if needed)	
2-week diary	If no clear assessment can be made based on the above questions, ask the child or parent/carer to keep a daily diary of asthma symptoms, reliever use and peak expiratory flow (best of three) for 2 weeks (Appendix Chapter 4).
Exercise challenge (laboratory)	Provides information about airway hyperresponsiveness and fitness (Box 1-2, p.23). 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 (Box 2-2B, p.36) is to identify whether the patient is at risk of adverse asthma outcomes, particularly exacerbations, persistent airflow limitation, and side-effects of medications (Box 2-2B). Asthma symptoms, although an important outcome for patients, and themselves a strong predictor of future risk of exacerbations, are not sufficient on their own for assessing asthma because:

- Asthma symptoms can be controlled by placebo or sham treatments[112,113] or by inappropriate use of long-acting beta$_2$-agonist (LABA) alone,[114] which leaves airway inflammation untreated.
- Respiratory symptoms may be due to other conditions such as lack of fitness, or comorbidities such as inducible laryngeal obstruction.[38]
- Anxiety or depression may contribute to symptom reporting.
- Some patients have impaired perception of bronchoconstriction, with few symptoms despite low lung function.

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

Risk factors for exacerbations

Poor asthma symptom control itself substantially increases the risk of exacerbations.[57-59] 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 exacerbation in the previous year, poor adherence, incorrect inhaler technique, chronic sinusitis and smoking, all of which can be assessed in primary care.[115] The risk of severe exacerbations and mortality increases incrementally with higher SABA use, independent of treatment step.[82] Prescribing of three or more 200-dose SABA inhalers in a year, corresponding to more than daily use, is associated with an increased risk of severe exacerbations[82,116] and, in one study, increased mortality.[82] Risk factors that are modifiable are sometimes called 'treatable traits'.

In children, the risk of exacerbations is greatly increased if there is a history of previous exacerbations; it is also increased with poor symptom control, suboptimal drug regimen, comorbid allergic disease and poverty.[102]

Risk factors for development of persistent airflow limitation

The average rate of decline in FEV_1 in non-smoking healthy adults is 15–20 mL/year.[117] People with asthma may have an accelerated decline in lung function and develop airflow limitation that is not fully reversible. This is often associated with more persistent dyspnea. Independent risk factors that have been identified for persistent airflow limitation include exposure to cigarette smoke or noxious agents, chronic mucus hypersecretion, and asthma exacerbations in patients not taking ICS[106] (see Box 2-2B, p.36). 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.[118]

Risk factors for medication side-effects

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

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ROLE OF LUNG FUNCTION IN ASSESSING ASTHMA CONTROL

Does lung function relate to other asthma control measures?

Lung function does not correlate strongly with asthma symptoms in adults[119] or children.[120] In some asthma control tools, lung function is numerically averaged or added with symptoms,[66,121] but if the tool includes several symptom items, these can outweigh clinically important differences in lung function.[122] 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 those at risk of decline in lung function (see Box 2-2B, p.36). 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,[20] but preferably the same conditions should apply at each visit.

How to interpret lung function test results in asthma

A low FEV_1 percent predicted:

- Identifies patients at risk of asthma exacerbations, independent of symptom levels, especially if FEV_1 is <60% predicted[89,94,123,124]
- Is a risk factor for lung function decline, independent of symptom levels[105]
- If symptoms are few, suggests limitation of lifestyle, or poor perception of airflow limitation,[125] which may be due to untreated airway inflammation.[126]

A 'normal' or near-normal FEV_1 in a patient with frequent respiratory symptoms (especially when symptomatic):

- Prompts consideration of alternative causes for the symptoms; e.g. cardiac disease, or cough due to post-nasal drip or gastroesophageal reflux disease (Box 1-3, p.26).

Persistent bronchodilator responsiveness:

- Finding significant bronchodilator responsiveness (increase in FEV_1 >12% and >200 mL from baseline[18]) 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 (or 24 hours for a once-daily LABA), suggests uncontrolled asthma.

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

How to interpret changes in lung function in clinical practice

With regular ICS treatment, FEV_1 starts to improve within days, and reaches a plateau after around 2 months.[127] The patient's highest FEV_1 reading (personal best) should be documented, as this provides a more useful comparison for clinical practice than FEV_1 percent predicted. If predicted values are used in children, measure their height at each visit.

Some patients may have a faster than average decrease in lung function, and develop persistent (incompletely 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 (up to 12% week to week or 15% year to year in healthy individuals[18]) limits its use in adjusting asthma treatment or identifying accelerated decline in clinical practice. The minimal important difference for improvement and worsening in FEV_1 based on patient perception of change has been reported to be about 10%.[128,129]

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

Once the diagnosis of asthma is made, short-term peak expiratory flow (PEF) monitoring may be used to assess response to treatment, to evaluate triggers (including at work) for worsening symptoms, or to establish a baseline for action plans. After starting ICS, personal best PEF (from twice daily readings) is reached on average within 2

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weeks.[130] Average PEF continues to increase, and diurnal PEF variability to decrease, for about 3 months.[119,130] Excessive variation in PEF suggests suboptimal asthma control, and increases the risk of exacerbations.[131]

Long-term PEF monitoring is now generally only recommended for patients with severe asthma, or those with impaired perception of airflow limitation[126,132-135] (Appendix Chapter 4). For clinical practice, displaying PEF results on a standardized chart may improve accuracy of interpretation.[136]

ASSESSING ASTHMA SEVERITY

The currently accepted definition of asthma severity is based on 'difficulty to treat'

The current definition of asthma severity, recommended by an ATS/ERS Task Force and included in most asthma guidelines, is that severity should be assessed retrospectively from the level of treatment required to control the patient's symptoms and exacerbations, i.e. after at least several months of treatment. Hence:

- *Severe asthma* is defined as asthma that remains uncontrolled despite optimized treatment with high dose ICS-LABA, or that requires high dose ICS-LABA to prevent it from becoming uncontrolled. Severe asthma must be distinguished from asthma that is difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, as there are very different treatment implications compared with if asthma is relatively refractory to high dose ICS-LABA or even OCS. See Box 2-4 (p.42) for how to distinguish difficult-to-treat and severe asthma, and Chapter 3E (p.104) for more detail about assessment, referral and treatment.
- *Moderate asthma* is currently defined as asthma that is well controlled with Step 3 or Step 4 treatment e.g. with low or medium dose ICS-LABA in either treatment track.
- *Mild asthma* is currently defined as asthma that is well controlled with as-needed ICS-formoterol, or with low dose ICS plus as-needed SABA.

By this retrospective definition, asthma severity can only be assessed after good asthma control has been achieved and treatment stepped down to find the patient's minimum effective dose (p.74), or if asthma remains uncontrolled despite at least several months of optimized maximal therapy.

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

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

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

Most *clinical trials of biologic therapy*, although requiring patients to have uncontrolled asthma despite taking medium- or high-dose ICS-LABA, do not require contributory factors such as incorrect inhaler technique, poor adherence, or untreated comorbidities to have been addressed, and asthma control re-checked, prior to considering the patient's eligibility for enrolment. Some patients may therefore have 'difficult-to-treat' rather than severe asthma.

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

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

Commented [A26]: Reference replaced 2022 with Barnes PJ, Szefler SJ, Reddel HK, Chipps BE. Symptoms and perception of airway obstruction in asthmatic patients: Clinical implications for use of reliever medications. J Allergy Clin Immunol 2019;144(5):1180-1186. (In eng). DOI: 10.1016/j.jaci.2019.06.040 [replaces: Rosi E, Stendardi L, Binazzi B, Scano G. Perception of airway obstruction and airway inflammation in asthma: a review. Lung 2006;184:251-8.]

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Taylor DR, Bateman ED, Boulet LP, et al. A new perspective on concepts of asthma severity and control. Eur Respir J 2008;32(3):545-54. (In eng). DOI: 10.1183/09031936.00155307.

Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009; 180: 59-99

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Chung KF, Wenzel SE, Brozek JL, et al., *International ERS/ATS Guidelines on Definition, Evaluation and Treatment of Severe Asthma.* Eur. Respir. J., 2014. **43**: 343-373

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Sulaiman I, Greene G, MacHale E, et al. A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma. Eur Respir J. 2018;51(1):1701126. doi:10.1183/13993003.01126-2017

Lee J, Tay TR, Radhakrishna N, et al.
Nonadherence in the era of severe asthma biologics and thermoplasty. Eur Respir J. 2018;51(4):1701836. doi:10.1183/13993003.01836-2017

Commented [A34]: Please add:
National Asthma Education and Prevention Program, *Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007.* J. Allergy Clin. Immunol., 2007. **120**: S94-138.

Cloutier MM, Baptist AP, Blake KV, et al., *2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group.* J Allergy Clin Immunol, 2020. **146**: 1217-1270.

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Reddel HK, Busse WW, Pedersen S, et al., Should recommendations about starting inhaled corticosteroid treatment for mild asthm ... [18]

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National Asthma Education and Prevention Program, *Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis a* ... [19]

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The patient's view of asthma severity

Patients may perceive their asthma as severe if they have intense or frequent symptoms, but this does not necessarily indicate underlying severe disease, as symptoms and lung function can rapidly become well controlled with commencement of ICS-containing treatment, or improved inhaler technique or adherence. Likewise, patients often perceive their asthma as mild if they have symptoms that are easily relieved by SABA, or that are infrequent. Of concern, patients often interpret the term 'mild asthma' to mean that they are not at risk of severe exacerbations and do not need to take controller treatment. This is often described as patients 'underestimating' their asthma severity, but instead it reflects their different interpretation of the words 'severity' and 'mild'.

How useful is the current retrospective definition of asthma severity?

The retrospective definition of *severe asthma* based on 'difficulty to treat' has been widely accepted in guidelines and in specialist clinical practice. It has obvious clinical utility as it identifies patients who, because of their burden of disease and incomplete response to optimized conventional ICS-based treatment, may benefit from referral to a respiratory physician (if available) for further investigation, phenotyping, and consideration of additional treatment such as biologic therapy (See Chapter 3E, p.104). Classifying patients who have modifiable factors, such as incorrect inhaler technique, poor adherence or untreated comorbidities, as having 'difficult-to-treat' rather than 'severe' asthma is appropriate, because their asthma may become well-controlled when such issues are addressed.

By contrast, the clinical utility of the retrospective definition of *mild asthma* is much less clear. By this definition, asthma can be classified as 'mild' only after several months of treatment, and if asthma remains well-controlled on low-dose ICS or as-needed ICS-formoterol. However, many patients with well-controlled asthma have not had their treatment stepped down. In addition, academics have differing opinions about the specific criteria for mild asthma, for example whether occurrence of an isolated exacerbation (e.g. virus-triggered) precludes classification of a patient's asthma as 'mild' for the next 12 months. Further, because 'mild asthma' is assessed retrospectively, it is of little value in deciding on future treatment. Instead, decisions about ongoing treatment should be based upon an individualized assessment of symptom control, exacerbation risk, predictors of response, and patient preferences.

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

Interim advice about asthma severity descriptors

1. *Severe asthma*: GINA continues to support the current definition of severe asthma as asthma that remains uncontrolled despite optimized treatment with high dose ICS-LABA, or that requires high dose ICS-LABA to prevent it from becoming uncontrolled; and the clinically important distinction between difficult-to-treat and severe asthma. See Box 2-4 (p.42) and Chapter 3E (p.104) for more detail about assessment and treatment.
2. *'Mild' asthma, in clinical practice*
   - We suggest that the term 'mild asthma' should generally be avoided in clinical practice, because of the common assumption by patients and clinicians that it equates to low risk. Instead, describe the patient's symptom control and risk factors on their current treatment (p.33).
   - If the term 'mild asthma' needs to be used in clinical practice, qualify it with a reminder that patients with infrequent or mild asthma symptoms can still have severe or fatal exacerbations, and that this risk is reduced by half to two-thirds with low dose ICS or as-needed low-dose ICS-formoterol.
3. *For population-level observational studies*, if clinical details are not available, describe the prescribed (or dispensed) treatment, without imputing severity, e.g. 'patients prescribed SABA with no ICS' rather than 'mild asthma'. Since treatment options change over time, and may differ between guidelines, state the actual treatment, rather than a treatment Step (e.g. 'low dose maintenance and reliever therapy with ICS-formoterol rather than 'Step 3 treatment').
4. *For clinical trials*, describe the patient population by their level of asthma control and treatment, e.g. 'patients with uncontrolled asthma despite medium-dose ICS-LABA plus as-needed SABA' rather than 'moderate asthma'.

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Chung KF, Wenzel SE, Brozek JL, et al., *International ERS/ATS Guidelines on Definition, Evaluation and Treatment of Severe Asthma.* Eur. Respir. J., 2014. **43**: 343-373.

Taylor DR, Bateman ED, Boulet LP, et al. A new perspective on concepts of asthma severity and control. Eur Respir J 2008;32(3):545-54. (In eng). DOI: 10.1183/09031936.00155307.

Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009; 180: 59-99

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Commented [A51]: Please add:
Dusser D, Montani D, Chanez P, et al., Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. Allergy, 2007. 62: 591-604.
Bergstrom SE, Boman G, Eriksson L, et al., *Asthma mortality among Swedish children and young adults, a 10-year study.* Respir. Med., 2008. **102**: 1335-41.

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Dusser D, Montani D, Chanez P, et al., Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. Allergy, 2007. 62: 591-604.
Bergstrom SE, Boman G, Eriksson L, et al., *Asthma mortality among Swedish children and young adults, a 10-year study.* Respir. Med., 2008. **102**: 1335-41.

Commented [A53]: Please add:
Reddel HK, Busse WW, Pedersen S, et al., Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet, 2017. 389: 157-166.
Crossingham I, Turner S, Ramakrishnan S, et al., Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma. Cochrane Database Syst Rev, 2021. 5: Cd013518.

5. *Further discussion is clearly needed.* Given the importance of the issues around mild asthma, GINA proposes holding a stakeholder discussion about the concept of asthma severity and the definition of mild asthma. The aim will be to obtain agreement among health professionals, researchers, industry and regulators about the implications for clinical practice and clinical research of current knowledge about asthma pathophysiology and treatment, and whether/how the term 'mild asthma' should be used in the future. Pending this discussion, no change has been made to use of the term 'mild asthma' elsewhere in this GINA report.

HOW TO DISTINGUISH BETWEEN UNCONTROLLED ASTHMA AND SEVERE ASTHMA

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

It is important to distinguish between severe asthma and uncontrolled asthma, as the latter is a much more common reason for persistent symptoms and exacerbations, and may be more easily improved. Box 2-4 (p.42) shows the initial steps that can be carried out to identify common causes of uncontrolled asthma. More details are given in Section 3E (p.104) about investigation and management of difficult-to-treat and severe asthma, including referral to a respiratory physician or severe asthma clinic where possible, and use of add-on treatment including biologic therapy. The most common problems that need to be excluded before making a diagnosis of severe asthma are:

- Poor inhaler technique (up to 80% of community patients) (Box 3-12, p.88)
- Poor medication adherence (Box 3-13, p.90)
- Incorrect diagnosis of asthma, with symptoms due to alternative conditions such as inducible laryngeal obstruction, cardiac failure or lack of fitness (Box 1-5, p.27)
- Multimorbitidy such as rhinosinusitis, GERD, obesity and obstructive sleep apnea (Chapter 3D, p.94)
- 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

See Chapter 3E (p.104) for more details about assessment and management of difficult-to-treat and severe asthma.

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Taylor DR, Bateman ED, Boulet LP, et al. A new perspective on concepts of asthma severity and control. Eur Respir J 2008; 32: 545-554.

Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009; 180: 59-99.

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Chapter 3.

Treating asthma to control symptoms and minimize risk

This chapter is divided into five parts:

Part A. General principles of asthma management (p.44)

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

- Medications, including treatment steps (p.50)
- Treating modifiable risk factors (p.75)
- Non-pharmacological therapies and strategies (p.75)

Part C. Guided asthma self-management education and skills training (p.87)

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

Part D. Managing asthma with multimorbidity and in specific populations (p.94)

Part E. Difficult-to-treat and severe asthma in adults and adolescents (including decision tree) (p.104)

Management of worsening and acute asthma is described in Chapter 4 (p.123).

PART A. GENERAL PRINCIPLES OF ASTHMA MANAGEMENT

KEY POINTS

Goals of asthma management

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

The patient-health professional partnership

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

Making decisions about asthma treatment

- Asthma treatment is adjusted in a continual cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk (of exacerbations and side-effects), and of patient preferences.
- For population-level decisions about asthma treatment in Steps 1–4, the 'preferred' options represent the best treatments for most patients, based on evidence from randomized controlled trials, meta-analyses and observational studies about safety, efficacy and effectiveness, with a particular emphasis on symptom burden and exacerbation risk. For Steps 1–5, there are different population-level recommendations for different age-groups (adults/adolescents, children 6–11 years, children 5 years and younger). In Step 5, there are also different population-level recommendations depending on the inflammatory phenotype, Type 2 or non-Type 2.
- 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 goals or concerns and practical issues (inhaler technique, adherence, medication access and cost to the patient).

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LONG-TERM GOALS OF ASTHMA MANAGEMENT

The long-term goals of asthma management from a clinical perspective are:

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

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

THE PATIENT-HEALTH CARE PROVIDER PARTNERSHIP

Effective asthma management requires the development of a partnership between the person with asthma (or the parent/carer) and health care providers.[143] 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[144] (Evidence A) and children[145] (Evidence A).

There is emerging evidence that shared decision-making is associated with improved outcomes.[146] 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[147-149] (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[147-149] without lengthening consultation times.[150] It can also enhance patient adherence.[150] Training patients to give information clearly, seek information, and check their understanding of information provided is also associated with improved adherence with treatment recommendations.[150]

Box 3-1. Communication strategies for health care providers

Key strategies to facilitate good communication[148,149]
• A congenial demeanor (friendliness, humor and attentiveness) • Allowing the patient to express their goals, beliefs and concerns • Empathy, reassurance, and prompt handling of any concerns • Giving encouragement and praise • Giving appropriate (personalized) information • Providing feedback and review

How to reduce the impact of low health literacy[151]

- Order information from most to least important.
- Speak slowly and use simple words (avoid medical language, if possible).
- Simplify numeric concepts (e.g. use numbers instead of percentages).
- Frame instructions effectively (use illustrative anecdotes, drawings, pictures, table or graphs).
- Confirm understanding by using the 'teach-back' method (ask patients to repeat instructions).
- Ask a second person (e.g. nurse, family member) to repeat the main messages.
- Pay attention to non-verbal communication by the patient.
- Make patients feel comfortable about asking questions.

Health literacy and asthma

There is increasing recognition of the impact of low health literacy on health outcomes, including in asthma.[151,152] 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'.[151] Low health literacy is associated with reduced knowledge and worse asthma control.[153] In one study, low numeracy among parents of children with asthma was associated with higher risk of exacerbations.[152] Interventions adapted for cultural and ethnicity perspectives have been associated with improved knowledge and significant improvements in inhaler technique.[154] Suggested communication strategies for reducing the impact of low health literacy are shown in Box 3-1.

PERSONALIZED CONTROL-BASED ASTHMA MANAGEMENT

Asthma control has two domains: symptom control and risk reduction (see Box 2-2, p.36). In control-based asthma management, pharmacological and non-pharmacological treatment is adjusted in a continual cycle that involves assessment, treatment and review by appropriately trained personnel (Box 3-2). Asthma outcomes have been shown to improve after the introduction of control-based guidelines[155,156] or practical tools for implementation of control-based management strategies.[146,157] 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. From 2014, GINA asthma management has focused not only on asthma symptom control, but also on personalized management of the patient's modifiable risk factors for exacerbations, other adverse outcomes and comorbidities, and taking into account the patient's preferences and goals.

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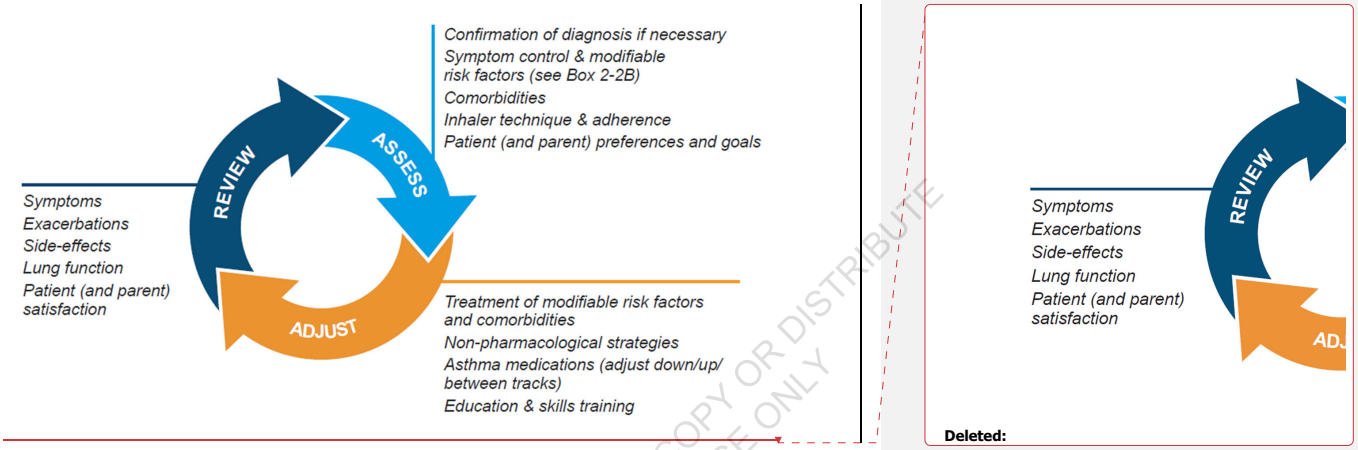
Box 3-2. The asthma management cycle for personalized asthma care



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For many patients in primary care, symptom control is a good guide to a reduced risk of exacerbations.[158] 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][159,160]) or different treatment regimens (such as as-needed ICS-formoterol in mild asthma[161-164] and ICS-formoterol maintenance and reliever therapy[165,166]), and in patients with mild or severe asthma, there may be discordance between responses for symptom control and exacerbations.

In particular, **patients with apparently mild asthma and few or intermittent symptoms may be still at risk of severe exacerbations**[138] (Box 2-2B, p.36). 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.

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Therefore, in control-based management, ***both*** domains of asthma control (symptom control and future risk – see Box 2-2, p.36) should be taken into account when choosing asthma treatment and reviewing the response.[20,55]

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Alternative strategies for adjusting asthma treatment

Some alternative strategies have been evaluated for adjusting asthma treatment:

- *Treatment guided by sputum eosinophil count*: in adults, this approach, when compared with guidelines-based treatment, leads to a reduced risk of exacerbations and similar levels of symptom control and lung function.[167] The benefits have primarily been seen in patients with frequent exacerbations and severe asthma.[167] However, only a limited number of centers have routine access to induced sputum analysis. There are insufficient data available in children to assess this approach.[167]
- *Treatment guided by fractional concentration of exhaled nitric oxide (FeNO):* In several studies of FeNO-guided treatment, problems with the design of the intervention and/or control algorithms make comparisons and conclusions difficult.[168] Results of FeNO measurement at a single point in time should be interpreted with caution (see p.26).[31,169] In children and young adults with asthma, FeNO-guided treatment was associated with a significant reduction in the number of patients with ≥1 exacerbation (OR 0.67 [95% CI 0.51–0.90]) and in exacerbation rate (mean difference -0.27 [-0.49 to -0.06] per year) compared with guidelines-based treatment[170]

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(Evidence A); similar differences were seen in comparisons between FeNO-guided treatment and non-guidelines-based algorithms.[170] However, in non-smoking adults with asthma, no significant reduction in risk of exacerbations and in exacerbation rates was observed with FeNO-guided treatment compared to guideline-based treatment; a difference was only seen in studies with other (non-typical) comparator approaches.[171] No significant differences were seen in symptoms or ICS dose with FeNO-guided treatment compared with other strategies.[170,171]

Sputum-guided treatment is recommended for adult patients with moderate or severe asthma who are managed in (or can be referred to) centers experienced in this technique[137,167] (Evidence A). In children, FeNO-guided treatment significantly reduces exacerbation rates compared with guidelines-based treatment (Evidence A).[170] However, further studies are needed to identify the populations most likely to benefit from sputum-guided[167] or FeNO-guided treatment,[170,171] and the optimal frequency of FeNO monitoring.

There is a need for evidence-based corticosteroid de-escalation strategies in patients with asthma. In a randomized controlled trial (RCT) of patients taking high dose ICS-LABA, a strategy based on a composite of Type 2 biomarkers only vs. an algorithm based on ACQ-7 and history of recent exacerbation was inconclusive because a substantial proportion of patients did not follow recommendations for treatment change.[172] Until more definitive evidence for a specific strategy is available, GINA continues to recommend a clinical evaluation that includes patient-reported symptoms as well as modifiable risk factors, comorbidities and patient preferences when making treatment decisions. Further evidence on the role of biomarkers in such decisions in Steps 1–4 is needed.

Choosing between asthma treatment options

At each treatment step in asthma management, different medication options are available that, although not of identical efficacy, may be alternatives for controlling asthma. Different considerations apply to recommendations or choices made for broad populations compared with those for individual patients (Box 3-3, p. 48), as follows:

- *Population-level medication choices*: Population-level medication choices are often applied by bodies such as national formularies or managed care organizations. Population-level recommendations aim to represent the best option for most patients in the particular population. At each treatment step, 'preferred' medications (controller and/or reliever) are recommended that provide the best benefit-to-risk ratio for both symptom control and risk reduction. Choice of the preferred controller and preferred reliever is based on evidence from efficacy studies (highly controlled studies in well-characterized populations) and effectiveness studies (from pragmatically controlled studies, or studies in broader populations, or strong observational data),[173] with a particular focus on symptoms and exacerbation risk. Safety and relative cost are also taken into account. In **Step 5**, there are different population-level recommendations depending on the inflammatory phenotype, Type 2 or non-Type 2. In GINA 2021, the recommendations for adults and adolescents have been clarified in the treatment figure (Box 3-5A, p.60) by showing treatment options in two 'tracks' based on the choice of reliever. **Track 1**, with as-needed low dose ICS-formoterol as the reliever, is the preferred approach for most patients, based on evidence of overall lower exacerbation risk and similar symptom control compared with treatments in **Track 2** in which the reliever is short-acting beta$_2$ agonist (SABA) (for more details, see Chapter 3B, p.50).
- *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 goals 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 evidence and research activity about individualized treatment is focused on severe asthma[174,175] (see Chapter 3E, p.104).

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)

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

- Efficacy
- Effectiveness
- Safety

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

- Availability and cost at the population level

For Steps 1–5, there are different population-level recommendations by age-group (adults/adolescents, children 6–11 years, children 5 years and younger). In Step 5, there are also different population-level recommendations depending on the inflammatory phenotype, Type 2 or non-Type 2.

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) based on evidence 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 views***
   - 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

- For safety, GINA no longer recommends treatment of asthma in adults and adolescents with SABA alone. All adults and adolescents with asthma should receive ICS-containing controller treatment to reduce their risk of serious exacerbations and to control symptoms. ICS-containing controller can be delivered either with regular daily treatment or, in mild asthma, with as-needed ICS-formoterol taken whenever needed for symptom relief.

Treatment tracks for adults and adolescents

- For clarity, the treatment figure for adults and adolescents now shows two 'tracks', based on the choice of reliever. Treatment may be stepped up or down within a track using the same reliever at each step, or treatment may be switched between tracks, according to the individual patient's needs.
- ***Track 1***, in which the reliever is low dose ICS-formoterol, is the preferred approach recommended by GINA. When a patient at any step has asthma symptoms, they use low dose ICS-formoterol as needed for symptom relief. In Steps 3–5, they also take ICS-formoterol as regular daily treatment. This approach is preferred because it reduces the risk of severe exacerbations compared with using a SABA reliever, with similar symptom control.
- ***Track 2***, in which the reliever is a SABA, is an alternative if Track 1 is not possible, or if a patient is stable, with good adherence and no exacerbations in the past year on their current therapy. In Step 1, the patient takes a SABA and a low dose ICS together for symptom relief (in combination, or with the ICS taken right after the SABA). In Steps 2–5, the reliever is a SABA. Before considering a SABA reliever, consider whether the patient is likely to be adherent with their ICS-containing controller therapy, as otherwise they would be at higher risk of exacerbations.

Steps 1 and 2

- In adults and adolescents with mild asthma, treatment with as-needed-only low dose ICS-formoterol reduces the risk of severe exacerbations by about two-thirds compared with SABA-only treatment, and is non-inferior to daily low dose ICS for severe exacerbations, with no clinically important difference in symptom control. The risk of emergency department visits and hospitalizations is reduced with as-needed ICS-formoterol compared with daily ICS. In patients previously using SABA alone, as-needed ICS-formoterol significantly reduced the risk of severe exacerbations compared with daily ICS.
- Treatment with regular daily low dose ICS, with as-needed SABA, is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization and death. However, adherence with ICS in the community is poor, leaving patients taking SABA alone and at increased risk of exacerbations.

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

- Before considering any step up, *first* confirm that the symptoms are due to asthma and identify and address *common problems* such as inhaler technique, adherence, allergen exposure and multimorbidity; provide patient education.
- For adults and adolescents, the preferred Step 3 treatment is low dose ICS-formoterol as maintenance and reliever therapy (MART). This reduces the risk of severe exacerbations compared with maintenance ICS-LABA controller plus as-needed SABA, with similar or better symptom control. If needed, the maintenance dose of ICS-formoterol can be increased to medium (i.e. Step 4). MART is also a preferred treatment option for children 6–11 years.
- Other Step 3 options for adults, adolescents and children include maintenance ICS-LABA plus as-needed SABA or, for children 6–11 years, medium dose ICS plus as-needed SABA.
- For children, try other controller options at the same step before stepping up.
- ICS-formoterol should not be used as the reliever for patients taking a different ICS-LABA maintenance treatment, since clinical evidence for safety and efficacy is lacking.

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Stepping down to find the minimum effective dose

- Once good asthma control has been achieved and maintained for 2–3 months, consider stepping down gradually to find the patient's lowest treatment that controls both symptoms and exacerbations
- Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit.
- Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma.

For all patients with asthma, provide asthma education and training in essential skills

- 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.

For patients with one or more risk factors for exacerbations

- Prescribe ICS-containing medication, preferably from Track 1 options, i.e. with as-needed ICS-formoterol as reliever; 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, over-use of SABA).
- Consider non-pharmacological strategies and interventions to assist with symptom control and risk reduction, (e.g. smoking cessation advice, breathing exercises, some avoidance strategies).

Difficult-to-treat and severe asthma (see section 3E, p.104)

- Patients with poor symptom control and/or exacerbations despite medium or high dose ICS-LABA treatment should be assessed for contributing factors, and asthma treatment optimized.
- If the problems continue or diagnosis is uncertain, refer to a specialist center for phenotypic assessment and consideration of add-on therapy including biologics.

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

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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 medications contain ICS and are used to reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and related decline in lung function.[106] In patients with mild asthma, controller treatment may be delivered through as-needed low dose ICS-formoterol, taken when symptoms occur and before exercise. The dose and regimen of controller medications should be optimized to minimize the risk of medication side-effects, including risks of needing oral corticosteroids (OCS).
- *Reliever 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 (EIB). Relievers are divided into as-needed low dose ICS-formoterol (the preferred reliever, but not if the maintenance controller contains a different ICS-LABA), or as-needed SABA. Over-use of SABA (e.g. dispensing of three or more 200-dose canisters in a year, corresponding to average use more than daily) increases the risk of asthma exacerbations.[123,82] Reducing and, ideally, eliminating the need for SABA reliever is both an important goal in asthma management and a measure of the success of asthma treatment.

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- *Add-on therapies for patients with severe asthma* (Section 3E, p.104): these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications (usually a high dose of ICS plus a LABA) and treatment of modifiable risk factors (see Box 3-8, p.75).

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Initial controller treatment

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

- Early initiation of low dose ICS in patients with asthma leads to a greater improvement in lung function than if symptoms have been present for more than 2–4 years.[176,177] One study showed that after this time, higher ICS doses were required, and lower lung function was achieved.[178]
- Patients not taking ICS who experience a severe exacerbation have a greater long-term decline in lung function than those who are taking ICS.[106]
- For patients with occupational asthma, early removal from exposure to the sensitizing agent and early controller treatment increase the probability of resolution of symptoms, and improvement of lung function and airway hyperresponsiveness.[40,41]
- Starting treatment with SABA alone encourages patients to regard it as their main asthma treatment, and increases the risk of poor adherence when daily ICS is subsequently prescribed.

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Recommended options for initial controller treatment in adults and adolescents, based on evidence (where available) and consensus, are listed in Box 3-4A (p.54) and shown in Box 3-4B (p.55). The corresponding resources for children 6–11 years are on p.57 and p.58. 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.60).

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Does FeNO help in deciding whether to commence ICS?

In studies mainly limited to non-smoking patients, FeNO >50 parts per billion (ppb) has been associated with a good short-term response to ICS.[169,179] However, these studies did not examine the longer-term risk of exacerbations. Such evidence therefore does not mean that it is safe with regard to exacerbations to withhold ICS in patients with low initial FeNO. More recently, in two 12-month studies in mild asthma, severe exacerbations were reduced with as-needed ICS-formoterol versus as-needed SABA and versus maintenance ICS, independent of baseline inflammatory characteristics including FeNO.[163,164]

Consequently, in patients with a diagnosis or suspected diagnosis of asthma, measurement of FeNO can support the decision to start ICS, but cannot be used to decide against treatment with ICS. Based on past and current evidence, GINA recommends treatment with daily low dose ICS or as-needed low dose ICS-formoterol for all patients with mild asthma, to reduce the risk of serious exacerbations.[141]

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O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med 2018; 378: 1865-1876.
Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. N Engl J Med 2018; 378: 1877-1887.
Beasley R, Holliday M, Reddel HK, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med 2019; 380: 2020-2030.
Hardy J, Baggott C, Fingleton J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. The Lancet 2019; 394: 919-928.

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

Once asthma treatment has been commenced (Boxes 3-4A-D), ongoing treatment decisions are based on a personalized cycle of assessment, adjustment of treatment, and review of the response. For each patient, in addition to treatment of modifiable risk factors, controller medication can be adjusted up or down in a stepwise approach (Box 3-5A-B) to achieve good symptom control and minimize future risk of exacerbations, persistent airflow limitation and medication side-effects. Once good asthma control has been maintained for 2–3 months, treatment may be stepped down in order to find the patient's minimum effective treatment (Box 3-7, p.74).

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People's ethnic and racial backgrounds may be associated with different responses to treatment. These are not necessarily associated with genetic differences.[180] The contributors are likely to be multifactorial, including differences in exposures, social disadvantage, diet and health-seeking behavior.

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

ASTHMA TREATMENT TRACKS FOR ADULTS AND ADOLESCENTS

In the main treatment figure for adults and adolescents (Box 3-5A, p.60), the options for ongoing treatment are shown as two treatment 'tracks', with the key difference being the medication that is used for symptom relief: as-needed low dose ICS-formoterol in Track 1 (preferred), and as-needed SABA in Track 2.

The reasons for showing treatment in two tracks are, first, to show clinicians how treatment can be stepped up and down using the same reliever at each step, and second, to show that SABA is the appropriate reliever for patients prescribed ICS-non-formoterol-LABA maintenance treatment.

***Track 1*: The reliever is as-needed low dose ICS-formoterol.** This is the preferred approach recommended by GINA for adults and adolescents, because using low dose ICS-formoterol as reliever (sometimes called 'anti-inflammatory reliever' or AIR) reduces the risk of severe exacerbations compared with regimens with SABA as reliever, with similar symptom control.

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

***Track 2*: The reliever is as-needed SABA.** This is an alternative approach if Track 1 is not possible, or if a patient's asthma is stable with good adherence and no exacerbations on their current therapy. However, before prescribing a regimen with SABA reliever, consider whether the patient is likely to be adherent with their ICS-containing controller therapy, as otherwise they will be at higher risk of exacerbations.

- In Step 1, the patient takes a SABA and a low dose ICS together for symptom relief when symptoms occur (in a combination inhaler, or with the ICS taken right after the SABA).
- In Steps 2–5, a SABA (alone) is used for symptom relief, and the patient takes ICS-containing controller medication regularly every day.

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

Before stepping up, check for common problems such as incorrect inhaler technique, poor adherence, and environmental exposures, and confirm that the symptoms are due to asthma (Box 2-4, p.42).

Underneath the two treatment tracks for adults and adolescents are some additional controller options, that either have limited indications, or for which there is less evidence for their safety and/or efficacy, compared with the treatments in Tracks 1 and 2.

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

Presenting symptoms	Preferred INITIAL treatment (Track 1)	Alternative INITIAL treatment (Track 2)
Infrequent asthma symptoms, e.g. less than twice a month and no risk factors for exacerbations, including no exacerbations in the last 12 months (Box 2-2B, p.36)	**As-needed low dose ICS-formoterol** (Evidence B)	**Low dose ICS taken whenever SABA is taken**, in combination or separate inhalers (Evidence B)
Asthma symptoms or need for reliever twice a month or more	**As-needed low dose ICS-formoterol** (Evidence A)	**Low dose ICS with as-needed SABA** (Evidence A). Before choosing this option, consider likely adherence with daily ICS.
Troublesome asthma symptoms most days (e.g. 4–5 days/week); or waking due to asthma once a week or more, especially if any risk factors exist (Box 2-2B, p.36)	**Low dose ICS-formoterol maintenance and reliever therapy** (Evidence A)	**Low dose ICS-LABA with as-needed SABA** (Evidence A), OR Medium dose ICS with as-needed SABA (Evidence A). Consider likely adherence with daily controller.
Initial asthma presentation is with severely uncontrolled asthma, or with an acute exacerbation	**Medium dose ICS-formoterol maintenance and reliever therapy** (Evidence D). A short course of oral corticosteroids may also be needed.	**Medium or high dose ICS-LABA** (Evidence D) with as-needed SABA. Consider likely adherence with daily controller. A short course of oral corticosteroids may also be needed. High dose ICS with as-needed SABA is another option (Evidence A) but adherence is poor compared with combination ICS-LABA.

Before starting initial controller treatment

- Record evidence for the diagnosis of asthma.
- Record the patient's level of symptom control and risk factors, including lung function (Box 2-2, p.36).
- Consider factors influencing choice between available treatment options (Box 3-3, p.48), including likely adherence with daily controller, particularly if the reliever is SABA.
- Ensure that the patient can use the inhaler correctly.
- Schedule an appointment for a follow-up visit.

After starting initial controller treatment

- Review patient's response (Box 2-2, p.36) after 2–3 months, or earlier depending on clinical urgency.
- See Box 3-5 (p.60) for recommendations for ongoing treatment and other key management issues.
- Check adherence and inhaler technique frequently.
- Step down treatment once good control has been maintained for 3 months (Box 3-7, p.74).

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

This table is based on evidence from available studies and consensus, including considerations of cost and likely adherence with controller therapy. See also Box 3-4B (p.55) for where to start on the main treatment figure for adults and adolescents. See Box 3-6, p.62 for low, medium and high ICS doses for adults and adolescents.

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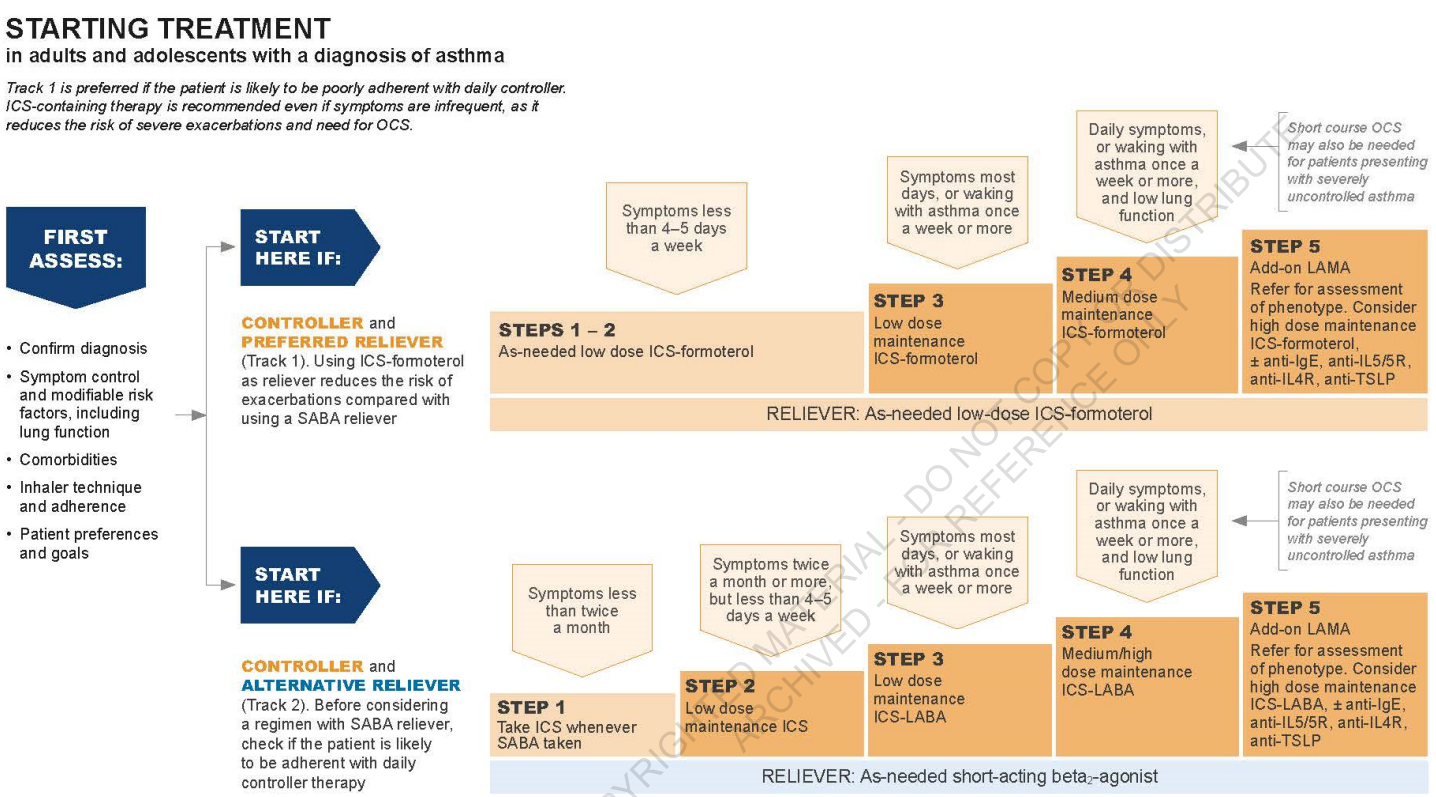
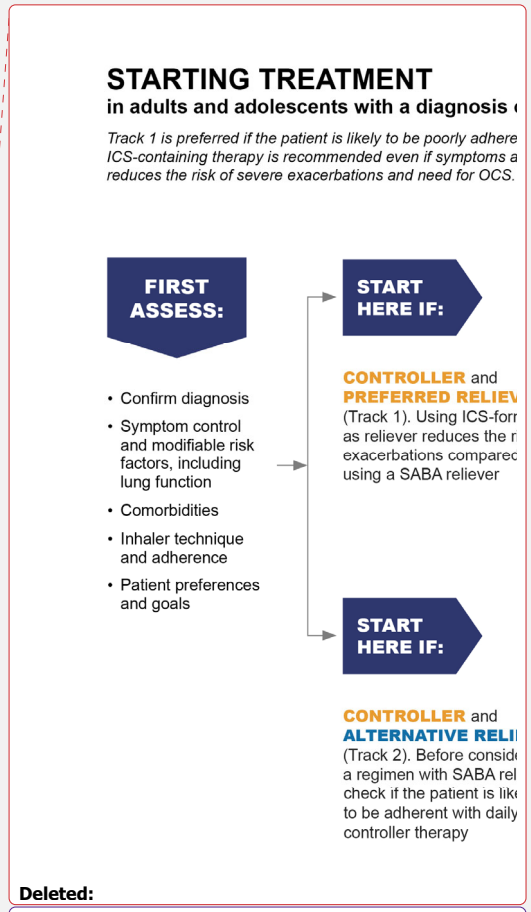
Box 3-4Bi. Selecting initial controller treatment in adults and adolescents with a diagnosis of asthma (V1)



ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; MART: maintenance and reliever therapy with ICS-formoterol; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist. See Box 3-6, p.62 for low, medium and high ICS doses for adults and adolescents.



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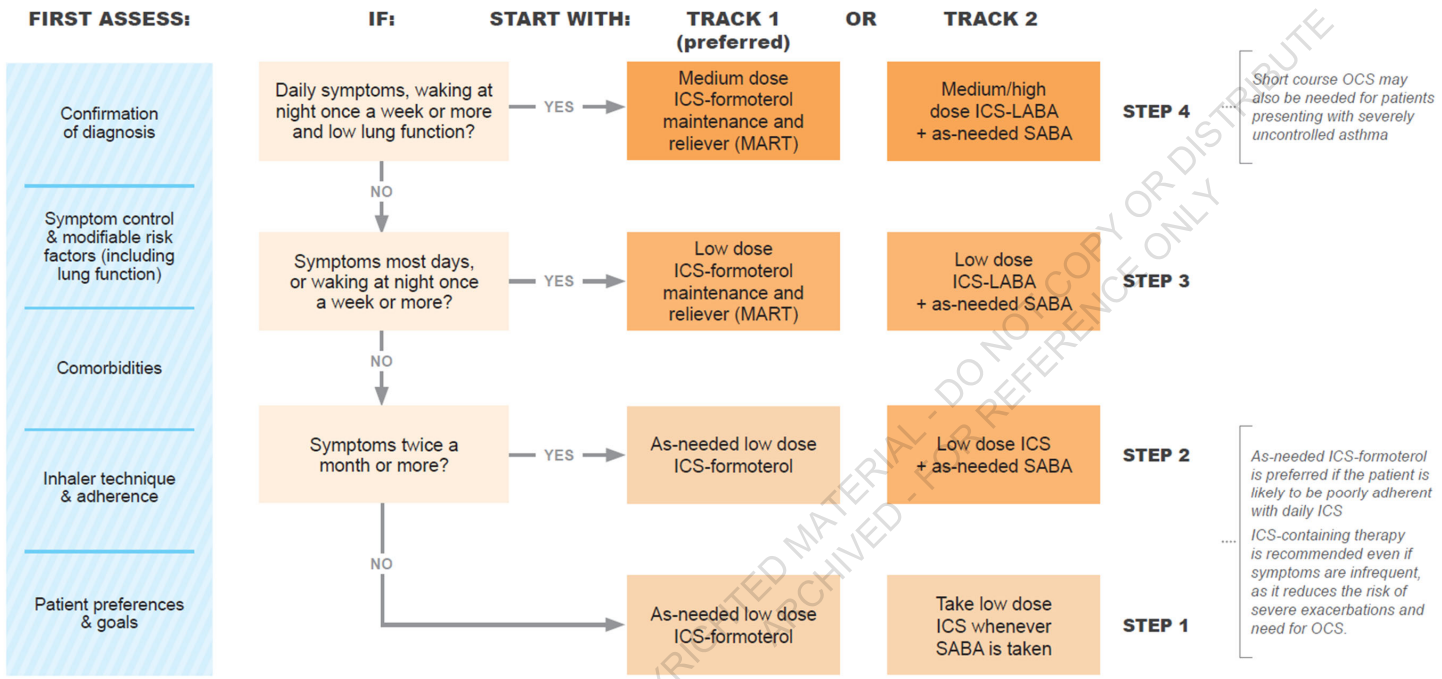
Box 3-4Bii. Selecting initial controller treatment in adults and adolescents with a diagnosis of asthma (V2)



ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; MART: maintenance and reliever therapy with ICS-formoterol; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist

See Box 3-6, p.62 for low, medium and high ICS doses for adults and adolescents.

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Box 3-4C. Initial asthma treatment - recommended options for children aged 6–11 years

Presenting symptoms	Preferred INITIAL treatment
Infrequent asthma symptoms, e.g. less than twice a month and no risk factors for exacerbations (Box 2-2B, p.36)	**As-needed SABA** Other options include taking ICS whenever SABA is taken, in combination or separate inhalers.
Asthma symptoms or need for reliever twice a month or more, but less than daily	**Low dose ICS with as-needed SABA** (Evidence A), or Other options include daily LTRA (less effective than ICS, Evidence A), or taking ICS whenever SABA is taken in combination or separate inhalers (Evidence B). Consider likely adherence with controller if reliever is SABA.
Troublesome asthma symptoms most days (e.g. 4–5 days/week); or waking due to asthma once a week or more, especially if any risk factors exist (Box 2-2B)	**Low dose ICS-LABA with as needed SABA** (Evidence A), OR **Medium dose ICS with as-needed SABA** (Evidence A), OR **Very low dose ICS-formoterol maintenance and reliever** (Evidence B) Other options include low dose ICS with daily LTRA, with as needed SABA.
Initial asthma presentation is with severely uncontrolled asthma, or with an acute exacerbation	Start regular controller treatment with medium dose ICS-LABA with as-needed SABA or low dose ICS-formoterol maintenance and reliever (MART). A short course of OCS may also be needed.

Before starting initial controller treatment

- Record evidence for the diagnosis of asthma, if possible.
- Record the child's level of symptom control and risk factors, including lung function (Box 2-2, p.36, Box 2-3, p.37).
- Consider factors influencing choice between available treatment options (Box 3-3, p.48).
- Ensure that the child can use the inhaler correctly.
- Schedule an appointment for a follow-up visit.

After starting initial controller treatment

- Review child's response (Box 2-2, p.36) after 2–3 months, or earlier depending on clinical urgency.
- See Box 3-5B (p.61) 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.74).

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. See also Box 3-4D (p.58) for where to start on the main treatment figure for children 6–11 years. See Box 3-6, p.62 for low, medium and high ICS doses in children.

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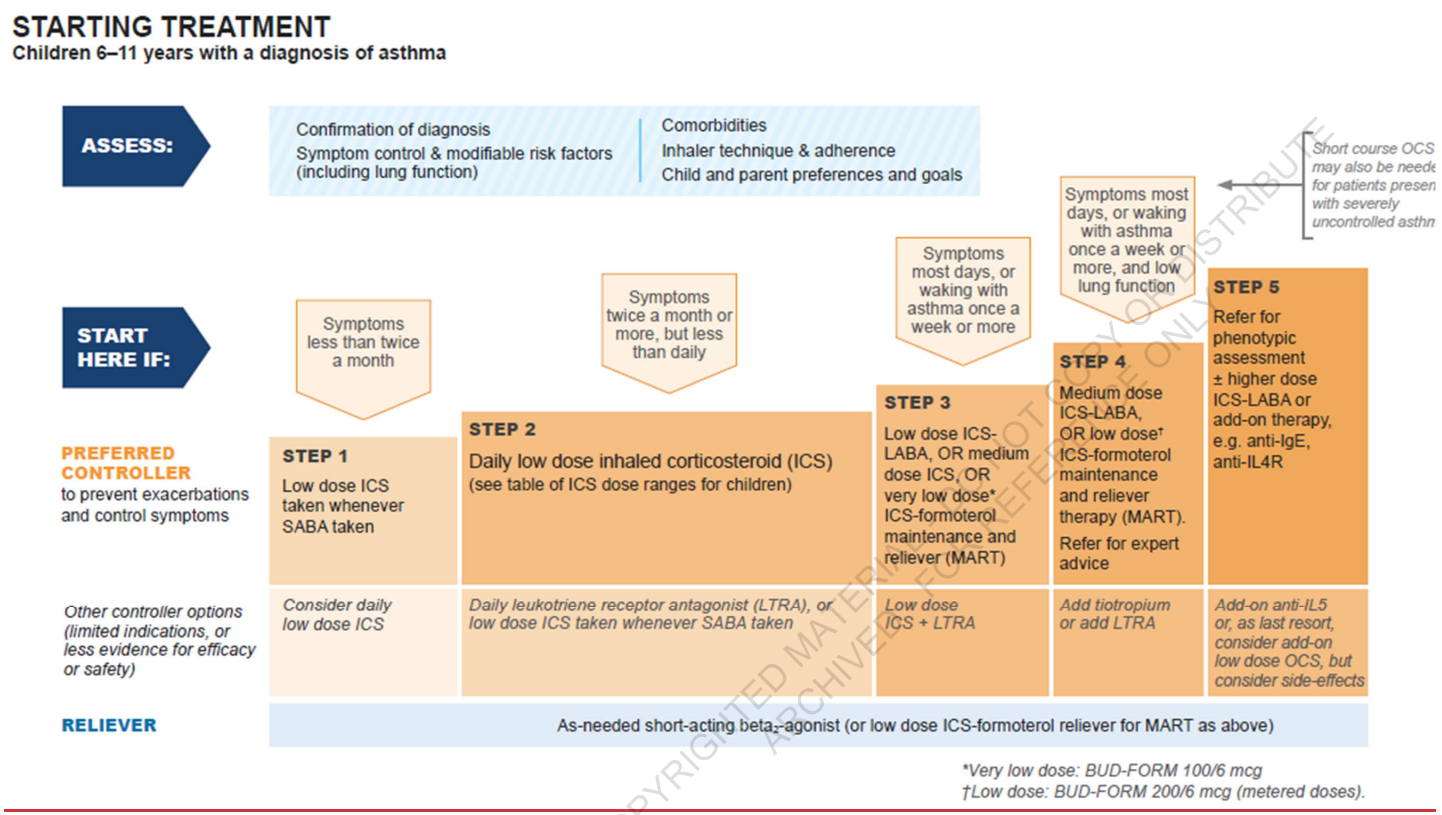
Box 3-4Di. Selecting initial controller treatment in children aged 6–11 years with a diagnosis of asthma (V1)



BUD-FORM: budesonide-formoterol; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LTRA: leukotriene receptor antagonist; MART: maintenance and reliever therapy with ICS-formoterol; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist. See Box 3-6, p.62 for low, medium and high ICS doses in children.

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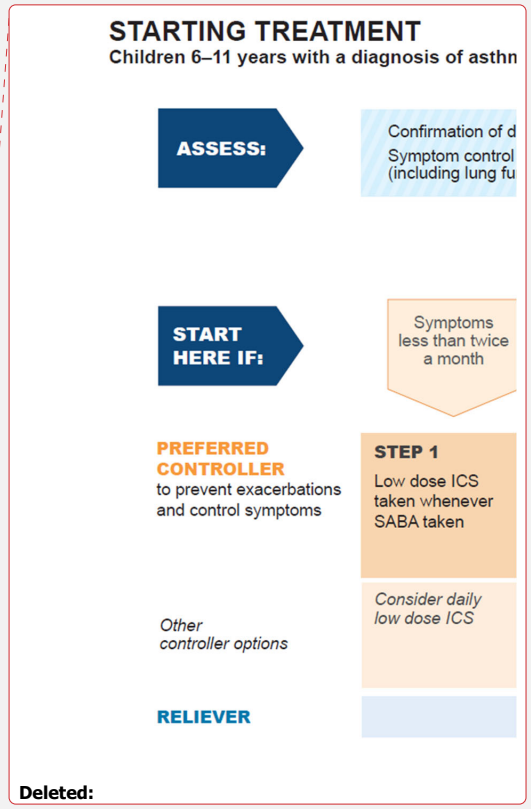

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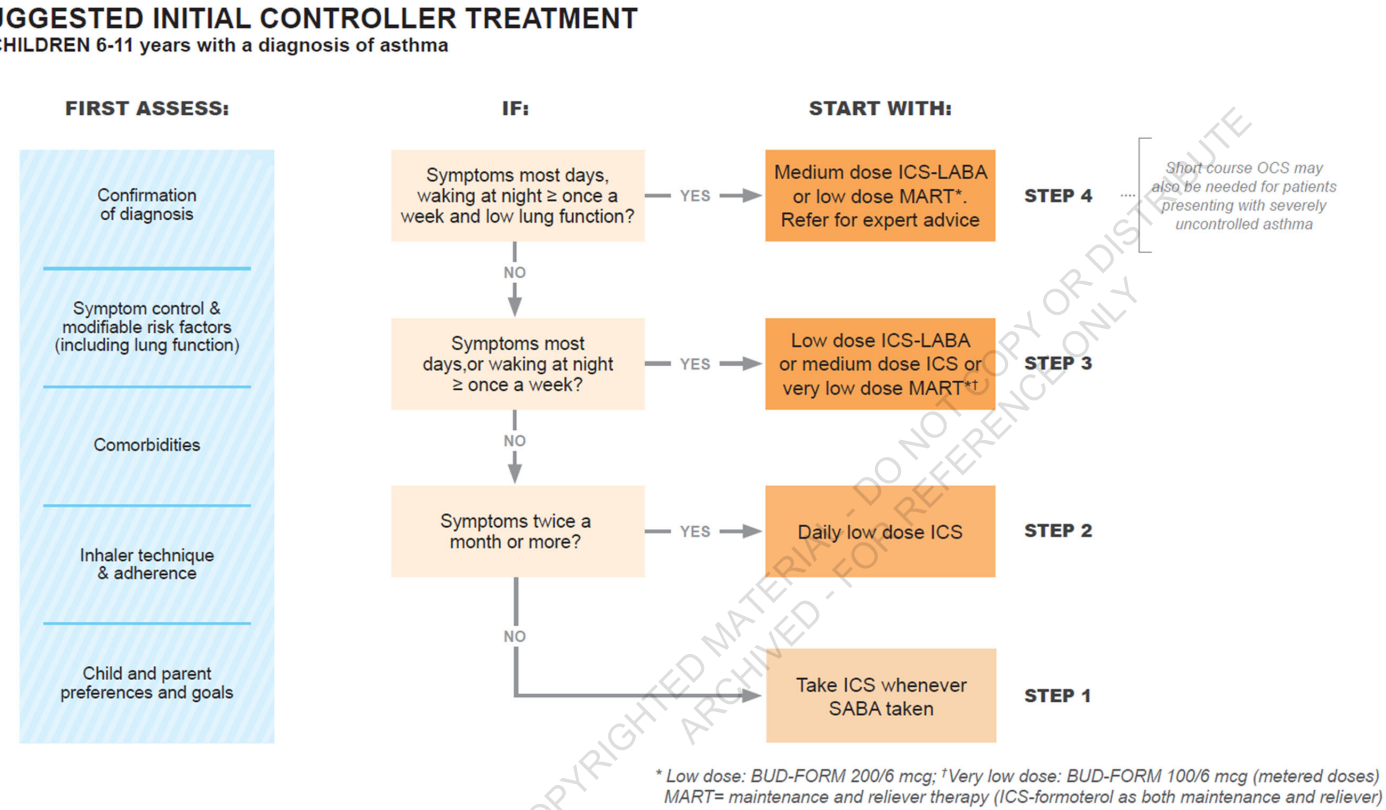
Box 3-4Dii. Selecting initial controller treatment in children aged 6–11 years with a diagnosis of asthma (V2)



BUD-FORM: budesonide-formoterol; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; MART: maintenance and reliever therapy with ICS-formoterol; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist. See Box 3-6, p.62 for low, medium and high ICS doses in children.

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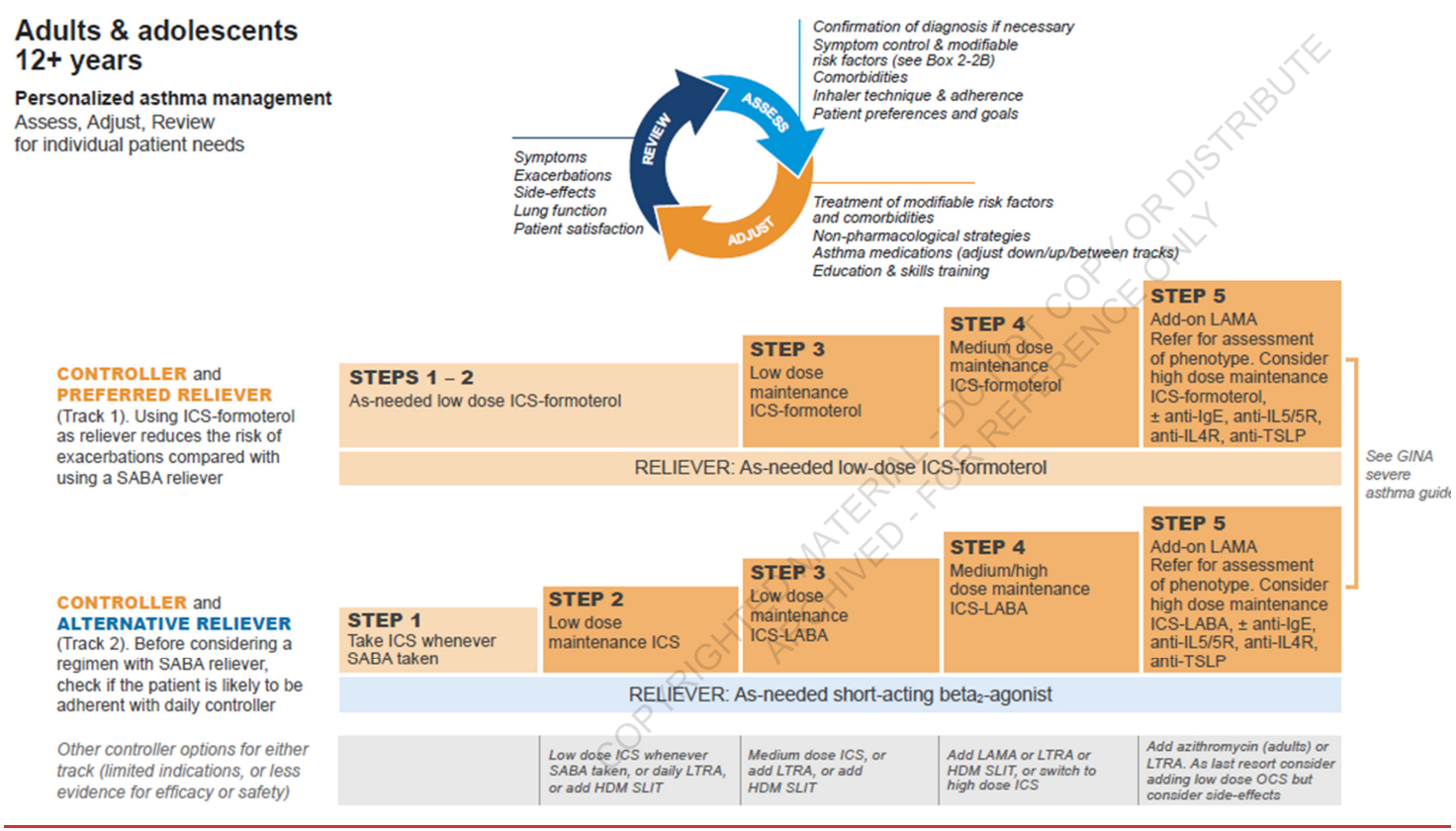
Box 3-5A. Personalized management for adults and adolescents to control symptoms and minimize future risk



HDM: house dust mite; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist; SLIT: sublingual immunotherapy. For recommendations about *initial* asthma treatment in adults and adolescents, see Box 3-4A (p.54) and 3-4B (p.55). See Box 3-6, p.62 for low, medium and high ICS doses for adults and adolescents.

Adults & adolescents
12+ years
Personalized asthma management
Assess, Adjust, Review
for individual patient needs
CONTROLLER and PREFERRED RELIEVER
(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever
CONTROLLER and ALTERNATIVE RELIEVER
(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller
Other controller options for either track

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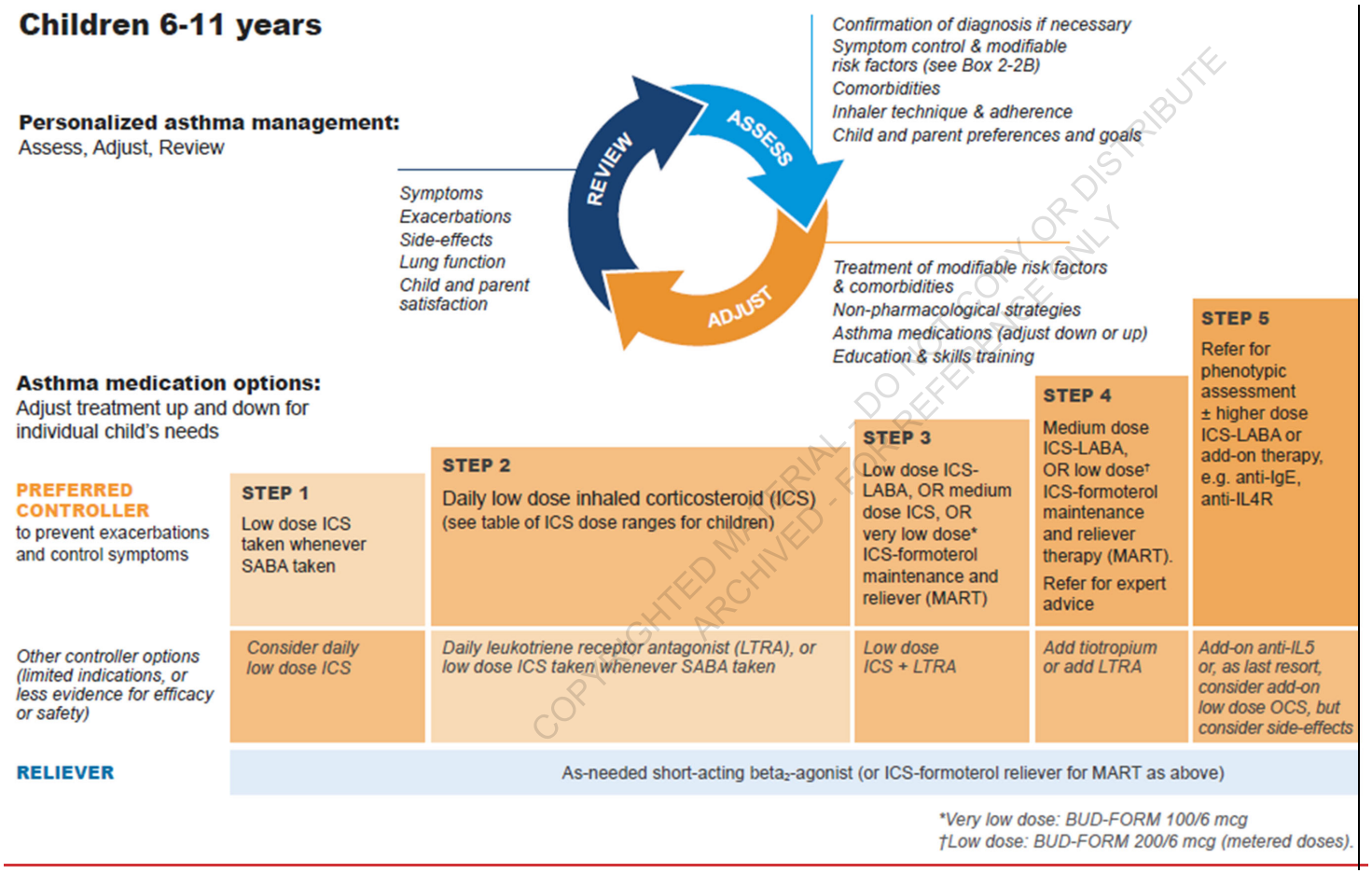
Box 3-5B. Personalized management for children 6–11 years to control symptoms and minimize future risk



Children 6-11 years
Personalized asthma management:
Assess, Adjust, Review
Asthma medication options:
Adjust treatment up and down for individual child's needs
PREFERRED CONTROLLER
to prevent exacerbations and control symptoms
STEP 1
Low dose ICS taken whenever SABA taken
Other controller options
Consider daily low dose ICS
RELIEVER

BUD-FORM: budesonide-formoterol; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LTRA: leukotriene receptor antagonist; MART: maintenance and reliever therapy with ICS-formoterol; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist. For *initial* asthma treatment in children aged 6–11 years, see Box 3-4C (p.57) and Box 3-4D (p.58)

See Box 3-6, p.62 for low, medium and high ICS doses in children.

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Box 3-6. Low, medium and high daily metered doses of inhaled corticosteroids (alone or with LABA)

This is not a table of equivalence, but instead, suggested total daily doses for 'low', 'medium' and 'high' dose ICS options for adults/adolescents (Box 3-5A, p.60) and children 6–11 years (Box 3-5B, p.61), based on product information. Few data are available for comparative potency, so **this table does NOT imply potency equivalence**. Doses may differ by country, depending on local products, regulatory labelling and clinical guidelines or, for one product, with addition of a LAMA to an ICS-LABA.[181]

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

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

Adults and adolescents (12 years and older)

Inhaled corticosteroid	Total daily ICS dose (mcg) – see notes above		
	Low	Medium	High
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400
Children 6–11 years – see notes above (for children 5 years and younger, see Box 6-6, p.166)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle, HFA)	50-100	>100-200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80-160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50-100	>100-200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50-100	>100-200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; n.a. not applicable; pMDI: pressurized metered dose inhaler; ICS by pMDI should preferably be used with a spacer.

For new preparations, including generic ICS, the manufacturer's information should be reviewed carefully, as products containing the same molecule may not be clinically equivalent. For more detailed discussion see Raissy et al.[107] Combination inhalers that include a long-acting muscarinic antagonist (LAMA) may have different ICS dosing – see product information.

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Choice of medication, device and dose

In clinical practice, the choice of medication, device and dose for controller and reliever should be based for each individual patient on assessment of symptom control, risk factors, patient preference, and practical issues (cost, ability to use the device, and adherence) (Box 3-3, p.48). It is important to monitor the response to treatment and any side-effects, and to adjust the dose accordingly (Box 3-5, p.60). Once good symptom control has been maintained for 2–3 months, the ICS dose should be carefully titrated to the minimum dose that will maintain good symptom control and minimize exacerbation risk, while reducing the potential for side-effects (Box 3-7, p.74). Patients who are being considered for a high daily dose of ICS (except for short periods) should be referred for expert assessment and advice, where possible (Chapter 3E, p.104). There is currently insufficient good quality evidence to support use of extra-fine particle ICS aerosols over others.[182] More detail about asthma medications is provided in Appendix Chapter 5 (adults and adolescents: Part 5A; children 6–11 years: Part 5B).

Below is more detail about the evidence for each of the treatments shown in Box 3-5A and 3-5B. Clinicians should check local eligibility and payer criteria before prescribing. As shown in these figures, GINA recommends that all adults and adolescents should receive an ICS-containing controller, incorporated as part of the patient's personalized asthma management. The ICS-containing medication should be taken every day or, in mild asthma, an alternative is to take as-needed low dose ICS-formoterol for symptom relief. Box 3-6 (p.62) lists suggested low, medium and high doses for several different ICS formulations.

ASTHMA TREATMENT STEPS

GINA treatment recommendations for adults, adolescents and children were updated in 2021 after a review of evidence for Steps 1–5. The treatment figure for adults and adolescents (Box 3-5A, p.60) shows treatment options in two 'tracks', with the key difference between the 'tracks' being the type of reliever (low dose ICS-formoterol or SABA; see p.53). Track 1, with as-needed low dose ICS-formoterol as the reliever, is the preferred approach, based on evidence for efficacy, effectiveness and safety for lower risk of severe exacerbations, with similar symptom control compared with controller medications plus as-needed SABA in Track 2.

STEP 1

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

GINA Step 1 recommendations are for:

- Initial asthma treatment in patients with symptoms less than twice a month and no exacerbation risk factors, a group that is rarely studied
- Step-down treatment for patients whose asthma is well-controlled on regular ICS or LTRA

Use of low dose ICS-formoterol as needed for symptom relief in Step 1 for adults and adolescents (Evidence B) is supported by indirect evidence for a reduction in risk of severe exacerbations compared with as-needed SABA alone, from a large double-blind study[161] and an open-label study[163] in patients who were eligible for Step 2 therapy (see below), and by direct evidence from two studies for stepping down from maintenance controller treatment.

Four large studies showed a similar or greater reduction in severe exacerbations compared with daily ICS, with no clinically important difference in symptom control or lung function.[173,174,180,182] For patients previously taking SABA alone the risk of severe exacerbations was 26% lower with as-needed ICS-formoterol compared with daily ICS; it was also significantly lower than with daily ICS in an open-label study in patients previously taking SABA alone.

Among patients stepping down from regular ICS or LTRA, as-needed ICS-formoterol was associated with a similar or greater reduction in severe exacerbations compared with taking daily ICS. Findings were similar in the adolescent subgroup. No new safety signals were seen with as-needed budesonide-formoterol in mild asthma.[162-164,183]

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Commented [A71]: Added 2022: Hardy J, Baggott C, Fingleton J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. The Lancet 2019; 394: 919-928

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The most important considerations for GINA in extending the recommendation for as-needed low dose ICS-formoterol to Step 1 were:

- Patients with few interval asthma symptoms can still have severe or fatal exacerbations.[184] GINA recommends assessing and addressing risk factors for exacerbations as well as symptom control (Box 2-2).
- The historic distinction between so-called 'intermittent' and 'mild persistent' asthma is arbitrary, with no evidence of difference in response to ICS.[138] A large reduction in risk of severe exacerbations with as-needed ICS-formoterol compared with as-needed SABA was seen even in patients with SABA use twice a week or less at baseline.[163]
- A post hoc analysis of one study found that a single day with increased as-needed budesonide-formoterol reduced the short-term (21-day) risk of severe exacerbations compared to as needed SABA alone, suggesting that timing of use of ICS-formoterol is important.[185]
- In patients with infrequent symptoms, adherence with prescribed daily ICS is very poor,[186] exposing them to risks of SABA-only treatment if they are prescribed daily ICS plus as-needed SABA
- There is a *lack* of evidence for the safety or efficacy of SABA-only treatment. Historic recommendations for SABA-only treatment were based on the assumption that patients with mild asthma would not benefit from ICS
- Taking SABA regularly for as little as one week significantly increases exercise-induced bronchoconstriction, airway hyperresponsiveness and airway inflammation, and decreases bronchodilator response.[187]
- Even modest over-use of SABA (indicated by dispensing of 3 or more 200-dose canisters a year) is associated with increased risk of severe exacerbations[123] and, in one study, asthma mortality.[82]
- An important consideration for GINA was to avoid establishing patient reliance on SABA, and the priority to avoid conflicting messages in asthma education. Previously, patients were initially provided only with SABA for symptom relief, but later, despite this treatment being effective from the patient's perspective, they were told that in order to reduce their SABA use, they needed to take a daily controller even when they had no symptoms. Recommending that all patients should be provided with a controller from the start of therapy (including, in mild asthma, the option of as-needed ICS-formoterol) allows consistent messaging about the need for both symptom relief and risk reduction, and may avoid establishing patient reliance on SABA as their main asthma treatment.

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

The **usual dose** of as-needed budesonide-formoterol in mild asthma is a single inhalation of 200/6 mcg (delivered dose 160/4.5), taken whenever needed for symptom relief. The **maximum recommended dose** of as-needed budesonide-formoterol in a single day corresponds to a total of 72 mcg formoterol (54 mcg delivered dose). However, in RCTs in mild asthma, such high usage was rarely seen, with average use around 3–4 doses per week.[161-163] See Appendix Chapter 5 for an illustration of relevant medications and doses.

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

ICS-formoterol formulations other than budesonide-formoterol have not been studied for as-needed-only use, but beclometasone-formoterol may also be suitable. Both of these medications are well-established for as-needed use within maintenance and reliever therapy in GINA Steps 3–5.[166]

For **pre-exercise use** in patients with mild asthma, one 6-week study showed that use of low dose budesonide-formoterol for symptom relief and before exercise reduced exercise-induced bronchoconstriction to a similar extent as regular daily low dose ICS with SABA for symptom relief and before exercise.[188] More studies are needed, but this study suggests that patients with mild asthma who are prescribed as-needed ICS-formoterol to prevent exacerbations and control symptoms can use the same medication prior to exercise, if needed, and do not need to be prescribed a SABA for pre-exercise use (Evidence B).

Alternative Step 1 treatment options for adults and adolescents (Track 2)

Low dose ICS taken whenever SABA is taken (Evidence B): There is much less evidence about the safety and efficacy of this approach than for as-needed ICS-formoterol, but it may be an option in countries where ICS-formoterol is not available or affordable. In Step 1, the evidence for this strategy is indirect, from studies with separate or combination ICS

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and SABA inhalers in patients eligible for Step 2 treatment (see below).[189-192] In making this recommendation, the most important considerations were reducing the risk of severe exacerbations, and the difficulty of achieving good adherence with regularly prescribed ICS in patients with infrequent symptoms.

Regular daily low dose ICS has been suggested by GINA since 2014 for consideration in Step 1, for patients with symptoms less than twice a month, to reduce the risk of exacerbations. This was based on indirect evidence from studies in patients eligible for Step 2 treatment[138,183,193] (Evidence B). However, patients with symptoms less than twice a month are extremely unlikely to take ICS regularly even if prescribed, leaving them exposed to the risks of SABA-only treatment, so for feasibility reasons, this regimen is no longer recommended for general use in such patients.

Step 1 treatment options for children 6–11 years

Possible controller options for this age-group include taking ICS whenever SABA is taken, based on indirect evidence from Step 2 studies with separate inhalers in children and adolescents. One of these studies showed substantially fewer exacerbations compared with SABA-only treatment,[190] and another showed similar outcomes as physician-adjusted treatment but with lower average ICS dose[192] (Evidence B). Regular ICS with as-needed SABA is also a possible option for this age-group (Evidence B), but the likelihood of poor adherence in children with infrequent symptoms should be taken into account.

There have been no studies of as needed-only ICS-formoterol in children aged 6–11 years. However, concerns around SABA-only treatment are also relevant to children and should be considered when initiating Step 1 treatment (see other controller options for children below).

Not recommended

GINA no longer recommends SABA-only treatment of asthma in adults or adolescents. Although inhaled SABAs are highly effective for the quick relief of asthma symptoms,[194] patients whose asthma is treated with SABA alone (compared with ICS) are at increased risk of asthma-related death (Evidence A)[82,195] and urgent asthma-related healthcare (Evidence A),[196] even if they have good symptom control.[197] The risk of asthma exacerbations and mortality increases incrementally with higher SABA use, including in patients treated with SABA alone.[82] One long-term study of regular SABA in patients with newly diagnosed asthma showed worse outcomes and lower lung function than in patients who were treated with daily low dose ICS from the start.[198]

In adults, inhaled anticholinergic agents like ipratropium are potential alternatives to SABA for routine relief of asthma symptoms; however, these agents have a slower onset of action than inhaled SABA. Oral SABA and theophylline have a higher risk of side-effects and are not recommended. No long-term safety studies have been performed to assess the risk of severe exacerbations with these reliever medications in patients not also taking ICS. Use of long-acting muscarinic antagonists (LAMA) in asthma without concomitant ICS is associated with an increased risk of severe exacerbations.

The rapid-onset LABA, formoterol, is as effective as SABA as a reliever medication in adults and children,[199] and reduces the risk of severe exacerbations by 15–45% compared with as-needed SABA,[200-202] but use of regular or frequent LABA without ICS is strongly discouraged because of the risk of exacerbations[114,203] (Evidence A).

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STEP 2

Preferred Step 2 treatment for adults and adolescents: low dose ICS-formoterol, taken as-needed for relief of symptoms and, if needed, before exercise (Track 1)

The current evidence for this combination controller + reliever treatment is with low dose budesonide-formoterol:

- A large double-blind study in mild asthma found a 64% reduction in severe exacerbations compared with SABA-only treatment,[161] with a similar finding in an open-label study in patients with mild asthma previously taking SABA alone.[163] (Evidence A).

- Two large double-blind studies in mild asthma showed as-needed budesonide-formoterol was non-inferior for severe exacerbations compared with regular ICS.[161,162]
- In two open-label randomized controlled trials, representing the way that patients with mild asthma would use as-needed ICS-formoterol in real life, as-needed budesonide-formoterol was superior to maintenance ICS in reducing the risk of severe exacerbations[163,164] (Evidence A).
- In all four studies, the as-needed ICS-formoterol strategy was associated with a substantially lower average ICS dose than with maintenance low dose ICS.[173,174,180,182]
- Clinical outcomes with as-needed ICS-formoterol were similar in adolescents as in adults.
- A post hoc analysis of one study[161] found that a day with >2 doses of as-needed budesonide-formoterol reduced the short-term (21 day) risk of severe exacerbations compared to as needed terbutaline alone, suggesting that timing of use of ICS-formoterol is important.[185]
- A Cochrane review provided moderate to high certainty evidence that as-needed ICS-formoterol was clinically effective in adults and adolescents with mild asthma, significantly reducing important clinical outcomes including need for oral corticosteroids, severe exacerbation rates, and emergency department visits or hospital admissions compared with daily ICS (Evidence A).
- No new safety signals were seen with as-needed budesonide-formoterol in mild asthma.[162-164,183]

The most important considerations for GINA in making this recommendation for as-needed ICS-formoterol, were:

- The need to prevent severe exacerbations in patients with mild or infrequent symptoms; these can occur with unpredictable triggers such as viral infection, allergen exposure, pollution or stress.
- The desire to avoid the need for daily ICS in patients with mild asthma, who in clinical practice are often poorly adherent with prescribed ICS, leaving them exposed to the risks of SABA-only treatment.
- The greater reduction in severe exacerbations with as-needed ICS-formoterol compared with daily ICS among patients previously taking SABA alone, with no significant difference for patients with well-controlled asthma on ICS or LTRA at baseline.
- The very small differences in FEV_1, (~30–50 mL), symptom control (difference in ACQ-5 of ~0.15 vs minimal clinically important difference 0.5), and symptom-free days (mean difference 10.6 days per year)[161,162] compared with regular ICS were considered to be less important. These differences were not cumulative over the 12-month studies. The primary outcome variable of one study[161] was 'well-controlled asthma weeks', but this outcome was not considered reliable because it was based on an earlier concept of asthma control, and was systematically biased against the as-needed ICS-formoterol treatment group because much less ICS was permitted in a week for patients on ICS-formoterol than those on maintenance ICS before the week was classified as not well-controlled.
- FeNO was significantly reduced with both as-needed budesonide-formoterol and maintenance ICS, and there was no significant difference in treatment effect with as-needed budesonide-formoterol by baseline eosinophils or baseline FeNO.[163,164]

Because as-needed ICS-formoterol is the preferred treatment for both Steps 1 and 2 in adults and adolescents, these steps have been combined in the treatment figure (Box 3-5A, p.60) to avoid confusion.

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

The **usual dose** of as-needed budesonide-formoterol in mild asthma is a single inhalation of 200/6 mcg (delivered dose 160/4.5), taken whenever needed for symptom relief. Based on product information, the **maximum recommended dose** of budesonide-formoterol in a single day is a total of 72mcg formoterol (54 mcg delivered dose). However, in the randomized controlled trials in mild asthma, such high usage was rarely seen, and average use of as-needed ICS-formoterol was around 3–4 doses per week.[161-164]

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

Other ICS-formoterol formulations have not been studied for as-needed-only use, but beclometasone-formoterol may also be suitable. Both of these medications are well-established for as-needed use within maintenance and reliever

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Bateman ED, O'Byrne PM, FitzGerald JM, et al. Positioning as-needed budesonide-formoterol for mild asthma: effect of prestudy treatment in pooled analysis of SYGMA 1 and 2. Ann Am Thorac Soc 2021; 18: 2007-2017

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therapy (MART) in GINA Steps 3–5.[166] No new safety signals were seen in four studies with as-needed budesonide-formoterol in mild asthma.[162-164,183]

For **pre-exercise use** in patients with mild asthma, one study showed that budesonide-formoterol taken as-needed and before exercise had similar benefit in reducing exercise-induced bronchoconstriction as daily ICS with SABA as-needed and pre-exercise.[188] More studies are needed, but this suggests that patients with mild asthma who are prescribed as-needed ICS-formoterol to prevent exacerbations and control symptoms can use the same medication prior to exercise, if needed, and do not need to be prescribed a SABA for pre-exercise use (Evidence B).

Alternative Step 2 treatment for adults and adolescents: daily low dose ICS plus as-needed SABA (Track 2)

For **regular daily low dose ICS plus as-needed SABA** in patients with mild asthma, the burden of symptoms is low, so the most important consideration was to reduce the risk of severe exacerbations. There is a large body of evidence from RCTs and observational studies showing that the risks of severe exacerbations, hospitalizations and mortality are substantially reduced with regular low dose ICS; symptoms and exercise-induced bronchoconstriction are also reduced[183,193,195,204,205] (Evidence A). Severe exacerbations are halved with low dose ICS even in patients with symptoms 0–1 days a week.[138] In a meta-analysis of longitudinal studies, regular ICS was associated with a very small increase in pre- and post-bronchodilator FEV_1 % predicted, in adults but not in children, compared with SABA alone.

However, when prescribing daily ICS for a patient with mild asthma, clinicians should be aware that adherence with maintenance ICS in the community is extremely low. They should consider the likelihood that the patient will be poorly adherent with daily ICS, exposing them to the risks of SABA-only treatment.

Over-use of SABA, indicated by dispensing of three or more 200-dose canisters of SABA in a year (i.e. average use more than daily), is associated with an increased risk of severe exacerbations[82,116] and, in one study, with increased mortality,[82] even in patients also taking ICS-containing controller.

Other Step 2 treatment options for adults and adolescents

Low dose ICS taken whenever SABA is used (in combination or separate inhalers) is another option if as-needed ICS-formoterol is not available, and the patient is unlikely to take regular ICS. The evidence is from two studies in adults and two studies in children and adolescents, with separate or combination ICS and SABA inhalers,[189-191,206] showing no difference in exacerbations compared with daily ICS.

Leukotriene receptor antagonists (LTRA) are less effective than ICS,[207] particularly for exacerbations (Evidence A). Before prescribing montelukast, health professionals should consider its benefits and risks, and patients should be counselled about the risk of neuropsychiatric events. In 2020, the US Food and Drug Administration (FDA) required a boxed warning to be added about the risk of serious mental health adverse effects with montelukast.[208]

For adult or adolescent patients not previously using controller treatment, *regular daily combination low dose ICS-LABA* as the initial maintenance controller treatment reduces symptoms and improves lung function compared with low dose ICS alone.[209] However, it is more expensive and does not further reduce the risk of exacerbations compared with ICS alone[209] (Evidence A). No comparison between regular and as-needed ICS-formoterol has been studied in patients eligible for Step 2 treatment.

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

Preferred Step 2 treatment for children 6–11 years

The preferred controller option for children at Step 2 is regular low dose ICS with as-needed SABA (see Box 3-6, p.62 for ICS dose ranges in children).

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Alternative Step 2 treatment for children 6–11 years

Another controller option for children is taking low dose ICS whenever SABA is taken, based on the results of two studies with separate ICS and SABA inhalers in patients aged between 5 years and 17 or 18 years.[190,192] Interviews with parents indicated that those whose children were randomized to as-needed ICS+SABA felt more in control of their child's asthma than those whose children were randomized to physician-based adjustment.[192]

Another option is daily LTRA, which overall is less effective than ICS.[207] The FDA warning about montelukast (above) also applies to its use in children.[208]

Not recommended

Sustained-release theophylline has only weak efficacy in asthma[210-212] (Evidence B) and side-effects are common, and may be life-threatening at higher doses.[213] Use of long-acting muscarinic antagonists (LAMA) in asthma without concomitant ICS is associated with an increased risk of severe exacerbations. Chromones (nedocromil sodium and sodium cromoglycate) had a favorable safety profile but low efficacy[214-216] (Evidence A), and their pMDI inhalers required burdensome daily washing to avoid blockage; these medications have been discontinued globally.

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STEP 3

Before considering a step up, check for common problems such as incorrect inhaler technique, poor adherence, and environmental exposures, and confirm that the symptoms are due to asthma (Box 2-4, p.42).

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

For adults and adolescents, the 'preferred' Step 3 option is low dose ICS-formoterol as both maintenance and reliever treatment (MART). In this regimen, low dose ICS-formoterol, either budesonide-formoterol or beclometasone-formoterol, is used as both the maintenance treatment and for symptom relief.

In adult and adolescent patients with ≥1 exacerbation in the previous year, ICS-formoterol maintenance and reliever therapy reduced exacerbations and provided similar levels of asthma control at relatively low doses of ICS, compared with a fixed dose of ICS-LABA as maintenance treatment or a higher dose of ICS, both with as-needed SABA[217-222] (Evidence A). In open-label studies that did not require a history of severe exacerbations, maintenance and reliever therapy with ICS-formoterol also significantly reduced severe exacerbations, with a lower average dose of ICS.[217,223]

For patients prescribed ICS-formoterol maintenance and reliever therapy, the maximum recommended dose of formoterol in a single day, based on product information, is 72 mcg metered dose (54 mcg delivered dose) for budesonide-formoterol and 48 mcg metered dose (36 mcg delivered dose) for beclometasone-formoterol.

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

Alternative Step 3 treatment for adults and adolescents: maintenance ICS-LABA plus as-needed SABA (Track 2)

Maintenance ICS-LABA with as-needed SABA: This is an alternative approach if MART is not possible, or if a patient's asthma is stable with good adherence and no exacerbations on their current therapy. For patients receiving maintenance ICS with as-needed SABA, adding LABA in a combination inhaler provides additional improvements in symptoms and lung function with a reduced risk of exacerbations compared with the same dose of ICS,[224,225] (Evidence A) but there is only a small reduction in reliever use.[226,227] However, before prescribing a regimen with SABA reliever, consider whether the patient is likely to be adherent with their ICS-containing controller therapy, as otherwise they will be at higher risk of exacerbations.

Currently approved combination ICS-LABA inhalers for Step 3 maintenance treatment of asthma include low doses of fluticasone propionate-formoterol, fluticasone furoate-vilanterol, fluticasone propionate-salmeterol, beclometasone-

formoterol, budesonide-formoterol, mometasone-formoterol and mometasone-indacaterol (see Box 3-6, p.62). Effectiveness of fluticasone furoate-vilanterol over usual care was demonstrated for asthma symptom control in a large real-world study; there was no difference in risk of exacerbations.[228,229]

Other Step 3 controller options for adults and adolescents

For adult patients with allergic rhinitis and sensitized to house dust mite, with suboptimally controlled asthma despite low to high dose ICS, consider adding sublingual allergen immunotherapy (SLIT), provided FEV_1 is >70% predicted.[230,231] (see p.76).

Another option for adults and adolescents is to increase ICS to medium dose[128] (see Box 3-6, p.62), but at a group level this is less effective than adding a LABA[232,233] (Evidence A). Other less efficacious options are low dose ICS-containing therapy plus either LTRA[234] (Evidence A) or low dose, sustained-release theophylline[235] (Evidence B). See note above about the FDA warning for montelukast.[208]

Preferred Step 3 treatment for children 6–11 years

In children, after checking inhaler technique and adherence, and treating modifiable risk factors, there are three preferred options at a population level: to increase ICS to medium dose (see Box 3-6, p.62),[236] (Evidence A) or change to combination low dose ICS-LABA (Evidence A),[237] both with as-needed SABA reliever, or to switch to maintenance and reliever therapy with a very low dose of ICS-formoterol (Evidence B).[238] In a large study of children aged 4-11 years with a history of an exacerbation in the previous year, combination ICS-LABA was non-inferior to the same dose of ICS alone for severe exacerbations, with no difference in symptom control or reliever use.[239] In children, a single study of maintenance and reliever therapy with very low dose budesonide-formoterol (100/6 metered dose, 80/4.5 mcg delivered dose for both maintenance and reliever) showed a large reduction in exacerbations compared with the same dose of budesonide-formoterol with SABA reliever, or compared with higher dose ICS.[238]

Individual children's responses vary, so the other controller options above should be tried before considering Step 4 treatment.

Other Step 3 treatment options for children 6–11 years

In children, there is little evidence for adding LTRA to low dose ICS.[234] The FDA warning about montelukast (above) also applies to its use in children.[208]

STEP 4

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

Before stepping up, check for common problems such as incorrect inhaler technique, poor adherence, and environmental exposures, and confirm that the symptoms are due to asthma (Box 2-4, p.42).

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

For adult and adolescent patients, combination 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[221] (Evidence A). The greatest reduction in risk was seen in patients with a history of severe exacerbations,[166] but MART was also significantly more effective than conventional best practice in open label studies in which patients were not selected for greater exacerbation risk.[223] In Step 4, the MART regimen can be prescribed with medium dose budesonide-formoterol or beclometasone-formoterol maintenance treatment, but the reliever remains low dose ICS-formoterol. Based on product information, the maximum recommended total dose of formoterol in a single day is 72 mcg metered dose (54 mcg

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delivered dose) for budesonide-formoterol and 48 mcg metered dose (36 mcg delivered dose) for beclometasone-formoterol).

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

This is an alternative approach if MART is not possible, or if a patient's asthma is stable with good adherence and no exacerbations on their current therapy. As above, individual ICS responsiveness varies, and some patients whose asthma is uncontrolled or who have frequent exacerbations on low dose ICS-LABA despite good adherence and correct inhaler technique may benefit from medium dose ICS-LABA[160] (Evidence B) with as-needed SABA, if maintenance and reliever therapy is not available. However, before prescribing a regimen with SABA reliever, consider whether the patient is likely to be adherent with their ICS-containing controller therapy, as otherwise they will be at higher risk of exacerbations. Occasionally, high dose ICS-LABA may be needed.

Other Step 4 controller options for adults and adolescents

Long-acting muscarinic antagonists (LAMA) may be considered as add-on therapy in a separate inhaler for patients aged ≥6 years (tiotropium), or in a combination ('triple') inhaler for patients aged ≥18 years (beclometasone-formoterol-glycopyrronium; fluticasone furoate-vilanterol-umeclidinium; mometasone-indacaterol-glycopyrronium) if asthma is persistently uncontrolled despite medium or high dose ICS-LABA. Adding LAMA to medium or high dose ICS-LABA modestly improved lung function[181,240-244,252] (Evidence A) but with no difference in symptoms. In some studies, adding LAMA to ICS-LABA modestly reduced exacerbations compared with some medium or high dose ICS-LABA comparators.[181,240-242,245] In a meta-analysis, there was a 17% reduction in risk of severe exacerbations with addition of LAMA to medium or high dose ICS-LABA.

However, for patients experiencing exacerbations despite low dose ICS-LABA, the ICS dose should be increased to at least medium, or treatment switched to maintenance and reliever therapy with ICS-formoterol, before considering adding a LAMA. In one study, the severe exacerbation rate was lower in patients receiving high dose fluticasone furoate-vilanterol (ICS-LABA) than with low-medium dose fluticasone furoate-vilanterol-umeclidinium (ICS-LABA-LAMA).[243] For patients prescribed an ICS-LABA-LAMA with a non-formoterol LABA, the appropriate reliever is SABA.

In Step 4, there is insufficient evidence to support ICS-LAMA over low or medium dose ICS-LABA combination; all studies were with ICS and tiotropium in separate inhalers.[241] In one analysis, response to adding LAMA to medium dose ICS, as assessed by FEV_1, ACQ, and exacerbations, was not modified by baseline demographics, body-mass index, FEV_1, FEV_1 reversibility, or past vs. never smoking.[246]

Consider adding *sublingual allergen immunotherapy* (SLIT) for adult patients with allergic rhinitis and sensitization to house dust mite, with suboptimally controlled asthma despite low-high dose ICS, provided FEV_1 is >70% predicted.[230,231] (see p.76).

For medium or high dose budesonide, efficacy may be improved with dosing four times daily[247,248] (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[249-253] (Evidence A), or low dose sustained-release theophylline[211] (Evidence B), but neither of these has been compared with maintenance and reliever therapy with ICS-formoterol. See note above about the FDA warning for montelukast.[208]

Preferred Step 4 treatment for children 6–11 years

For children whose asthma is not adequately controlled by low dose maintenance ICS-LABA with as-needed SABA, treatment may be increased to medium dose ICS-LABA[239] (Evidence B). For maintenance and reliever therapy with budesonide-formoterol, the maintenance dose may be increased to 100/6 mcg twice daily (metered dose; 80/4.5 mcg delivered dose) (Evidence D); this is still a low dose regimen.

If asthma is not well controlled on medium dose ICS (see Box 3-6B, p.62), the recommendation is to refer the child for expert assessment and advice.

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Other Step 4 options for children 6–11 years

Other controller options include increasing to high pediatric dose ICS-LABA (Box 3-6B, p.62), but adverse effects must be considered. Tiotropium (long-acting muscarinic antagonist) by mist inhaler may be used as add-on therapy in children aged 6 years and older; it modestly improves lung function and reduces exacerbations[240] (Evidence A) largely independent of baseline IgE or blood eosinophils.[254] If not trialed before, LTRA could be added (see note above about FDA warning).[208] Add-on theophylline is not recommended for use in children due to lack of efficacy and safety data.

STEP 5

Preferred treatment at Step 5 in adults, adolescents and children: refer for expert assessment, phenotyping, and add-on therapy

Patients of any age with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered, should be referred to a specialist with expertise in investigation and management of severe asthma[137] (Evidence D).

In severe asthma, as in mild-moderate asthma,[255] participants in randomized controlled trials may not be representative of patients seen in clinical practice. For example, a registry study found that over 80% of patients with severe asthma would have been excluded from major regulatory studies evaluating biologic therapy.[256]

The contents of the **GINA Guide and decision tree** on Diagnosis and Management of difficult-to-treat and severe asthma in adolescent and adult patients is included in Chapter 3E (p.104). Treatment options that may be considered after optimization of existing therapy may include the following (**always check local eligibility and payer criteria):**

- **Combination high dose ICS-LABA**: this may be considered in adults and adolescents, but for most patients, the increase in ICS dose generally provides little additional benefit[121,128,233] (Evidence A), and there is an increased risk of side-effects, including adrenal suppression.[257] 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[211,252] Evidence B).
- **Add-on long-acting muscarinic antagonists (LAMA)** can be prescribed in a separate inhaler for patients aged ≥6 years (tiotropium), or in a combination ('triple') inhaler for patients aged ≥18 years (beclometasone-formoterol-glycopyrronium; fluticasone furoate-vilanterol-umeclidinium; mometasone-indacaterol-glycopyrronium) if asthma is not well controlled with medium or high dose ICS-LABA. Adding LAMA to ICS-LABA modestly improves lung function,[181,240-244,252181,241-243,246] (Evidence A) but not quality of life, with no clinically important change in symptoms. Some studies showed a reduction in exacerbation risk; in meta-analysis, overall, there was a 17% reduction in risk of severe exacerbations requiring oral corticosteroids (Evidence A).[188,247-249,252] For patients with exacerbations despite ICS-LABA, it is essential that sufficient ICS is given, i.e. at least medium dose ICS-LABA, before considering adding a LAMA. For patients prescribed an ICS-LABA-LAMA with a non-formoterol LABA, the appropriate reliever is SABA; patients prescribed ICS-formoterol-LAMA can continue ICS-formoterol reliever.
- **Add-on azithromycin** (three times a week) can be considered after specialist referral for adult patients with persistent symptomatic asthma despite high dose ICS-LABA. Before considering add-on azithromycin, sputum should be checked for atypical mycobacteria, ECG should be checked for long QTc (and re-checked after a month on treatment), and the risk of increasing antimicrobial resistance should be considered.[258] Diarrhea is more common with azithromycin 500mg 3 times a week.[259] Treatment for at least 6 months is suggested, as a clear benefit was not seen by 3 months in the clinical trials.[259,505] The evidence for this recommendation includes a meta-analysis of two clinical trials[259,505] in adults with persistent asthma symptoms that found reduced asthma exacerbations among those taking medium or high dose ICS-LABA who had either an eosinophilic or non-eosinophilic profile and in those taking high dose ICS-LABA[260] (Evidence B) The option of add-on azithromycin for

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adults is recommended only after specialist consultation because of the potential for development of resistance at the patient or population level.[259]

- **Add-on biologic therapy for severe asthma**
  - **Add-on anti-immunoglobulin E** (anti-IgE) (omalizumab) treatment: for patients aged ≥6 years with moderate or severe allergic asthma that is uncontrolled on Step 4–5 treatment[261,262] (Evidence A).
  - **Add-on anti-interleukin-5/5R** treatment (subcutaneous mepolizumab for patients aged ≥6 years; intravenous reslizumab for ages ≥18 years or subcutaneous benralizumab for ages ≥12 years), with severe eosinophilic asthma that is uncontrolled on Step 4–5 treatment (Evidence A).[263-267] Efficacy data for mepolizumab in children 6–11 years are limited to one very small open label uncontrolled study.[268]
  - **Add-on anti-interleukin-4R α** treatment (subcutaneous dupilumab) for patients aged ≥6 years with severe eosinophilic/Type 2 asthma, or for adults or adolescents requiring treatment with maintenance OCS (Evidence A).[269-271]
  - **Add-on anti-thymic stromal lymphopoietin** (anti-TSLP) (subcutaneous tezepelumab): for patients aged ≥12 years with severe asthma (Evidence A).
- **Sputum-guided treatment**: for adults with persisting symptoms and/or exacerbations despite high dose ICS or ICS-LABA, treatment may be adjusted based on eosinophilia (>3%) in induced sputum. In severe asthma, this strategy leads to reduced exacerbations and/or lower doses of ICS[167] (Evidence A), but few clinicians currently have access to routine sputum testing.
- **Add-on treatment with bronchial thermoplasty**: may be considered for some adult patients with severe asthma[137,272] (Evidence B). Evidence is limited and in selected patients (see p.77). The long-term effects compared with control patients, including for lung function, are not known.
- **As a last resort, add-on low dose oral corticosteroids** (≤7.5 mg/day prednisone equivalent): this may be considered for some adults with severe asthma[137] (Evidence D), but they are often associated with substantial side effects[273-275] (Evidence A). They should only be considered for adults with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence with Step 5 treatment, and after exclusion of other contributory factors and other add-on treatments including biologics where available and affordable. Patients should be counseled about potential side-effects.[274] They should be assessed and monitored for risk of adrenal suppression and corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counseling and prescription of therapy for prevention of osteoporosis (where appropriate).[276]
- **Maintenance and reliever therapy (MART) with ICS-formoterol:** there is no direct evidence about initiating MART in patients receiving add-on treatment such as LAMA or biologic therapy, but switching a patient from MART to conventional ICS-LABA plus as-needed SABA may increase the risk of exacerbations.

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.[277] In severe and chronically under-treated disease, it may take longer.[278]

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.[279] 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[280] (Evidence D).

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Bacharier LB, Maspero JF, Katelaris CH, et al., Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma. N. Engl. J. Med., 2021. 385: 2230-2240

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Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. N Engl J Med 2017; 377: 936-946.
Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med 2021; 384: 1800-1809.

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Stepping up asthma treatment

Asthma is a variable condition, and periodic treatment adjustments by the clinician and/or the patient may be needed.[281]

- *Day-to-day adjustment:* For patients whose reliever inhaler is combination budesonide-formoterol or beclometasone-formoterol (with or without maintenance ICS-formoterol), the patient adjusts the number of as-needed doses of ICS-formoterol from day to day according to their symptoms. This strategy reduces the risk of developing a severe exacerbation requiring oral corticosteroids within the next 3–4 weeks.[185,282,283]
- *Short-term step up (for 1–2 weeks)*: A 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, p.61), or by the health care provider.
- *Sustained step up (for at least 2–3 months)*: Although at a group level most benefit from ICS is obtained at low dose, individual ICS responsiveness varies, and some patients whose asthma is uncontrolled on low dose ICS-LABA despite good adherence and correct technique may benefit from increasing the maintenance dose to medium. A step up in treatment may be recommended (Box 3-5, p.31) 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, p.38). Any step-up should be regarded as a therapeutic trial. If there is no response after 2–3 months, treatment should be reduced to the previous level, and alternative treatments or referral considered.

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Stepping down treatment when asthma is well controlled

Once good asthma control has been achieved and maintained for 2–3 months and lung function has reached a plateau, treatment can often be successfully reduced, without loss of asthma control. The aims of stepping down are:

- To find the patient's minimum effective treatment, i.e. to maintain good control of symptoms and exacerbations, and to minimize the costs of treatment and potential for side-effects
- To encourage the patient to continue controller treatment. Patients often experiment with intermittent treatment through concern about the risks or costs of daily treatment,[284] but this leaves them exposed to the risks of SABA-only treatment. For patients whose asthma is well-controlled on maintenance low dose ICS with as-needed SABA, an alternative is to cease maintenance ICS and switch to as-needed ICS-formoterol.[161,162]

Before stepping down

The approach to stepping down will differ from patient to patient depending on their current treatment, risk factors and preferences. There are few data on the optimal timing, sequence and magnitude of treatment reductions in asthma. Factors associated with a greater risk of exacerbation after step-down include a history of exacerbations and/or emergency department visit for asthma in the previous 12 months,[285,286] and a low baseline FEV_1.[286] Other predictors of loss of control during dose reduction include airway hyperresponsiveness and sputum eosinophilia,[287] but these tests are not readily available in primary care.

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

How to step asthma treatment down

Decisions about treatment step-down should be made on an individual patient level. In one study of patients with well-controlled asthma on medium dose ICS-LABA, reducing the ICS dose and removing the LABA had similar effects on a composite treatment failure outcome. However, stopping LABA was associated with lower lung function and more hospitalizations; and decreasing the ICS dose was inferior to maintaining a stable dose of ICS-LABA.[288]

If treatment is stepped down too far or too quickly, exacerbation risk may increase even if symptoms remain reasonably controlled[289] (Evidence B). To date, higher baseline FeNO has not been found to be predictive of exacerbation following step-down of ICS dose.[290, 291] A meta-analysis suggested that greater reduction in ICS dose may be able to be achieved in patients with baseline FeNO <50 ppb, but the findings point to the need for further research.[291] Complete cessation of ICS is associated with a significantly increased risk of exacerbations[292] (Evidence A). Step-down strategies for different

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controller treatments are summarized in Box 3-7, p.74; 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, p.36), for example a history of exacerbations in the past year,[285] or persistent airflow limitation, step down only with close supervision.
- Choose an appropriate time (no respiratory infection, patient not travelling, not pregnant).
- Approach each step as a therapeutic trial. Engage the patient in the process; document their asthma status (symptom control, lung function and risk factors, Box 2-2, p.36); provide clear instructions; provide a written asthma action plan (Box 4-2, p.130) and ensure the patient has sufficient medication to resume their previous dose if necessary; monitor symptoms and/or PEF; and schedule a follow-up visit (Evidence D).
- Stepping down ICS doses by 25–50% at 3 month intervals is feasible and safe for most patients[293] (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[294]	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[293]	B
Step 3	Low dose ICS-LABA maintenance	• Reduce ICS-LABA to once daily • Discontinuing LABA may lead to deterioration[294]	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
	Medium or high dose ICS	• Reduce ICS dose by 50%[293] • Adding LTRA† may allow ICS dose to be stepped down[295]	A B
Step 2	Low dose ICS	• Once-daily dosing (budesonide, ciclesonide, mometasone)[296,297] • Switch to as-needed low dose ICS-formoterol[161,162,164] • Switch to taking ICS whenever SABA is taken[189,190,192]	A A B
	Low dose ICS or LTRA	• Switch to as-needed low dose ICS formoterol[161-164] • Complete cessation of ICS in adults and adolescents is not advised as the risk of exacerbations is increased with SABA-only treatment[292]	A 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. †Note FDA warning on neuropsychiatric effects with montelukast.[208]

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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.[101] There is increasing research interest in identifying at-risk patients (Box 2-2B, p.36), 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 potentially 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 an ICS-containing controller.	A
	• Maintenance and reliever therapy (MART) with ICS-formoterol reduces risk of severe exacerbations compared with if the reliever is SABA.	A
	• Ensure patient has a written action plan appropriate for their health literacy.	A
	• Review patient more frequently than low-risk patients.	A
	• Check inhaler technique and adherence frequently.	A
	• Identify any modifiable risk factors (Box 2-2, p.36).	D
≥1 severe exacerbation in last year	• ICS-formoterol maintenance and reliever regimen reduces risk of severe exacerbations compared with if the reliever is SABA.	A
	• Consider stepping up treatment if no modifiable risk factors.	A
	• Identify any avoidable triggers for exacerbations.	C
Exposure to tobacco smoke	• Encourage smoking cessation by patient/family; provide advice and resources.	A
	• Consider higher dose of ICS if asthma poorly controlled.	B
Low FEV_1, especially if <60% predicted	• Consider trial of 3 months' treatment with high dose ICS.	B
	• Consider 2 weeks' OCS, but take short- and long-term risks into account	B
	• Exclude other lung disease, e.g. COPD.	D
	• Refer for expert advice if no improvement.	D
Obesity	• Strategies for weight reduction	B
	• Distinguish asthma symptoms from symptoms due to deconditioning, mechanical restriction, and/or sleep apnea.	D
Major psychological problems	• Arrange mental health assessment.	D
	• Help patient to distinguish between symptoms of anxiety and asthma; provide advice about management of panic attacks.	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.	C
	• Consider step up of controller treatment.	D
	• Consider adding SLIT in symptomatic adult HDM-sensitive patients with allergic rhinitis despite ICS, provided FEV_1 is >70% predicted.	B
Sputum eosinophilia (limited centers)	• Increase ICS dose independent of level of symptom control.	A*

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; HDM: house dust mite; ICS: inhaled corticosteroids; OCS: oral corticosteroids; SLIT: sublingual immunotherapy. * Based on evidence from relatively small studies in selected populations. Also see Box 3-9 and p.78 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 3-12, p.88), 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.74).

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OTHER THERAPIES

Allergen immunotherapy

Allergen-specific immunotherapy may be a treatment option where allergy plays a prominent role, including asthma with allergic rhinoconjunctivitis.[298,299] There are currently two approaches: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). In the past, few studies in asthma have compared immunotherapy with pharmacological therapy, or used standardized outcomes such as exacerbations, and most studies have been in patients with mild asthma. The allergens most commonly included in allergen immunotherapy studies have been house dust mite and grass pollens. There is insufficient evidence about safety and efficacy of allergen immunotherapy in patients sensitized to mold.[300]

GINA plans to review evidence about allergen immunotherapy for asthma, and will update its advice based on the findings.

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Subcutaneous immunotherapy (SCIT)

SCIT involves the identification and use of clinically relevant allergens, and administration of extracts in progressively higher doses to induce desensitization and/or tolerance. European physicians tend to favor single allergen immunotherapy whereas Northern American physicians often prescribe multiple allergens for treatment.[301] In people with asthma and allergic sensitization, SCIT is associated with a reduction in symptom scores and medication requirements, and improved allergen-specific and non-specific airway hyperresponsiveness.[301]

For SCIT, analysis of pooled safety data from clinical trials and post-marketing surveillance in house dust mite allergic respiratory disease suggests the incidence of adverse drug reactions is approximately 0.5%.[302] Studies to date suggest that serious adverse effects of SCIT are uncommon, but may include life-threatening anaphylactic reactions.

Advice

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

Sublingual immunotherapy (SLIT)

Modest effects were identified in a systematic review of SLIT for asthma in adults and children,[299,303,304] but there was concern about the design of many of the studies.[305] The evidence for important outcomes such as exacerbations and quality of life remains limited.[306] There are few studies comparing SLIT with pharmacological therapy for asthma.[307] A trial of SLIT for house dust mites (HDM) in patients with asthma and HDM allergic rhinitis demonstrated a modest reduction of ICS with high dose SLIT.[231] In another study in patients with asthma and HDM allergic rhinitis, SLIT added to low or medium dose ICS showed increased time to exacerbation during ICS reduction in suboptimally controlled asthma.[230]

Commented [A104]: Reference replaced 2022: Fortescue R, Kew KM, Leung MST. Sublingual immunotherapy for asthma. Cochrane Database Syst Rev 2020;9:CD011293. [replaces Normansell R, Kew KM, Bridgman A. Sublingual immunotherapy for asthma. Cochrane Database Syst Rev 2015]

Side effects[308-310] from SLIT for inhalant allergens are predominantly limited to oral and gastrointestinal symptoms.[299]

Advice

- For adult patients with allergic rhinitis and sensitized to house dust mite, with persisting asthma symptoms despite low-medium dose ICS-containing therapy, consider adding SLIT, provided FEV_1 is >70% predicted (Evidence B)
- As for any treatment, potential benefits of SLIT for individual patients should be weighed against the risk of adverse effects, and the cost to the patient and health system.

Vaccinations

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

The risk of influenza infection itself can be reduced by annual vaccination. A systematic review of placebo-controlled randomized controlled trials of influenza vaccination showed no reduction in asthma exacerbations,[311] but no such studies had been performed since 2001. However, a systematic review and meta-analysis that included observational studies with a wide range of study designs suggested that influenza vaccination reduced the risk of asthma exacerbations, although for most of the studies, bias could not be excluded.[312] There is no evidence for an increase in asthma exacerbations after influenza vaccination compared to placebo.[312] Limited evidence exists with respect to the efficacy of live attenuated intranasal vaccination in children; from a safety perspective, an open-label study in children 2–18 years with moderate-severe asthma showed no short-term effects on asthma symptoms or asthma control.

People with asthma, particularly children and the elderly, are at higher risk of pneumococcal disease,[313] but there is insufficient evidence to recommend routine pneumococcal vaccination in people with asthma.[314]

Advice

- Advise patients with moderate to severe asthma to receive an influenza vaccination every year, or at least when vaccination of the general population is advised (Evidence C).
- There is insufficient evidence to recommend routine pneumococcal vaccination in people with asthma (Evidence D).
- Advice about COVID-19 vaccination is on p.18.
- COVID-19 vaccination and influenza vaccination may be given on the same day.

Bronchial thermoplasty

Bronchial thermoplasty is a potential treatment option at Step 5 in some countries for adult patients whose asthma remains uncontrolled despite optimized therapeutic regimens and referral to an asthma specialty center (Evidence B). Bronchial thermoplasty involves treatment of the airways during three separate bronchoscopies with a localized radiofrequency pulse.[113] The treatment is associated with a large placebo effect.[113] In patients taking high dose ICS-LABA, bronchial thermoplasty was associated with an increase in asthma exacerbations during the 3 month treatment period, and a subsequent decrease in exacerbations, but no beneficial effect on lung function or asthma symptoms compared with sham-controlled patients.[113] Extended follow up of some treated patients reported a sustained reduction in exacerbations compared with pre-treatment.[315] However, longer-term follow up of larger cohorts comparing effectiveness and safety, including for lung function, in both active and sham-treated patients is needed.

Advice

- For adult patients whose asthma remains uncontrolled despite optimization of asthma therapy and referral to a severe asthma specialty center, bronchial thermoplasty is a potential treatment option at Step 5 in some countries (Evidence B).
- Caution should be used in selecting patients for this procedure. The number of studies is small, people with chronic sinus disease, frequent chest infections or FEV_1 <60% predicted were excluded from the pivotal sham-controlled study, and patients did not have their asthma treatment optimized before bronchial thermoplasty was performed.
- Bronchial thermoplasty should be performed in adults with severe asthma only in the context of an independent Institutional Review Board-approved systematic registry or a clinical study, so that further evidence about effectiveness and safety of the procedure can be accumulated.[137]

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.[316] Vitamin D supplementation may reduce the rate of asthma exacerbation requiring treatment with systemic corticosteroids or may improve symptom control in asthma patients with baseline 25(OH)D of less than approximately 25–30 nmol/L.[317] In a meta-analysis, benefit for worsening

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Deleted: ; most of the evidence that does exist is restricted to children 3 years and older

Commented [A106]: Replaced 2022: Li L, Cheng Y, Tu X, et al. Association between asthma and invasive pneumococcal disease risk: a systematic review and meta-analysis. Allergy Asthma Clin Immunol 2020; 16: 94. [replaces: Talbot TR, Hartert TV, Mitchel E, et al. Asthma as a risk factor for invasive pneumococcal disease. N Engl J Med 2005;352:2082-90]

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Commented [A107]: Reference replaced 2022: Chaudhuri R, Rubin A, Sumino K, et al. Safety and effectiveness of bronchial thermoplasty after 10 years in patients with persistent asthma (BT10+): a follow-up of three randomised controlled trials. Lancet Respir Med 2021; 9: 457-466. [replaces: Wechsler ME, Laviolette M, Rubin AS, et al. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin Immunol 2013;132:1295-302.e3.]

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Commented [A108]: Added 2022: Andújar-Espinosa R, Salinero-González L, Illán-Gómez F, et al. Effect of vitamin D supplementation on asthma control in patients with vitamin D deficiency: the ACVID randomised clinical trial. Thorax 2021; 76: 126-133.

asthma 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.[318-320] More studies are needed.

NON-PHARMACOLOGICAL STRATEGIES

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

Box 3-9. Non-pharmacological interventions - summary

Intervention	Advice/recommendation (continued on next page)	Evidence
Cessation of smoking and ETS exposure	• 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.141), as additional treatment strategies may be required.	D
Physical activity	• Encourage people with asthma to engage in regular physical activity for its general health benefits.	A
	• Provide advice about prevention of exercise-induced bronchoconstriction with regular ICS.	A
	• Provide advice about prevention of breakthrough exercise-induced bronchoconstriction with ○ warm-up before exercise ○ SABA before exercise ○ low dose ICS-formoterol before exercise.	 A A B
	• Regular physical activity improves cardiopulmonary fitness, and can have a small benefit for asthma control and lung function, including with 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.	D
	• In management of occupational asthma, identify and eliminate occupational sensitizers as soon as possible, and remove sensitized patients from any further exposure to these agents.	A
	• Patients with suspected or confirmed occupational asthma should be referred for expert assessment and advice, if available.	A
Avoidance of medications that may make asthma worse	• Always ask about asthma before prescribing NSAIDs, and advise patients to stop using them if asthma worsens.	D
	• Always ask people with asthma about concomitant medications.	D
	• Aspirin and NSAIDs (non-steroidal anti-inflammatory drugs) are not generally contraindicated unless there is a history of previous reactions to these agents (see p.102).	A
	• Decide about prescription of oral or ophthalmic beta-blockers on a case-by-case basis. Initiate treatment under close medical supervision by a specialist.	D
	• If cardioselective beta-blockers are indicated for acute coronary events, asthma is not an absolute contra-indication, but the relative risks/benefits should be considered.	D
Healthy diet	• Encourage patients with asthma to consume a diet high in fruit and vegetables for its general health benefits.	A

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

Intervention	Advice/recommendation	Evidence
Avoidance of indoor allergens	• Allergen avoidance is not recommended as a general strategy in asthma.	A
	• For sensitized patients, there is limited evidence of clinical benefit for asthma in most circumstances with single-strategy indoor allergen avoidance.	A
	• Remediation of dampness or mold in homes reduces asthma symptoms and medication use in adults.	A
	• For patients sensitized to house dust mite and/or pets, there is limited evidence of clinical benefit for asthma with avoidance strategies (only in children) .	B
	• Allergen avoidance strategies are often complicated and expensive, and there are no validated methods for identifying those who are likely to benefit.	D
Weight reduction	• Include weight reduction in the treatment plan for obese patients with asthma.	B
	• For obese adults with asthma a weight reduction program plus twice-weekly aerobic and strength exercises is more effective for symptom control than weight reduction alone.	B
Breathing exercises	• Breathing exercises may be a useful supplement to asthma pharmacotherapy for symptoms and quality of life, but they do not reduce exacerbation risk or have consistent effects on lung function.	A
Avoidance of indoor air pollution	• Encourage people with asthma to use non-polluting heating and cooking sources, and for sources of pollutants to be vented outdoors where possible.	B
Avoidance of outdoor allergens	• For sensitized patients, when pollen and mold counts are highest, closing windows and doors, remaining indoors, and using air conditioning may reduce exposure to outdoor allergens.	D
Dealing with emotional stress	• Encourage patients to identify goals and strategies to deal with emotional stress if it makes their asthma worse.	D
	• There is insufficient evidence to support one stress-reduction strategy over another, but relaxation strategies and breathing exercises may be helpful.	B
	• Arrange a mental health assessment for patients with symptoms of anxiety or depression.	D
Avoidance of outdoor air pollutants/weather conditions	• During unfavorable environmental conditions (very cold weather or high air pollution) it may be helpful to stay indoors in a climate-controlled environment, and to avoid strenuous outdoor physical activity; and to avoid polluted environments during viral infections, if feasible.	D
Avoidance of foods and food chemicals	• 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.

Smoking cessation and avoidance of environmental tobacco smoke

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

In people with asthma (children and adults), exposure to passive smoke increases the risk of hospitalization and poor asthma control. Active smoking is associated with increased risk of poor asthma control, hospital admissions and, in some studies, death from asthma; it increases the rate of decline of lung function and may lead to COPD; and it reduces the effectiveness of inhaled and oral corticosteroids.[321] After smoking cessation, lung function improves and airway inflammation decreases.[322] Reduction of passive smoke exposure improves asthma control and reduces hospital admissions in adults and children.[323] Use of e-cigarettes is associated with an increased risk of asthma symptoms or diagnosis, and an increased risk of asthma exacerbations.

Advice

- At every visit, strongly encourage people with asthma who smoke to quit. They should be provided with access to counseling and, if available, to smoking cessation programs (Evidence A).
- Strongly encourage people with asthma to avoid environmental smoke exposure (Evidence B).
- Advise parents/carers of children with asthma not to smoke and not to allow smoking in rooms or cars that their children use (Evidence A).
- Assess patients with a >10 pack-year smoking history for COPD or asthma–COPD overlap, as additional treatment strategies may be required (see Chapter 5, p.141).

Physical activity

For people with asthma, as in the general population, regular moderate physical activity has important health benefits including reduced cardiovascular risk and improved quality of life. There is some evidence that aerobic exercise training can have a small beneficial effect on asthma symptom control and lung function, although not airway inflammation.[324] Improved cardiopulmonary fitness may reduce the risk of dyspnea unrelated to airflow limitation being mistakenly attributed to asthma. In one study of non-obese patients with asthma, high intensity interval training together with a diet with high protein and low glycemic index improved asthma symptom control, although no benefit on lung function was seen.[325] In young people with asthma, swimming training is well tolerated and leads to increased lung function and cardio-pulmonary fitness;[326] however, there are some concerns about exposure to chlorine and trichloramine with indoor pools.[43]

Exercise is an important cause of asthma symptoms for many asthma patients, but EIB can usually be reduced with maintenance ICS.[43] Breakthrough exercise-related symptoms can be managed with warm-up before exercise,[43] and/or by taking SABA[43] or low dose ICS-formoterol[188] before or during exercise.

Advice

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

Avoidance of occupational exposures

Occupational exposures to allergens or sensitizers account for a substantial proportion of the incidence of adult-onset asthma.[327] Once a patient has become sensitized to an occupational allergen, the level of exposure necessary to induce symptoms may be extremely low, and resulting exacerbations become increasingly severe. Attempts to reduce

Commented [A109]: Added 2022:
Wills TA, Soneji SS, Choi K, et al. E-cigarette use and respiratory disorders: an integrative review of converging evidence from epidemiological and laboratory studies. Eur Respir J 2021; 57.

Cho JH, Paik SY. Association between electronic cigarette use and asthma among high school students in South Korea. PLoS One 2016; 11: e0151022

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occupational exposure have been successful, especially in industrial settings.[40]. Cost-effective minimization of latex sensitization can be achieved by using non-powdered low-allergen gloves instead of powdered latex gloves.[40]

Advice

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

Avoidance of medications that may make asthma worse

Aspirin and other NSAIDs can cause severe exacerbations.[328] Beta-blocker drugs, including topical ophthalmic preparations, may cause bronchospasm[329] and have been implicated in some asthma deaths. However, beta-blockers have a proven benefit in the management of cardiovascular disease. People with asthma who have had an acute coronary event and received beta-blockers within 24 hours of hospital admission have been found to have lower in-hospital mortality rates than those who did not receive beta-blockers.[330]

Advice

- Always ask people with asthma about concomitant medications, including eyedrops (Evidence D).
- Always ask about asthma and previous reactions before prescribing NSAIDs, and advise patients to stop using these medications if asthma worsens.
- Aspirin and NSAIDs are not generally contraindicated in asthma unless there is a history of previous reactions to these agents (Evidence A). (See '*Aspirin-exacerbated respiratory disease*', p.102)
- For people with asthma who may benefit from oral or ophthalmic beta-blocker treatment, a decision to prescribe these medications should be made on a case-by-case basis, and treatment should only be initiated under close medical supervision by a specialist (Evidence D).
- Asthma should not be regarded as an absolute contraindication to use cardioselective beta-blockers when they are indicated for acute coronary events, but the relative risks and benefits should be considered (Evidence D). The prescribing physician and patient should be aware of the risks and benefits of treatment.[331]

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Avoidance of indoor allergens

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

There is conflicting evidence about whether measures to reduce exposure to indoor allergens are effective at reducing asthma symptoms.[332,333] The majority of single interventions have failed to achieve a sufficient reduction in allergen load to lead to clinical improvement.[332,334,335] It is likely that no single intervention will achieve sufficient benefits to be cost effective (Box 3-10, p.82). One study of insecticidal bait in homes eradicated cockroaches for a year and led to a significant decrease in symptoms, improvement in pulmonary function, and less health care use for children with moderate to severe asthma.[336]

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Domestic mites: these mites live and thrive in many sites throughout the house so they are difficult to reduce and impossible to eradicate. A systematic review of multi-component interventions to reduce allergens including house dust mite showed no benefit for asthma in adults and a small benefit for children.[337] One study that used a rigorously applied integrated approach to dust mite control led to a significant decrease in symptoms, medication use and improvement in pulmonary function for children with dust mite sensitization and asthma.[338] However, this approach is complicated and expensive and is not generally recommended. A study in mite-sensitized children recruited after emergency department presentation showed a decrease in emergency department visits, but not oral corticosteroids, with the use of mite-impermeable encasement of the mattress, pillow and duvet.[339]

Furred pets: complete avoidance of pet allergens is impossible for sensitized patients as these allergens are ubiquitous outside the home[340] in schools,[341] public transport, and even cat-free buildings, probably transferred on clothes.[341] Although removal of such animals from the home of a sensitized patient is encouraged,[342] it can be many months before allergen levels decrease,[343] and the clinical effectiveness of this and other interventions remains unproven.[344]

Pest rodents: symptomatic patients suspected of domestic exposure to pest rodents should be evaluated with skin prick tests or specific IgE, as exposure may not be apparent unless there is an obvious infestation.[345] High level evidence for the effectiveness of removing rodents is lacking, as most integrated pest management interventions also remove other allergen sources;[345] one non-sham-controlled study showed comparable clinical improvement with pest reduction education and integrated pest management.[346]

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

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

This table is adapted from Custovic et al[347]

Cockroaches: avoidance measures for cockroaches are only partially effective in removing residual allergens[348] and evidence of clinical benefit is lacking.

Fungi: fungal exposure has been associated with asthma exacerbations. The number of fungal spores can best be reduced by removing or cleaning mold-laden objects.[349] Air conditioners and dehumidifiers may be used to reduce humidity to less than 50% and to filter large fungal spores. However, air conditioning and sealing of windows have also been associated with increases in fungal and house dust mite allergens.[350]

Advice

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

Healthy diet

In the general population, a diet high in fresh fruit and vegetables has many health benefits, including prevention of many chronic diseases and forms of cancer. Many epidemiological studies report that a high fruit and vegetable diet is associated with a lower risk of asthma and lung function decline. There is some evidence that increasing fruit and vegetable intake leads to an improvement in asthma control and a reduced risk of exacerbations.[351]

Advice

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

Weight reduction for obese patients

Asthma can be more difficult to control in obese patients,[352-354] the risk of exacerbations is greater,[85,86] and response to ICS may be reduced.[355] There is limited evidence about the effect of weight loss on asthma control. Studies have ranged from dietary restriction to multifactorial interventions with exercise training and cognitive behavioral therapy, but populations have generally been small, and interventions and results have been heterogeneous.[356] In some studies, weight loss has improved asthma control, lung function and health status, and reduced medication needs in obese patients with asthma.[357,358] The most striking results have been observed after bariatric surgery,[359,360] but even 5–10% weight loss with diet, with or without exercise, can lead to improved asthma control and quality of life.[361]

Advice

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

Breathing exercises

A systematic review of studies of breathing and/or relaxation exercises in adults with asthma and/or dysfunctional breathing, including the Buteyko method and the Papworth method, reported improvements in symptoms, quality of life and/or psychological measures, but with no consistent effect on lung function and no reduction in risk of exacerbations.[362]

In order for studies of non-pharmacological strategies such as breathing exercises to be considered high quality, control groups should be appropriately matched for level of contact with health professionals and for asthma education. A study of two physiologically contrasting breathing exercises, which were matched for contact with health professionals and instructions about rescue inhaler use, showed similar improvements in reliever use and ICS dose after down-titration in both groups.[363] This suggests that perceived improvement with breathing exercises may be largely due to factors such

as relaxation, voluntary reduction in use of rescue medication, or engagement of the patient in their care. The cost of some commercial programs may be a potential limitation.

Breathing exercises used in some of these studies are available at www.breathestudy.co.uk[364] and www.woolcock.org.au/moreinfo.[363]

Advice

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

Avoidance of indoor air pollution

In addition to passive and active smoking, other major indoor air pollutants that are known to impact on respiratory health include nitric oxide, nitrogen oxides, carbon monoxide, carbon dioxide, sulfur dioxide, formaldehyde, and biologicals (endotoxin).[365,366] Sources include cooking and heating devices, particularly if they are not externally flued (vented). Installation of non-polluting, more effective heating (heat pump, wood pellet burner, flued gas) in the homes of children with asthma does not significantly improve lung function but significantly reduces symptoms of asthma, days off school, healthcare utilization, and pharmacist visits.[367] Air filters can reduce fine particle exposure, but there is no consistent effect on asthma outcomes.

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Park HJ, Lee HY, Suh CH, et al. The effect of particulate matter reduction by indoor air filter use on respiratory symptoms and lung function: a systematic review and meta-analysis. Allergy Asthma Immunol Res 2021; 13: 719-732.
Phipatanakul W, Koutrakis P, Coull BA, et al. Effect of school integrated pest management or classroom air filter purifiers on asthma symptoms in students with active asthma: a randomized clinical trial. JAMA 2021; 326: 839-850.

Advice

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

Strategies for dealing with emotional stress

Emotional stress may lead to asthma exacerbations in children[368] and adults. Hyperventilation associated with laughing, crying, anger, or fear can cause airway narrowing.[369,370] Panic attacks have a similar effect.[371,372] However, it is important to note that asthma is not primarily a psychosomatic disorder. During stressful times, medication adherence may also decrease.

Advice

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

Avoidance of outdoor allergens

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

Advice

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

Avoidance of outdoor air pollution

Meta-analysis of epidemiological studies showed a significant association between air pollutants such as ozone, nitrogen oxides, acidic aerosols, and particulate matter and symptoms or exacerbations of asthma, including emergency department visits and hospitalizations.[91] Proximity to main roads at home and school is associated with greater asthma morbidity.[373] Certain weather and atmospheric conditions like thunderstorms[374,375] may trigger asthma exacerbations by a variety of mechanisms, including dust and pollution, by increasing the level of respirable allergens, and causing changes in temperature and/or humidity. Reduction of outdoor air pollutants usually requires national or local policy

changes. For example, short-term traffic restrictions imposed in Beijing during the Olympics reduced pollution and was associated with a significant fall in asthma outpatient visits.[376]

Advice

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

Avoidance of food and food chemicals

Food allergy as an exacerbating factor for asthma is uncommon and occurs primarily in young children. Confirmed food allergy is a risk factor for asthma-related mortality.[87]

Food chemicals, either naturally occurring or added during processing, may also trigger asthma symptoms especially when asthma is poorly controlled. Sulfites (common food and drug preservatives found in such foods as processed potatoes, shrimp, dried fruits, beer, and wine) have often been implicated in causing severe asthma exacerbations.[377] However, the likelihood of a reaction is dependent on the nature of the food, the level and form of residual sulfite, the sensitivity of the patient, and the mechanism of the sulfite-induced reaction.[377] There is little evidence to support any general role for other dietary substances including benzoate, the yellow dye, tartrazine, and monosodium glutamate in worsening asthma.

Advice

- Ask people with asthma about symptoms associated with any specific foods (Evidence D).
- Food avoidance should not be recommended unless an allergy or food chemical sensitivity has been clearly demonstrated (Evidence D), usually by carefully supervised oral challenges.[87]
- If food allergy is confirmed, food allergen avoidance can reduce asthma exacerbations (Evidence D).
- If food chemical sensitivity is confirmed, complete avoidance is not usually necessary, and sensitivity often decreases when overall asthma control improves (Evidence D).

INDICATIONS FOR REFERRAL FOR EXPERT ADVICE

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

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

Difficulty confirming the diagnosis of asthma

- Patient has symptoms of chronic infection, or features suggesting a cardiac or other nonpulmonary cause (Box 1-3, p.26) (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[40] for details.

Persistent or severely 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 (medium dose ICS-LABA, Box 3-5, p.60). Before referral, depending on the clinical context, identify and treat modifiable risk factors (Box 2-2, p.36; Box 3-8, p.75) and comorbidities (p.94).
- Patient has frequent asthma-related health care utilization (e.g. multiple ED visits or urgent primary care visits).
- See Section 3E (p.104) on difficult to treat and severe asthma, including a decision tree.

Any risk factors for asthma-related death (see Box 4-1, p.126)

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

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

- 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.102); 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 medium dose ICS (Box 3-6B, p.62) with correct inhaler technique and good adherence
- Suspected side-effects of treatment (e.g. growth delay)
- Concerns about the child's welfare or well-being

ED: emergency department; ICS: inhaled corticosteroids; ICU: intensive care unit. For indications for referral in children 0-5 years, see p.158.

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

KEY POINTS

- 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 or trained health care worker.
- In developing, customizing and evaluating self-management interventions for different cultures, sociocultural factors should be taken into account.[378]

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.[84] 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.[379] Most people with incorrect technique are unaware that they have a problem. There is no 'perfect' inhaler – patients can have problems using any inhaler device.

Strategies for ensuring effective use of inhaler devices are summarized in Box 3-12, p.88.[380]

These principles apply to all types of inhaler devices. For patients prescribed pressurized metered dose inhalers (pMDIs), use of a spacer improves delivery and (for ICS) reduces the potential for local side-effects such as dysphonia and oral candidiasis.[381] With ICS, the risk of candidiasis can also be reduced by rinsing and spitting out after use.

Checking and correcting inhaler technique using a standardized checklist takes only 2–3 minutes and leads to improved asthma control in adults[382,383] and older children[380] (Evidence A). A physical demonstration is essential to improve inhaler technique.[384] 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. Attaching a pictogram[385] or a list of inhaler technique steps[386] to the inhaler substantially increases the retention of correct technique at follow-up. Pharmacists, nurses and trained lay health workers can provide highly effective inhaler skills training.[380,387-389]

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

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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 or trained health care worker.¶
In developing, customizing and evaluating self-management interventions for different cultures, sociocultural factors should be taken into account.**Error! Hyperlink reference not valid.**¶

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Box 3-12. 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.60), 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.[382]
• 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.[390]
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.[387,388]

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.[391] Approximately 50% of adults and children on long-term therapy for asthma fail to take medications as directed at least part of the time.[392]

In clinical practice, poor adherence may be identified by an empathic question that acknowledges the likelihood of incomplete adherence and encourages an open discussion. See Box 3-13, p.90 for examples. Checking the date of the last prescription or the date on the inhaler may assist in identifying poor adherence. In some health systems, pharmacists can assist in identifying poorly adherent patients by monitoring dispensing records. Electronic inhaler monitoring has also been used in clinical practice to identify poor adherence in patients with difficult-to-treat asthma.

In clinical studies, poor adherence may be identified by short adherence behavior questionnaires, or from dispensing records; dose or pill counting; electronic inhaler monitoring;[393] and drug assay such as for prednisolone.[394]

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. Factors involved in poor adherence are listed in Box 3-13, p.90. They include both intentional and unintentional factors. Issues such as ethnicity,[395] health literacy,[396,397] and numeracy[152] are often overlooked. Patients' concerns about side-effects may be either real or perceived.[284,398]

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Sulaiman I, Greene G, MacHale E, et al. A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma. Eur Respir J. 2018;51(1):1701126. doi:10.1183/13993003.01126-2017

Lee J, Tay TR, Radhakrishna N, et al. Nonadherence in the era of severe asthma biologics and thermoplasty. Eur Respir J. 2018;51(4):1701836. doi:10.1183/13993003.01836-2017

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Interventions that improve adherence in asthma

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

- Shared decision-making for medication/dose choice improved adherence and asthma outcomes.[143,146]
- Electronic inhaler reminders, either proactively or for missed doses, improved adherence[399-401] and reduced exacerbations and oral corticosteroid use.[399-401]
- 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.[402]
- 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.[403]
- 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.[404]
- In one study, directly observed controller medication administration at school, combined with telemedicine oversight, was associated with more symptom-free days and fewer urgent visits than usual care.[405]

Improving adherence to controller medications may not necessarily translate to improved clinical outcomes.[406] Further studies are needed of adherence strategies that are feasible for implementation in primary care.

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Foster JM, Usherwood T, Smith L, et al. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. J Allergy Clin Immunol 2014;134:1260-8.
Chan AH, Stewart AW, Harrison J, Camargo CA, Jr., Black PN, Mitchell EA. The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. Lancet Respir Med 2015;3:210-9.
Morton RW, Elphick HE, Rigby AS, et al. STAAR: a randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma. Thorax 2017;72:347-54

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Box 3-13. 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-judgmental discussion. Examples are: '*Many patients don't use their inhaler as prescribed. In the last 4 weeks, how many days a week have you been taking it – not at all, 1, 2, 3 or more days a week?*'[407] '*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.[142,408]
Examples of successful adherence interventions	
• Shared decision-making for medication/dose choice[143,146] • Inhaler reminders, either proactively or for missed doses[399-401] • Prescribing low dose ICS once-daily versus twice-daily[409] • Home visits for a comprehensive asthma program by an asthma nurse[402]	

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.[410] These are complex interventions, and there have been few studies. Regional issues and the adolescent's developmental stage may affect the outcomes of such programs.[411]

The key features and components of an asthma education program are provided in Box 3-14. Information alone improves knowledge but does not improve asthma outcomes.[412] 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[413,414] 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, for both adults and children, can be delivered effectively by a range of health care providers including pharmacists and nurses[387,388,415,416] (Evidence A). Trained lay health workers (also known as community health workers) can deliver discrete areas of respiratory care such as asthma self-management education. Asthma education by trained lay health workers has been found to improve patient outcomes and healthcare utilization compared with usual care,[389,417] and to a similar extent as nurse-led education in primary care[418] (Evidence B). These findings suggest the need for additional studies to assess applicability in other settings and populations.

Box 3-14. Asthma information

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

Approach	Content
• 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.45). • Fully discuss expectations, fears and concerns. • Develop shared goals.	• 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 education are:[144]

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

Self-management education that includes these components dramatically reduces asthma morbidity in both adults[144,389,419] (Evidence A) and children[145,419] (Evidence A). Benefits include reduction of one-third to two-thirds in asthma-related hospitalizations, emergency department visits and unscheduled doctor or clinic visits, missed work/school days, and nocturnal wakening.[144] 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.[144,420] Less intensive interventions that involve self-management education but not a written action plan are less effective,[421] and information alone is ineffective.[412] A systematic meta-review of 270 RCTs on supported self-management for asthma confirmed that it reduces unscheduled healthcare use, improves asthma control, is applicable to a wide range of target groups and clinical settings, and does not increase health care costs (Evidence A).[419]

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[125]
  - For patients with a history of sudden severe exacerbations
  - For patients who have difficult-to-control or severe asthma

For patients carrying out PEF monitoring, use of a laterally compressed PEF chart (showing 2 months on a landscape format page) allows more accurate identification of worsening asthma than other charts.[136] 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[422] (Evidence B).

Commented [A114]: Reference replaced 2022! Barnes PJ, Szefler SJ, Reddel HK, et al. Symptoms and perception of airway obstruction in asthmatic patients: Clinical implications for use of reliever medications. J Allergy Clin Immunol 2019; 144: 1180-1186. [replaces: Killian KJ, Watson R, Otis J, St Amand TA, O'Byrne PM. Symptom perception during acute bronchoconstriction. Am J Respir Crit Care Med 2000;162:490-6.]

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.[423,424] The term 'written' action plan includes printed, digital or pictorial plans, i.e. the patient is given a record of the instructions.

The benefits of self-management education for asthma morbidity are greater in adults when the action plans include both a step up in ICS and the addition of OCS, and for PEF-based plans, when they are based on personal best rather than percent predicted PEF[424] (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[421] (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 adult and pediatric patients with low literacy, can be found on several websites (e.g. Asthma UK, www.asthma.org.uk; Asthma Society of Canada, www.asthma.ca; Family Physician Airways Group of Canada, www.fpagc.com; National Asthma Council Australia, www.nationalasthma.org.au) and in research publications.[425,426] 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.130).

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Regular review by a healthcare provider or trained healthcare worker

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

- Ask the patient if they have any questions 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.36).
  Ask about flare-ups to identify contributory factors and whether the patient's response was appropriate (e.g. was an action plan used?).

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Review the patient's symptom or PEF diary, if they keep one.
Assess comorbidities.

- Assess treatment issues.
  Watch the patient use their inhaler, and correct and re-check technique if necessary (Box 3-12 p.88).
  Assess medication adherence and ask about adherence barriers (Box 3-13, p.90).
  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.[427]

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A single page prompt to clinicians has been shown to improve the provision of preventive care to children with asthma during office visits.[428] 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.[422]

School-based programs for children

A systematic review found that school-based studies (most conducted in the US and Canada) that included self-management skills for children aged 5–18 years was associated with a 30% decrease in emergency department visits, and a significant decrease in hospitalizations and in days of reduced activity.[429]

PART D. MANAGING ASTHMA WITH MULTIMORBIDITY AND IN SPECIFIC POPULATIONS

KEY POINTS

- Multimorbidity is common in patients with chronic diseases such as asthma. It is important to identify and manage multimorbidity, as it contributes to impaired quality of life, increased healthcare utilization, and adverse effects of medications. In addition, comorbidities such as rhinosinusitis, obesity and gastro-esophageal reflux disease may contribute to respiratory symptoms and some contribute to poor asthma control.
- For patients with dyspnea or wheezing on exertion:
  - Distinguish between exercise-induced bronchoconstriction (EIB) and symptoms that result from obesity or a lack of fitness or are the result of alternative conditions such as inducible laryngeal obstruction.
  - Provide advice about preventing and managing EIB.
- All adolescents and adults with asthma should receive ICS-containing controller medication to reduce their risk of severe exacerbations. It should be taken every day or, as an alternative in mild asthma, by as-needed ICS-formoterol for symptom relief.
- Refer patients with difficult-to-treat or severe asthma to a specialist or severe asthma service, after addressing common problems such as incorrect diagnosis, incorrect inhaler technique, ongoing environmental exposures, and poor adherence (see Section 3E, p.104).

MANAGING COMORBIDITIES

Multimorbidity is a common problem in patients with chronic diseases such as asthma. It is associated with worse quality of life, increased healthcare utilization and increased adverse effects of treatment. Multimorbidity is particularly common among those with difficult-to-treat or severe asthma.[86] Active management of comorbidities such as rhinosinusitis, obesity and gastro-esophageal reflux disease is important, as these conditions may also contribute to respiratory symptom burden and lead to medication interactions. Some comorbidities also contribute to poor asthma control.[430]

Obesity

Clinical features

Being overweight or obese is a risk factor for childhood asthma and wheeze, particularly in girls.[431] Asthma is more difficult to control in obese patients.[352-355] 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 expiratory airflow limitation (Box 1-2, p.23). Asthma is more common in obese than non-obese patients,[53] but both over- and under-diagnosis of asthma occur in obesity.[33,54]

Management

As for other patients with asthma, ICS are the mainstay of treatment in obese patients (Evidence B), although their response may be reduced.[355] 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).[361] Weight loss can improve asthma control, lung function, health status and reduces medication needs in obese patients,[357,358] but the studies have generally been small, quality of some studies is poor, and the interventions and results have been variable.[356] The most striking results have been observed after bariatric surgery,[359,360,432] but even 5–10% weight loss can lead to improved

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asthma control and quality of life.[361] For patients with comorbid obstructive sleep apnea, one study showed a significant reduction in moderate exacerbations with 6 months of continuous positive airway pressure (CPAP) therapy.[433]

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,[430] 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.[430]

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

Clinical trials of proton pump inhibitors in patients with confirmed asthma, most of whom had a diagnosis of GERD, showed small benefits for lung function, but no significant benefit for other asthma outcomes.[434] 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.[435] In general, benefits of proton pump inhibitors in asthma appear to be limited to patients with both symptomatic reflux and night-time respiratory symptoms.[436] 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.[437,438]

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Anxiety and depression

Clinical features

Anxiety symptoms and psychiatric disorders, particularly depressive and anxiety disorders, are more prevalent among people with asthma.[439] Psychiatric comorbidity is also associated with worse asthma symptom control and medication adherence, and worse asthma-related quality of life.[440] Anxious and depressive symptoms have been associated with increased asthma-related exacerbations and emergency visits.[441] Panic attacks may be mistaken for asthma.

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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.[442] Results for anxiety were conflicting, and none of the studies found significant treatment differences for depression. Drug treatments and cognitive behavior therapy[443] 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.[87] 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.[444] 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.[445]

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

Rhinitis, sinusitis and nasal polyps

Clinical features

Evidence clearly supports a link between diseases of the upper and lower airways.[447] Most patients with asthma, either allergic or non-allergic, have concurrent rhinitis, and 10–40% of patients with allergic rhinitis have asthma.[448] 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).[449]

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).[450] 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.[451] 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.[452]

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)[447] recommend intranasal corticosteroids for treatment of allergic rhinitis. In a case-control study, treatment of rhinitis with intranasal corticosteroids was associated with less need for asthma-related hospitalization and emergency department visits,[453] but a meta-analysis found improvement in asthma outcomes only in patients not also receiving ICS.[454] However, few placebo-controlled studies have systematically evaluated the effect of proper treatment and management of chronic rhinosinusitis on asthma control. A 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.[455]

In patients with nasal polyposis, omalizumab,[456] mepolizumab[457,458] and dupilumab[459] improved subjective and objective assessments including nasal symptoms and polyp size, compared with placebo. In patients with chronic sinusitis with nasal polyposis and comorbid asthma, asthma symptom control and lung function were also improved with dupilumab.[459]

MANAGING ASTHMA IN SPECIFIC POPULATIONS OR SETTINGS

This section includes brief advice about managing asthma in specific populations or settings in which the usual treatment approach may need to be modified. Also refer to the *Diagnosis of respiratory symptoms in other settings* section of Chapter 1 (p.28).

Low- and middle-income countries

Clinical features

In 2019, 96% of asthma deaths and 84% of disability-adjusted life years (DALYs) were in LMICs. Symptoms of asthma are similar world-wide, but patient language may differ, and comorbidities may vary depending on environmental exposures such as smoking and biomass fuel exposure and incidence of chronic respiratory infections from tuberculosis and HIV/AIDS.

Management

The fundamental principles and aims of asthma treatment are the same in LMICs as in high-income countries, but common barriers to effective long-term asthma care include the lack of availability and affordability of inhaled medicines and prioritisation of acute care over chronic care by healthcare systems.

Recommendations by WHO and the International Union Against Tuberculosis and Lung Disease (The Union) form the basis of treatments offered in many LMICs. The WHO Model List of Essential Medicines (Appendix, Chapter 5) includes ICS, combination ICS-formoterol, and bronchodilators. Spacers are included in the WHO list of essential technology but are rarely available due to obstacles to their manufacture or purchase, practical issues of cleaning, and inconvenience for ambulatory use. Effective spacers can be made at no cost from plastic drink bottles.

Medicines selected as 'essential' are not necessarily the most effective or convenient, particularly for patients with more severe disease, and a limited choice does not allow for consideration of patient preferences and likelihood of adherence. However, ICS-containing controllers, when provided for large populations, have achieved impressive reductions in mortality and morbidity, including in LMICs. In Brazil, government policy ensuring nationwide easy access to ICS, at no cost to patients, was associated with a 34% reduction in hospitalisations for asthma. Prescribing ICS-formoterol as the symptom reliever, with (GINA Steps 3–5) or without (Steps 1–2) maintenance ICS-formoterol, provides the safest and most effective asthma treatment for adolescents and adults, and avoids the behavioral consequences of starting treatment with SABA alone.

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Inclusion of essential asthma medicines in formularies and guidelines does not assure sustained and equitable supply to patients. The supply of medicines in many LMICs tends to be sporadic for a wide variety of reasons, sometimes determined by the ability of governments to pay for supplies, issues relating to procurement, poor administration and record keeping, and problems in the supply chain, particularly to remote dispensaries.

Availability of asthma medicines varies widely between LMICs, with some having only oral bronchodilators (salbutamol and theophylline tablets/solutions) supplemented from time to time with oral corticosteroids. Oral bronchodilators have a slow onset of action and more adverse effects than inhaled SABA, and even occasional courses of OCS are associated with a significant risk of short-term adverse effects such as pneumonia and sepsis, and with long-term adverse effects including osteoporosis, cataract and diabetes. The largest (52 countries) survey of the accessibility and affordability of inhaled asthma medicines, conducted in 2011, reported that salbutamol was available in only half of public hospitals; ICS was available in fewer than one in five public pharmacies and not at all in 14 countries.

Obtaining asthma medicines often represents a catastrophic household expense. A recent systematic review of the availability, cost and affordability of essential medicines for asthma and COPD in LMICs found these to be largely unavailable and unaffordable particularly for ICS and combination ICS-LABA. This means that the essential cornerstone of treatment that achieves substantial reductions in morbidity and mortality is out of reach for the great majority of the world's children, adolescents and adults living with asthma.

It is not acceptable in 2022 to manage asthma with SABAs and oral corticosteroids instead of preventive ICS-containing treatments. The research community must develop and evaluate approaches designed to obviate barriers to care in resource-constrained settings. A World Health Assembly Resolution on equitable access to affordable care, including inhaled medicines, for children, adolescents and adults with asthma, wherever they live in the world, would be a valuable step forward – as was recently achieved for the supply of insulin for diabetes. GINA strongly supports this initiative.

In the meantime, in general, Track 2 treatment, although less effective in reducing asthma exacerbations, may be considered preferable in settings where current availability or affordability constrains the ability to implement Track 1 treatment. The "other controller options" in Figure 3.5A, though potentially less costly, may be considerably less effective (e.g. LTRAs) or more harmful (e.g. maintenance OCS), or not well supported by evidence especially in the low-resource setting (e.g. use of a low dose ICS inhaler whenever a SABA is taken for symptom relief). Of these three other controller options options, the third would be closest to the preferred recommendations in Tracks 1 and 2, as it would ensure that an ICS was provided, at least during symptomatic periods.

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

In a large meta-analysis of adherence with ICS by adolescents and young adults,[392] overall adherence was 28%, and slightly higher in those <18 years (36%). However, pharmacy refill data provided lower estimates of adherence than self-report measures. Predictors of adherence included personality, illness perceptions, and treatment beliefs.

Management

General principles for managing chronic disease in adolescents have been published by WHO.[461] 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. In adolescents with mild asthma, adherence as-needed ICS-formoterol reduced risk of severe exacerbations compared with SABA alone, and without the need for daily treatment. Change in height from baseline in younger adolescents was significantly greater with as-needed ICS-formoterol than with daily low-dose ICS plus as-needed SABA.

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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 inducible laryngeal obstruction.[38,43]

Management

Regular controller treatment with ICS significantly reduces EIB[43] (Evidence A). Training and sufficient warm-up reduce the incidence and severity of EIB[43] (Evidence A). Taking SABAs, LABAs or chromones prior to exercise prevents EIB (Evidence A), but tolerance to the protective effects of SABAs and LABAs against EIB develops with regular (more than once-daily) use (Evidence A).[43] However, in a 6-week study in patients with mild asthma, low dose budesonide-formoterol, taken as needed for relief of symptoms and before exercise, was non-inferior for reducing EIB to regular daily ICS with as-needed SABA.[188] More studies are needed, but this suggests that patients with mild asthma who are prescribed as-needed ICS-formoterol to prevent exacerbations and control symptoms can use the same medication prior to exercise, if needed, and do not need to be prescribed a SABA for pre-exercise use (Evidence B). Chromone pMDIs have been discontinued globally.

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

Athletes

Clinical features

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

Management

Preventative measures to avoid high exposure to air pollutants, allergens (if sensitized) and chlorine levels in pools, particularly during training periods, should be discussed with the athlete. They should avoid training in extreme cold or pollution (Evidence C), and the effects of any therapeutic trials of asthma medications should be documented. Adequate anti-inflammatory therapy, especially ICS, is advised; minimization of use of beta$_2$-agonists will help to avoid the development of tolerance.[43] 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[462] 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.[463] Exacerbations are common in pregnancy, particularly in the second trimester.[88] 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,[464] 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).[88] If asthma is well controlled throughout pregnancy there is little or no increased risk of adverse maternal or fetal complications.[45]

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[45] (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.[465]

Importantly, ICS reduce the risk of exacerbations of asthma during pregnancy[45,466,467] (Evidence A), and cessation of ICS during pregnancy is a significant risk factor for exacerbations[88] (Evidence A). A study using administrative data reported that uncontrolled maternal asthma increased the risk of early-onset asthma in the offspring.[468] One study reported that a treatment algorithm in non-smoking pregnant women based on monthly FeNO and ACQ was associated with significantly fewer exacerbations and better fetal outcomes than an algorithm based only on ACQ.[469] However, the ACQ-only algorithm did not reflect current clinical recommendations, as LABA was introduced only after ICS had been increased to medium dose, and ICS could be stopped; 58% of women in the ACQ-only group were being treated without ICS by the end of pregnancy. In a follow-up study after 4-6 years, the prevalence of asthma was over 50% lower both in children of women in the FeNO group and in children of women receiving ICS in the ACQ group, compared with women in the clinical group who did not receive ICS.[470] Use of ICS in early pregnancy (before randomization at weeks 12-20) also appeared to be protective for asthma in the child.[470]

On balance, given the evidence in pregnancy and infancy for adverse outcomes from exacerbations during pregnancy[45] (Evidence A), including due to lack of ICS or poor adherence,[88] and evidence for safety of usual doses of ICS and LABA[465] (Evidence A), **a low priority should be placed on stepping down treatment (however guided) until after delivery** (Evidence D), and **ICS should not be stopped in preparation for pregnancy or during pregnancy** (Evidence C).

Despite lack of evidence for adverse effects of asthma treatment in pregnancy, many women and doctors remain concerned.[471] Pregnant patients with asthma should be advised that poorly controlled asthma, and exacerbations, provide a much greater risk to their baby than do current asthma treatments. Educational resources about asthma management during pregnancy may provide additional reassurance.[472] During pregnancy, monthly monitoring of asthma is recommended.[472] It is feasible for this to be achieved by pharmacist-clinician collaboration, with monthly telephone monitoring of asthma symptom control.[473] One observational study found that pregnant women whose asthma was well-controlled without controller therapy and who have no history of previous exacerbations were at low risk for exacerbations during pregnancy.[474] However, they should still be closely monitored.

For women with severe asthma, evidence on use of biologic therapies during pregnancy is scarce. A registry study found no evidence of an increased risk of major congenital malformations when mothers received omalizumab during pregnancy. Women should be counselled that the potential risks associated with biologic exposure during pregnancy need to be balanced against the risks for themselves and their children caused by uncontrolled asthma.

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Respiratory infections should be monitored and managed appropriately during pregnancy.[464] During acute asthma exacerbations, pregnant women may be less likely to be treated appropriately than non-pregnant patients.[88] 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.[475]

A review of asthma guidelines for the management of asthma during pregnancy highlighted the need for greater clarity in current recommendations and the need for more RCTs among pregnant asthma patients.[476]

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Women – perimenstrual asthma (catamenial asthma)

Clinical features

In approximately 20% of women, asthma is worse in the premenstrual phase. These women tend to be older, have more severe asthma, a higher body mass index, a longer duration of asthma, and a greater likelihood of aspirin exacerbated respiratory disease. They more often have dysmenorrhea, premenstrual syndrome, shorter menstrual cycles, and longer menstrual bleeding. The role of hormone levels and systemic inflammation remains unclear.[477]

Management

In addition to the usual strategies for management of asthma, oral contraceptives and/or leukotriene receptor antagonists may be helpful[477] (Evidence D). Further research is needed.

Occupational asthma

Clinical features

In the occupational setting, rhinitis often precedes the development of asthma (see p.28 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.[40]

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Management

Detailed information is available in evidence-based guidelines about management of occupational asthma.[40] 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.[40] Cost-effective minimization of latex sensitization can be achieved by using non-powdered low-allergen gloves instead of powdered latex gloves.[40] 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.[478-480] 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.[479]

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.[478,479] 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.[478] Clearance of theophylline is also reduced.[478] 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,[479,481] 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.141

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Surgery and asthma

Clinical features

There is no evidence of increased peri-operative risk for the general asthma population.[482] However, there is an increased risk for patients with COPD,[482] 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.[483]

Management

For elective surgery, meticulous attention should be paid pre-operatively to achieving good asthma control, as detailed elsewhere in this chapter, especially for patients with more severe asthma, uncontrolled symptoms, exacerbation history, or persistent airflow limitation[483] (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[484] (Evidence B). More immediate intra-operative issues relating to asthma management are reviewed in detail elsewhere.[483] 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.[328] It starts with nasal congestion and anosmia, and progresses to chronic rhinosinusitis with nasal polyps that re-grow rapidly after surgery. Asthma and hypersensitivity to aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) develop subsequently. Following ingestion of aspirin or NSAIDs, an acute asthma attack develops within minutes to 1–2 hours. It is usually accompanied by rhinorrhea, nasal obstruction, conjunctival irritation, and scarlet flush of the head and neck, and may sometimes progress to severe bronchospasm, shock, loss of consciousness, and respiratory arrest.[485,486] AERD is more likely to be associated with low lung function and severe asthma,[487,488] and with increased need for emergency care.[488] The prevalence of AERD is 7% in general adult asthma populations, and 15% in severe asthma.[488,489]

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[490,491] 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.[490,491] Bronchial (inhalational) and nasal challenges with lysine aspirin are safer than oral challenges and may be safely performed in allergy centers.[491,492]

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[493,494] with appropriate health care provider supervision and observation for at least 2 hours after administration[495] (Evidence B). ICS are the mainstay of asthma therapy in AERD, but OCS are sometimes required; LTRA may also be useful[486,495] (Evidence B), but note the 2020 FDA warning about adverse effects with montelukast.[208] See Chapter 3E (p.104) for treatment options for patients with severe asthma. An additional option is aspirin desensitization, which may be conducted under specialist care in a clinic or hospital.[496] Desensitization to aspirin followed by daily aspirin treatment can significantly improve upper respiratory symptoms and overall quality of life, decrease recurrence of nasal polyps, reduce the need for OCS and sinus surgery, and improve nasal and asthma scores, but few double-blind studies have examined asthma outcomes.[491,497,498] Aspirin desensitization is associated with a significantly increased risk of adverse effects such as gastritis and gastrointestinal bleeding.[498]

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Allergic bronchopulmonary aspergillosis (ABPA)

Clinical features

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

Diagnosis

Diagnosis of ABPA is based on composite criteria including immediate hypersensitivity reaction to A. fumigatus, total serum IgE, specific IgG to A. fumigatus, radiological features and blood eosinophils.[499] Sensitization to fungal allergens, without the full picture of ABPA, is often found in asthma, particularly in severe asthma, where it is sometimes called 'severe asthma with fungal sensitization'.

Management

Current first-line therapy is with oral corticosteroids (e.g. 4 month tapering course), with itraconazole reserved for those with exacerbations or requiring long-term OCS.[499,500] One open-label study comparing itraconazole and OCS found that patients treated with itraconazole had a slightly lower response rate at 6 weeks but similar long-term response rates, with substantially fewer side-effects than with OCS.[501] A randomized double-blind placebo-controlled study in patients with severe asthma and ABPA found significantly fewer exacerbations with omalizumab (anti-IgE) than placebo.[502] In ABPA patients with bronchiectasis, regular physiotherapy and daily drainage are recommended.

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

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

KEY POINTS

What are difficult to treat and severe asthma?

- Difficult-to-treat asthma is asthma that is uncontrolled despite prescribing of medium or high dose ICS-LABA treatment or that requires high dose ICS-LABA treatment to maintain good symptom control and reduce exacerbations. It does not mean a 'difficult patient'.
- Severe asthma is asthma that is uncontrolled despite adherence with optimized high dose ICS-LABA therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased. Approximately 3–10% of people with asthma have severe asthma.
- Severe asthma places a large physical, mental, emotional, social and economic burden on patients. It is often associated with multimorbidity.

How should these patients be assessed?

- Assess all patients with difficult to treat asthma to confirm the diagnosis of asthma, and to identify and manage factors that may be contributing to symptoms, poor quality of life, or exacerbations.
- Refer for expert advice at any stage, or if asthma does not improve in response to optimizing treatment.
- For patients with persistent symptoms and/or exacerbations despite high dose ICS, the clinical or inflammatory phenotype should be assessed, as this may guide the selection of add-on treatment.

Management of severe asthma

- Depending on the inflammatory phenotype and other clinical features, add-on treatments for severe asthma include LAMA, LTRA, low dose azithromycin (adults), and biologic agents for severe asthma.
- Low-dose maintenance OCS should be considered only as a last resort if no other options are available, because of their serious long-term side-effects.
- Assess the response to any add-on treatment, stop ineffective treatments, and consider other options.
- Utilize specialist multidisciplinary team care for severe asthma, if available.
- For patients with severe asthma, continue to optimize patient care in collaboration with the primary care clinician, and taking into account the patient's social and emotional needs.
- Invite patients with severe asthma to enroll in a registry or clinical trial, if available and relevant, to help fill evidence gaps.

See Boxes 3-16A to 3-16D (starting on p.108) for the GINA severe asthma decision tree.

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Although the majority of patients can achieve the goal of well controlled asthma, some patients' asthma will not be well controlled even with optimal therapy. The material that follows is from the GINA Guide for health professionals on Diagnosis and Management of Difficult-to-Treat and Severe Asthma in Adolescent and Adult Patients v4.0, published in April 2022. A stand-alone copy of the Guide can be downloaded or ordered from the GINA website (www.ginasthma.org).

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

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

Understanding the definitions of difficult-to-treat and severe asthma starts with the concept of uncontrolled asthma.

Uncontrolled asthma includes one or both of the following:

- Poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma)
- Frequent exacerbations (≥2/year) requiring OCS, or serious exacerbations (≥1/year) requiring hospitalization

Difficult-to-treat asthma[137] is asthma that is uncontrolled despite prescribing of medium or high dose inhaled corticosteroids (ICS) with a second controller (usually a LABA) or with maintenance OCS, or that requires high dose treatment to maintain good symptom control and reduce the risk of exacerbations.[137] It does not mean a 'difficult patient'. In many cases, asthma may appear to be difficult-to-treat because of modifiable factors such as incorrect inhaler technique, poor adherence, smoking or comorbidities, or because the diagnosis is incorrect.

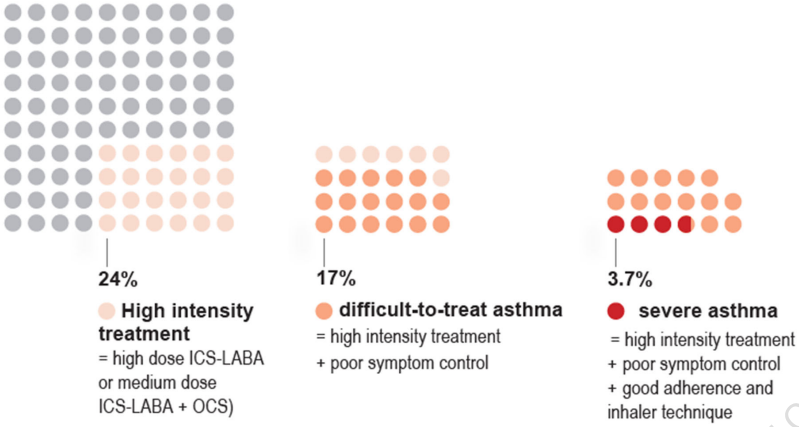
Severe asthma[137] is a subset of difficult-to-treat asthma (Box 3-15). It means asthma that is uncontrolled despite adherence with maximal optimized high dose ICS-LABA treatment and management of contributory factors, or that worsens when high dose treatment is decreased.[137] At present, therefore, 'severe asthma' is a retrospective label. It is sometimes called 'severe refractory asthma'[137] since it is defined by being relatively refractory to high dose inhaled therapy. However, with the advent of biologic therapies, the word 'refractory' is no longer appropriate.

Asthma is not classified as severe if it markedly improves when contributory factors such as inhaler technique and adherence are addressed.[137]

PREVALENCE: HOW MANY PEOPLE HAVE SEVERE ASTHMA?

A study in the Netherlands estimated that around 3.7% of asthma patients have severe asthma, based on the number of patients prescribed high dose ICS-LABA, or medium or high dose ICS-LABA plus long-term OCS, who had poor symptom control (by Asthma Control Questionnaire) and had good adherence and inhaler technique (Box 3-15).[503]

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



IMPORTANCE: THE IMPACT OF SEVERE ASTHMA

The patient perspective

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

Medication side-effects are particularly common and problematic with OCS,[274] which in the past were a mainstay of treatment for severe asthma. Adverse effects of long-term OCS include obesity, diabetes, osteoporosis, cataracts, hypertension and adrenal suppression; psychological side-effects such as depression and anxiety are particularly concerning for patients.[504] Even short- term use of OCS is associated with sleep disturbance, and increased risk of infection, fracture and thromboembolism.[505] Strategies to minimize need for OCS are therefore a high priority.

Severe asthma often interferes with family, social and working life, limits career choices and vacation options, and affects emotional and mental health. Patients with severe asthma often feel alone and misunderstood, as their experience is so different from that of most people with asthma.[504]

Adolescents with severe asthma

The teenage years are a time of great psychological and physiological development which can impact on asthma management. It is vital to ensure that the young person has a good understanding of their condition and treatment and appropriate knowledge to enable supported self-management. The process of transition from pediatric to adult care should help support the young person in gaining greater autonomy and responsibility for their own health and wellbeing. Severe asthma may improve over 3 years in approximately 30% of male and female adolescents; the only predictor of asthma becoming non-severe was higher baseline blood eosinophils.[506] Studies with longer follow-up time are needed.

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Healthcare utilization and costs

Severe asthma has very high healthcare costs due to medications, physician visits, hospitalizations, and the costs of OCS side-effects. In a UK study, healthcare costs per patient were higher than for type 2 diabetes, stroke, or COPD.[507] In a Canadian study, severe uncontrolled asthma was estimated to account for more than 60% of asthma costs.[508]

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

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

The clinical decision tree starting on page 108, provides brief information about what should be considered in each phase of diagnosis and management of difficult-to-treat and severe asthma. The decision tree is divided into three broad areas:

- **Sections 1–4 (green)** are for use in primary care and/or specialist care.
- **Sections 5–8 (blue)** are mainly relevant to respiratory specialists.
- **Sections 9–10 (brown)** are about maintaining ongoing collaborative care between the patient, GP, specialist and other health professionals.

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

Further information follows the decision tree.

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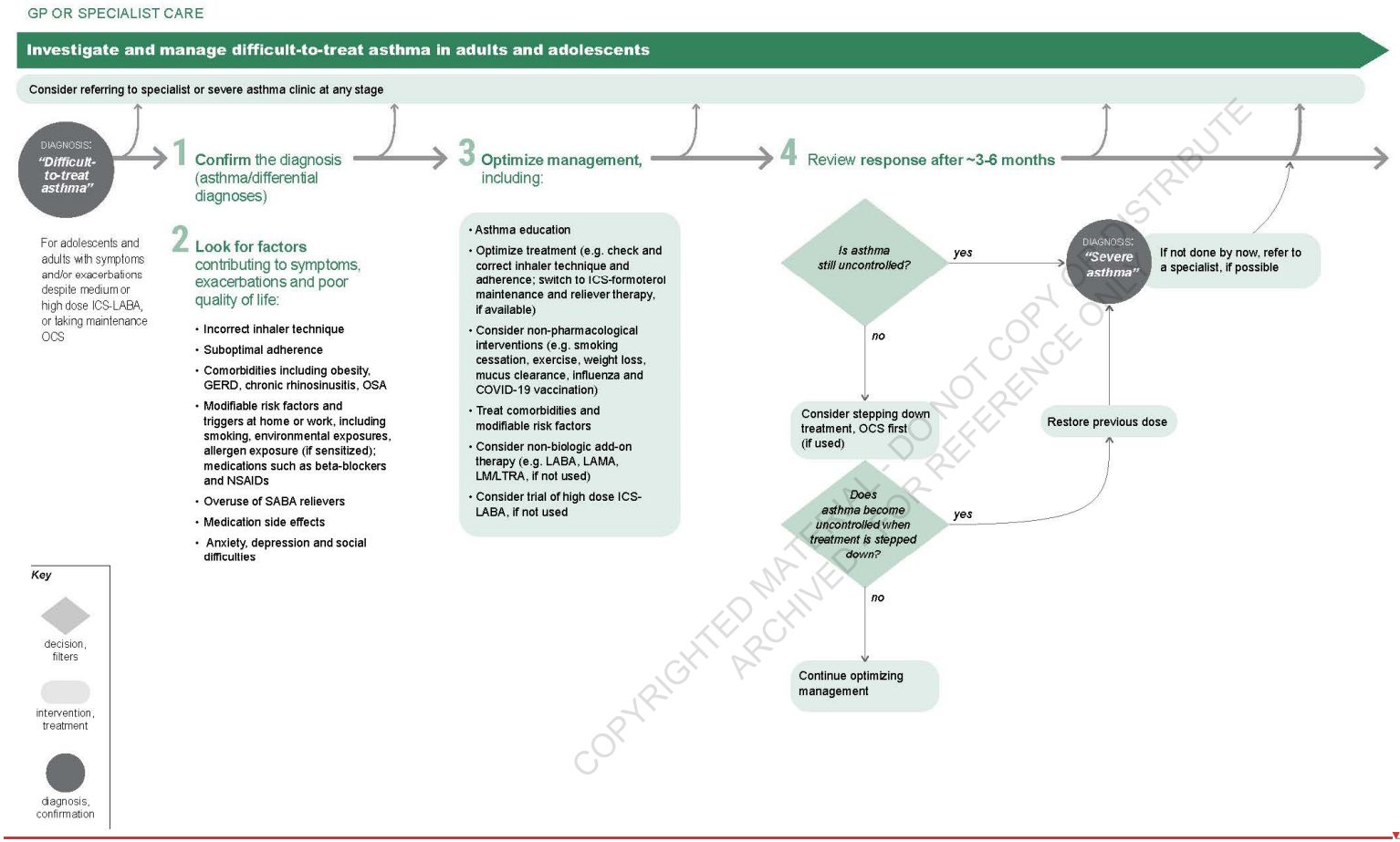
Box 3-16A. Decision tree – investigate and manage difficult to treat asthma in adult and adolescent patients



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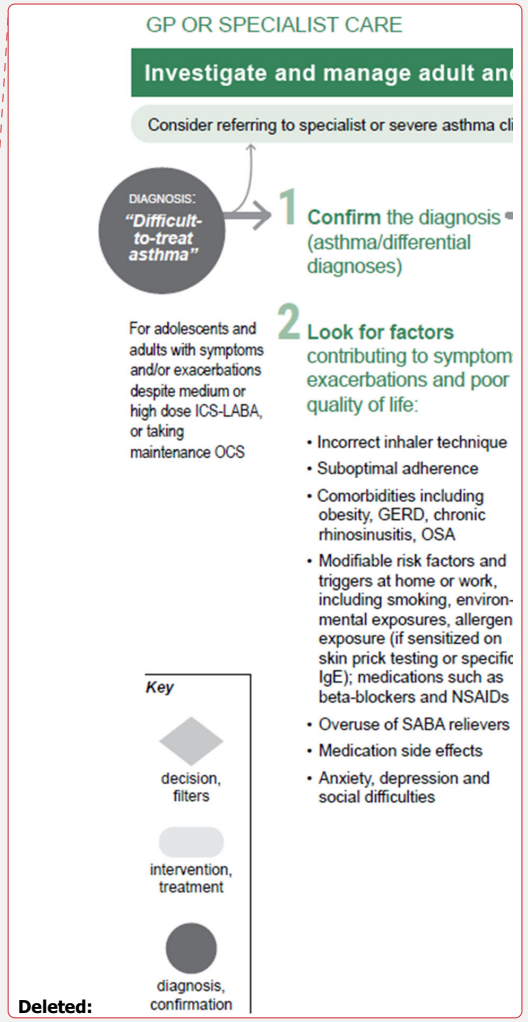

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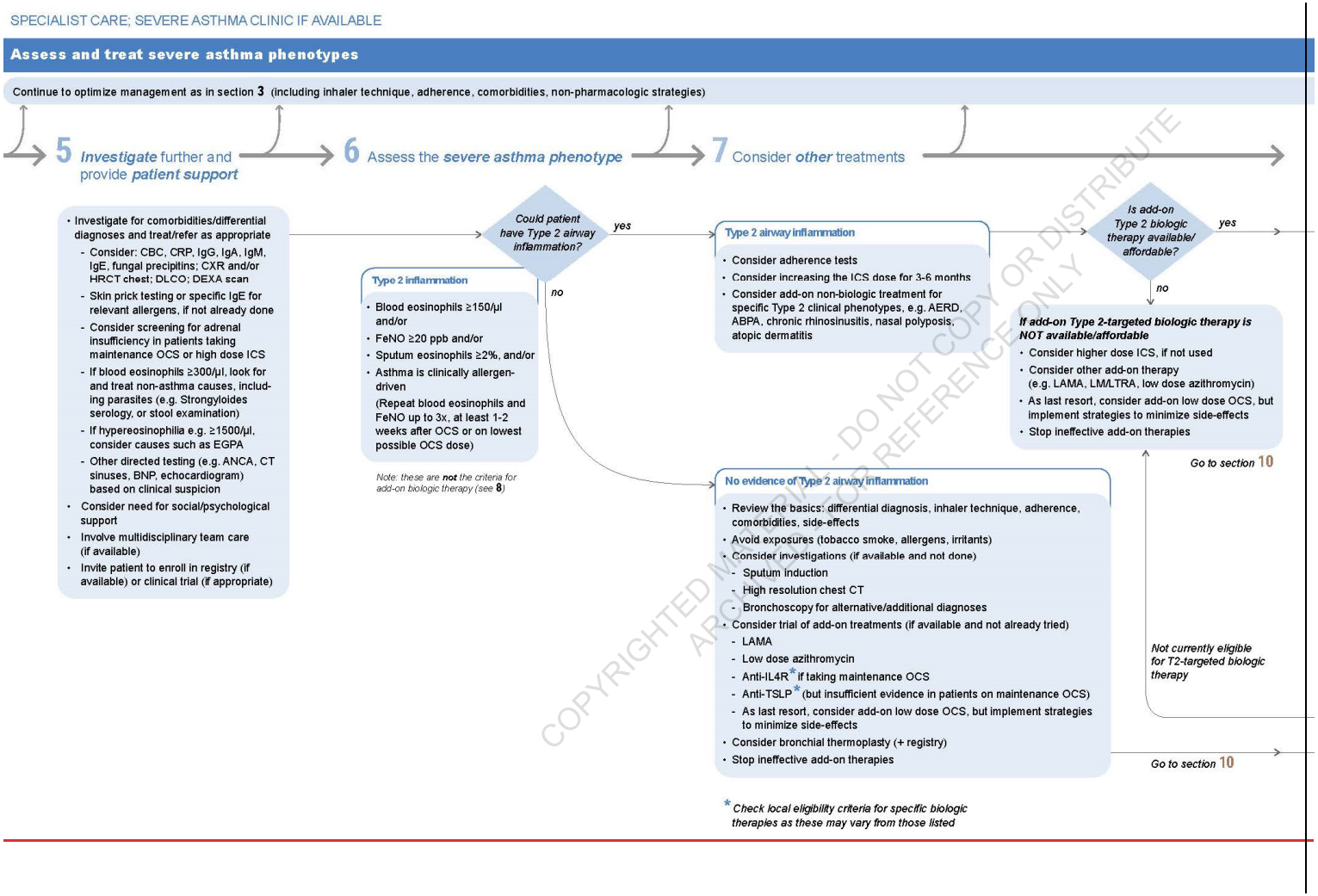
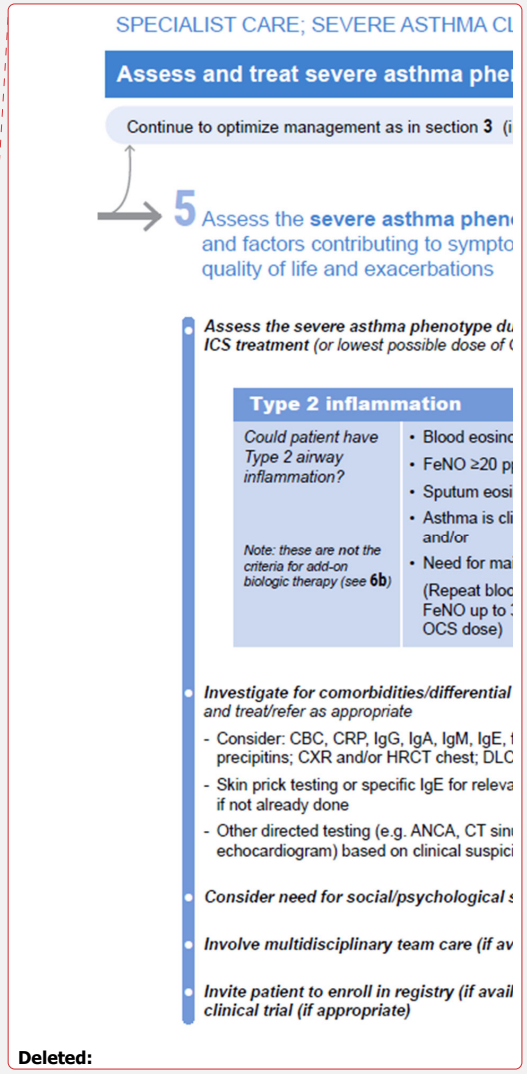
Box 3-16B. Decision tree – assess and treat severe asthma phenotypes





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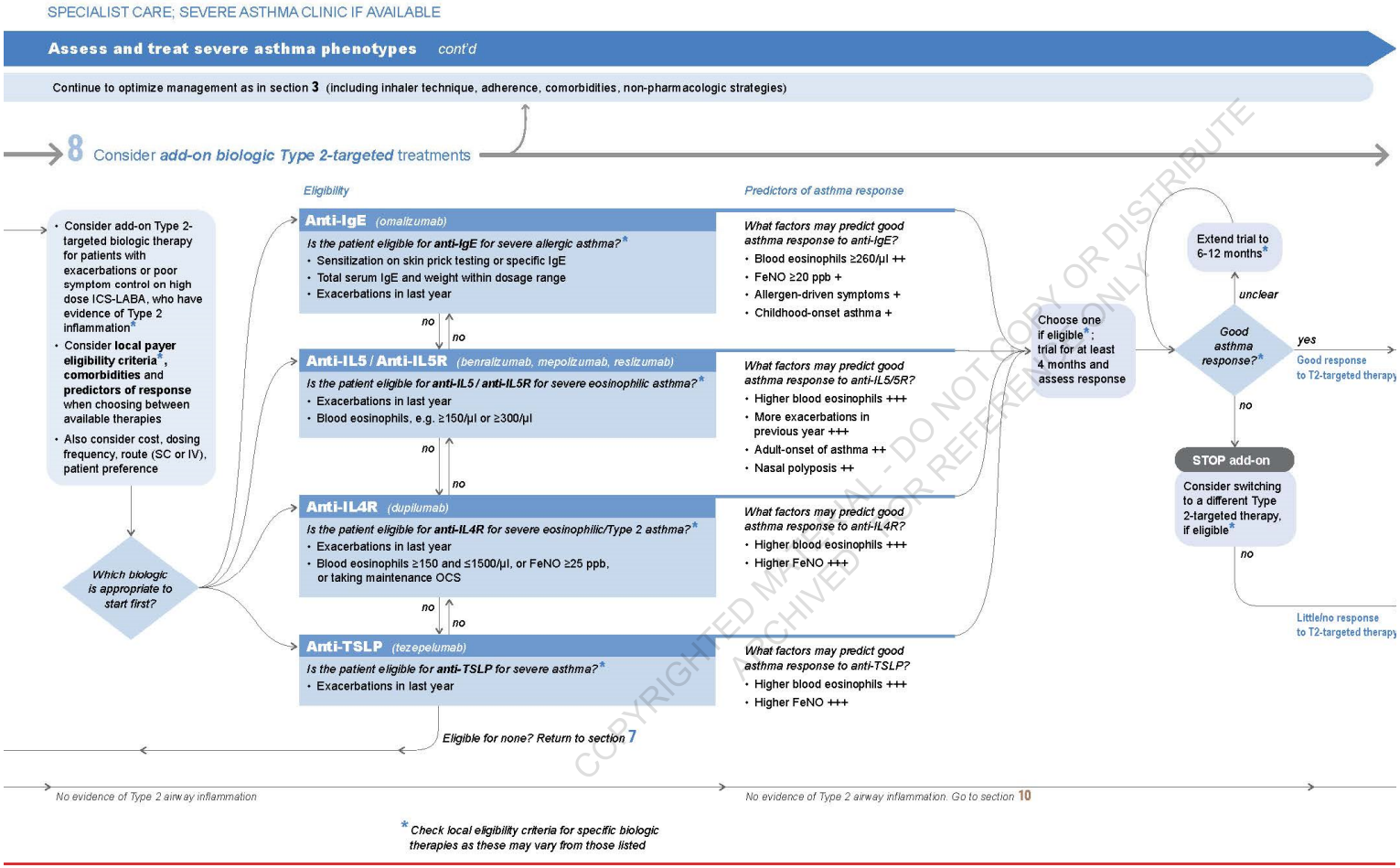
Box 3-16C. Decision tree – consider add-on biologic Type 2-targeted treatments



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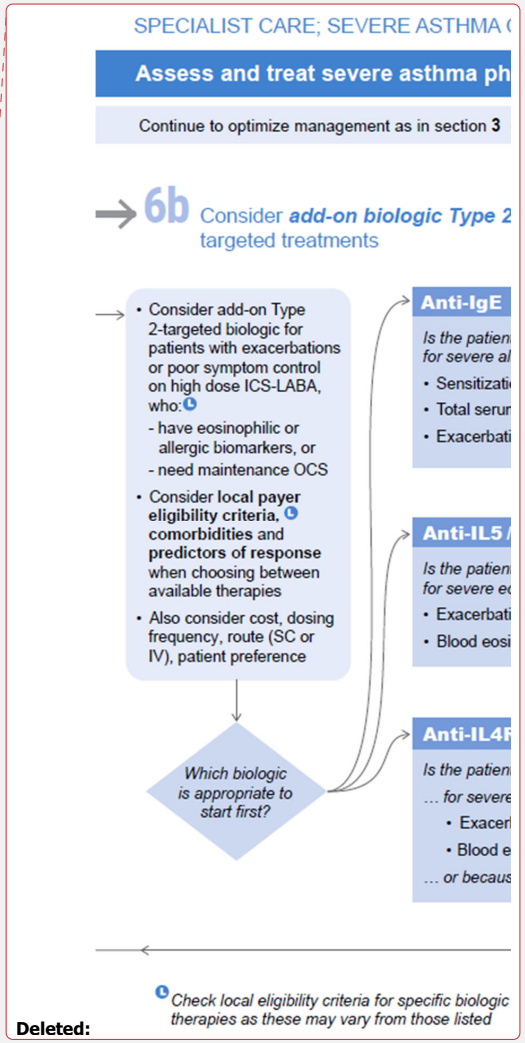

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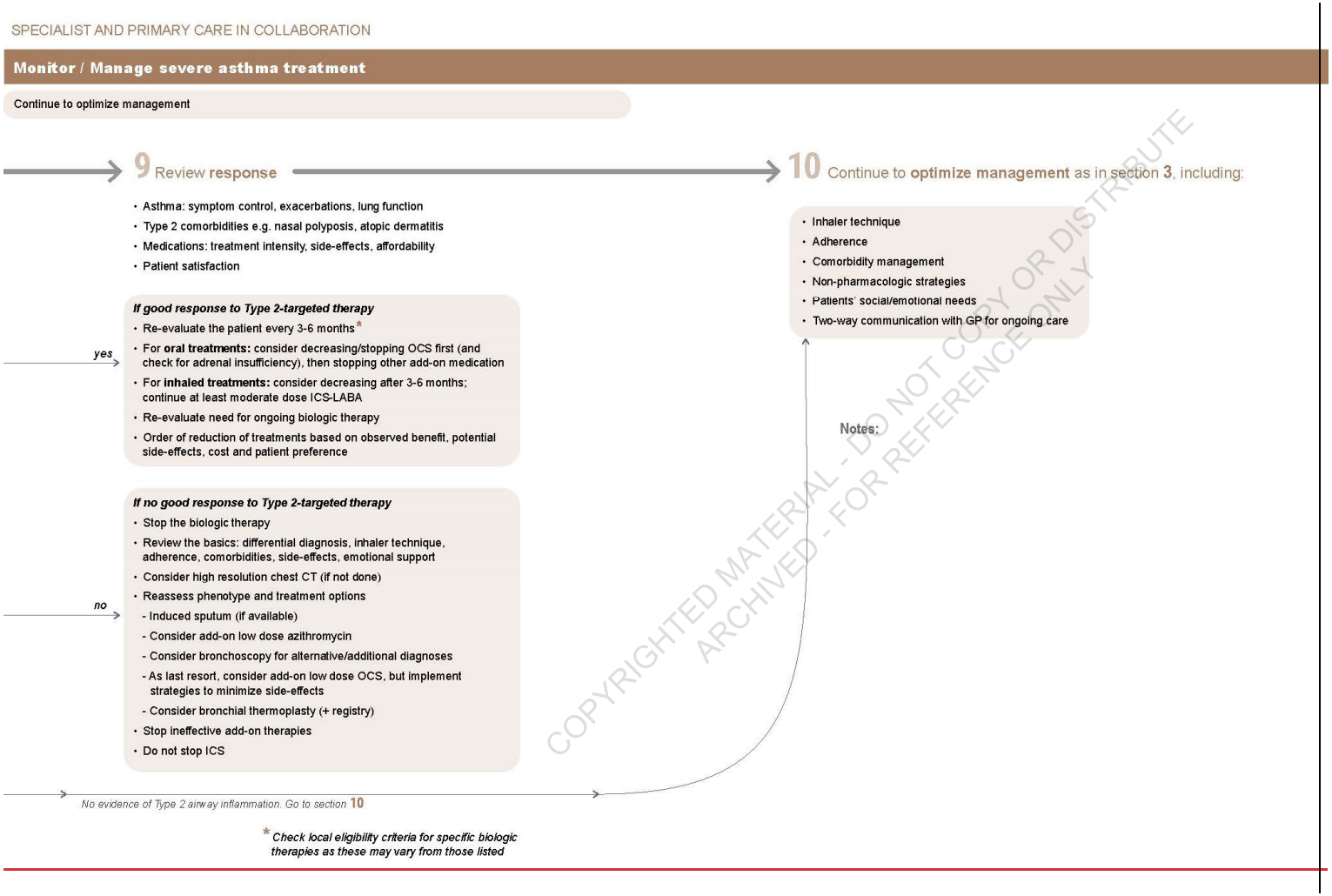
Box 3-16D. Decision tree – monitor and manage severe asthma treatment



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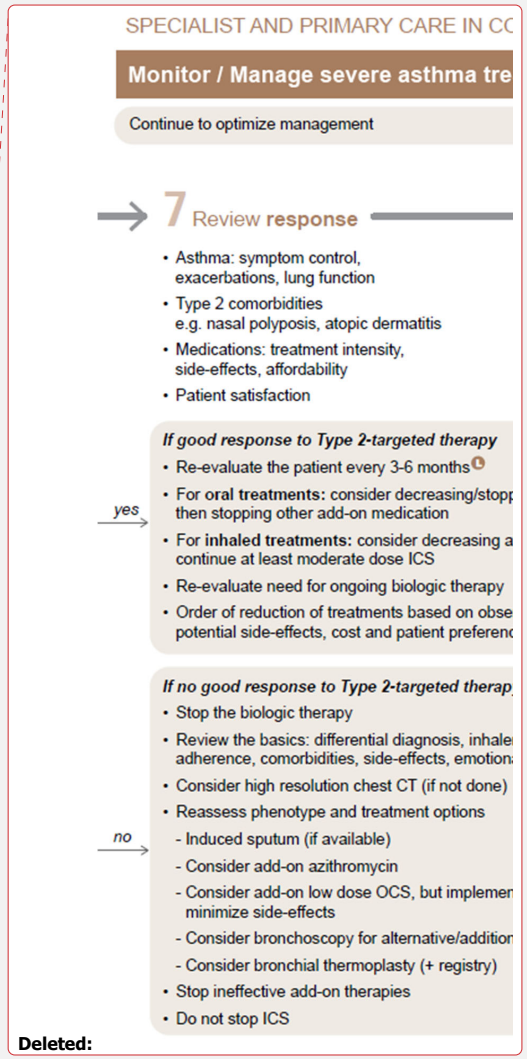

INVESTIGATE AND MANAGE DIFFICULT-TO-TREAT ASTHMA IN ADULTS AND ADOLESCENTS

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1. CONFIRM THE DIAGNOSIS (ASTHMA OR DIFFERENTIAL DIAGNOSES)

Stages 1-5 can be carried out in primary or specialist care. Difficult-to-treat asthma is defined if the patient has persistent symptoms and/or exacerbations despite prescribing of medium or high dose ICS with another controller such as LABA, or maintenance OCS, or requires high dose ICS-LABA treatment to maintain good symptom control and prevent exacerbations. It does not mean a 'difficult patient'.

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

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

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Are the symptoms due to asthma?

Perform a careful history and physical examination to identify whether symptoms are typical of asthma, or are more likely due to an alternative diagnosis or comorbidity. Investigate according to clinical suspicion and age (see Box 1-5, p.27).

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

How can the diagnosis of asthma be confirmed?

Confirmation of the diagnosis is important, because in 12–50% of people assumed to have severe asthma, asthma is not found to be the correct diagnosis.[509] Perform spirometry, before and after bronchodilator, to assess baseline lung function and seek objective evidence of variable expiratory airflow limitation. If initial bronchodilator responsiveness testing is negative (≤200 mL or ≤12% increase in FEV1), consider repeating after withholding bronchodilators or when symptomatic, or consider stepping controller treatment up or down before further investigations such as bronchial provocation testing (see Box 1-3, p.26). Check full flow-volume curve to assess for upper airway obstruction. If spirometry is normal or is not available, provide the patient with a peak flow meter and diary for assessing variability; consider bronchial provocation testing if patient is able to withhold bronchodilators (short-acting beta2-agonist (SABA) for at least 6 hours, LABA for up to 2 days depending on duration of action)[23]. Strategies for confirming the diagnosis of asthma in patients already taking controller treatment are shown in Box 1-3 (p.26).

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

2. LOOK FOR FACTORS CONTRIBUTING TO SYMPTOMS AND EXACERBATIONS

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

- **Incorrect inhaler technique** (seen in up to 80% patients): ask the patient to show you how they use their inhaler; compare with a checklist or video.
- **Suboptimal adherence** (up to 75% asthma patients): ask empathically about frequency of use (e.g. '*Many patients don't use their inhaler as prescribed. In the last 4 weeks, how many days a week have you been taking it – not at all, 1 day a week, 2, 3 or more?*' or, '*Do you find it easier to remember your inhaler in the morning or the evening?*' (see Box 3-13, p.90). Ask about barriers to medication use, including cost, and concerns about necessity or side-effects. Check dates on inhalers and view dispensing data, if available. Electronic inhaler monitoring, if available, can be helpful in screening for poor adherence.
- **Comorbidities**: review history and examination for comorbidities that can contribute to respiratory symptoms, exacerbations, or poor quality of life. These include anxiety and depression, obesity, deconditioning, chronic rhinosinusitis, inducible laryngeal obstruction, GERD, COPD, obstructive sleep apnea, bronchiectasis, cardiac disease, and kyphosis due to osteoporosis. Investigate according to clinical suspicion.
- **Modifiable risk factors and triggers**: identify factors that increase the risk of exacerbations, e.g. smoking, environmental tobacco exposure, other environmental exposures at home or work including allergens (if sensitized), indoor and outdoor air pollution, molds and noxious chemicals, and medications such as beta-blockers or non-steroidal anti-inflammatory drugs (NSAIDs). For allergens, check for sensitization using skin prick testing or specific IgE.
- **Regular or over-use of SABAs**: this causes beta-receptor down-regulation and reduction in response,[510] leading in turn to greater use. Overuse may also be habitual. Dispensing of ≥3 SABA canisters per year (corresponding to average use more than daily) is associated with increased risk of emergency department visit or hospitalization independent of severity,[82,116] and dispensing of ≥12 canisters per year (one a month) is associated with substantially increased risk of death.[81,82] Risks are higher with nebulized SABA.[511]
- **Anxiety, depression and social and economic problems**: these are very common in asthma, particularly in difficult asthma[504] and contribute to symptoms, impaired quality of life, and poor adherence.
- **Medication side-effects**: systemic effects, particularly with frequent or continuous OCS, or long-term high dose ICS may contribute to poor quality of life and increase the likelihood of poor adherence. Local side-effects of dysphonia or thrush may occur with high dose or potent ICS especially if inhaler technique is poor. Consider drug interactions including risk of adrenal suppression with use of P450 inhibitors such as itraconazole.

3. REVIEW AND OPTIMIZE MANAGEMENT

Review and optimize treatment for asthma, and for comorbidities and risk factors identified in Section 2. For more details, see Chapter 3D, p.94.

- Provide asthma self-management education, and confirm that patient has (and knows how to use) a personalized written or electronic asthma action plan. Refer to an asthma educator if available.
- Optimize inhaled controller medications: confirm that the inhaler is suitable for the patient; check and correct inhaler technique with a physical demonstration and teach-back method, check inhaler technique again at each visit.[512] Address suboptimal adherence, both intentional and unintentional.[406] Switch to ICS-formoterol maintenance and reliever regimen if available, to reduce the risk of exacerbations.[166]
- Consider non-pharmacologic add-on therapy, e.g. smoking cessation, physical exercise, healthy diet, weight loss, mucus clearance strategies, influenza vaccination, breathing exercises, allergen avoidance, if feasible, for patients who are sensitized and exposed. For details see Box 3-9, p.78.

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- Treat comorbidities and modifiable risk factors identified in Section 2 of the decision tree, where there is evidence for benefit; however, there is no evidence to support routine treatment of asymptomatic GERD (see p.95). Avoid medications that make asthma worse (beta-blockers including eye-drops; aspirin and other NSAIDs in patients with aspirin-exacerbated respiratory disease, p.102). Refer for management of mental health problems if relevant.
- Consider trial of non-biologic medication added to medium/high dose ICS, e.g. LABA, LAMA, leukotriene modifier if not already tried. Note FDA boxed warning about potential neuropsychiatric effects with leukotriene modifiers.
- Consider trial of high dose ICS-LABA if not currently used.

4. REVIEW RESPONSE AFTER APPROXIMATELY 3–6 MONTHS

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

When assessing the response to treatment, specifically review:

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

Is asthma still uncontrolled, despite optimized therapy?

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

NO: if asthma is now well controlled, consider stepping down treatment. Start by decreasing/ceasing OCS first (if used), checking for adrenal insufficiency, then remove other add-on therapy, then decrease ICS dose, but do not stop ICS. See Box 3-7 (p.74) for how to gradually down-titrate treatment intensity.

Does asthma become uncontrolled when treatment is stepped down?

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

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

ASSESS AND TREAT SEVERE ASTHMA PHENOTYPES

5. INVESTIGATE FURTHER AND PROVIDE PATIENT SUPPORT

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

What other tests may be considered at the specialist level?

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

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Commented [A138]: Reference added 2022: 1. US Food and Drug Administration. FDA requires Boxed Warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis. 3-4-2020 FDA Drug Safety Communication. [Web page]: FDA; 2020 [cited 2022 April]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug.

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Type 2 inflammation is found in the majority of people with severe asthma. It is characterized by cytokines such as interleukin (IL)-4, IL-5 and IL-13, which are often produced by the adaptive immune system on recognition of allergens. It may also be activated by viruses, bacteria and irritants that stimulate the innate immune system via production of IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) by epithelial cells. Type 2 inflammation is often characterized by eosinophilia or increased FeNO, and may be accompanied by atopy, whereas non-Type 2 inflammation is often characterized by increased neutrophils.**Error! Hyperlink reference not valid.** In many patients with asthma, Type 2 inflammation rapidly improves when ICS are taken regularly and correctly; this is classified as mild or moderate asthma. In severe asthma, Type 2 inflammation may be relatively refractory to high dose ICS. It may respond to OCS but their serious adverse effects**Error! Hyperlink reference not valid. Error! Hyperlink reference not valid.** mean that alternative treatments should be sought.¶
Could the patient have refractory or underlying Type 2 inflammation?¶
The possibility of refractory Type 2 inflammation should be considered if any of the following are found while the patient is taking high dose ICS or daily OCS:¶
Blood eosinophils ≥150/µl, and/or¶
FeNO ≥20 ppb, and/or¶
Sputum eosinophils ≥2%, and/or¶
Asthma is clinically allergen-driven¶
Patients requiring maintenance OCS may also have underlying Type 2 inflammation. However, biomarkers of Type 2 inflammation (blood eosinophils, sputum eosinophils and FeNO) are often suppressed by OCS. If possible, therefore, these tests should be performed before starting OCS (a short

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Assessment of the patient's inflammatory phenotype: Type 2 or non-Type 2?¶
More detailed assessment of comorbidities and differential diagnoses¶ … [55]

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

- Blood tests: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins including Aspergillus
- Allergy testing for clinically relevant allergens: skin prick test or specific IgE, if not already done
- Other pulmonary investigations: DLCO; CXR or high-resolution chest CT
- Bone density scan, because of risk of osteoporosis with maintenance or frequent OCS or long-term high dose ICS
- If blood eosinophils ≥300/µL, look for and treat non-asthma causes, including parasites (e.g. Strongyloides serology or stool examination), because parasitic infection may be the cause of the blood eosinophilia, and because OCS or biologic therapy in a patient with untreated parasitic infection could potentially lead to disseminated disease. Strongyloides infection is usually asymptomatic.
- If hypereosinophilia, e.g. blood eosinophils ≥1500/µL, consider causes such as eosinophilic granulomatosis with polyangiitis (EGPA)
- Other directed testing, e.g. ANCA, CT sinuses, BNP, echocardiogram, based on clinical suspicion

Consider need for social/psychological support

Refer patients to support services, where available, to help them deal with the emotional, social and financial burden of asthma and its treatment, including during and after severe exacerbations.[504] Consider the need for psychological or psychiatric referral, including for patients with anxiety and/or depression.

Involve multidisciplinary team care (if available)

Multidisciplinary assessment and treatment of patients with severe asthma increases the identification of comorbidities, and improves outcomes.[513]

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

Systematic collection of data will help in understanding the mechanisms and burden of severe asthma. There is a need for pragmatic clinical trials in severe asthma, including studies comparing two or more active treatments. Participants in randomized controlled trials designed for regulatory purposes may not necessarily be representative of patients seen in clinical practice. For example, a registry study found that over 80% of patients with severe asthma would have been excluded from key studies evaluating biologic therapy.[256]

6 ASSESS THE SEVERE ASTHMA PHENOTYPE

The next step is to assess the patient's inflammatory phenotype – is it Type 2 high or low?

What is Type 2 inflammation?

Type 2 inflammation is found in the majority of people with severe asthma. It is characterized by cytokines such as interleukin (IL)-4, IL-5 and IL-13, which are often produced by the adaptive immune system on recognition of allergens. It may also be activated by viruses, bacteria and irritants that stimulate the innate immune system via production of IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) by epithelial cells. Type 2 inflammation is often characterized by elevated eosinophils or increased FeNO, and may be accompanied by atopy, whereas non-Type 2 inflammation is often characterized by increased neutrophils.[514]

In many patients with asthma, Type 2 inflammation rapidly improves when ICS are taken regularly and correctly; this is classified as mild or moderate asthma. In severe asthma, Type 2 inflammation may be relatively refractory to high dose ICS. It may respond to OCS but their serious adverse effects[274,275] mean that alternative treatments should be sought.

In adult patients with uncontrolled asthma despite medium or high dose ICS plus LABA or other controllers, a history of exacerbations in the previous year, higher blood eosinophil counts and higher FeNO levels are associated with a greater risk of severe exacerbations.

Commented [A139]: Added 2022: Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis care & research 2017; 69: 1095-1110.

Commented [A140]: Added 2022: Centers for Disease Control and Prevention. Parasites - Stronglyoides. [web page]: U.S. Department of Health & Human Services; 2018 [updated 31 December 2018; cited 2022 April]. Available from: https://www.cdc.gov/parasites/strongyloides/.

Deleted: <#>Testing for parasitic infections. Consider this if Type 2 targeted biologic therapy is considered; this is because parasitic infection may be the cause of the blood eosinophilia, and because Type 2 targeted treatment in a patient with untreated parasitic infection could potentially lead to disseminated disease.¶

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[GINA search 41-09]

Could the patient have refractory or underlying Type 2 inflammation?

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

- Blood eosinophils ≥150/µl, and/or
- FeNO ≥20 ppb, and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven

Patients requiring maintenance OCS may also have underlying Type 2 inflammation. However, biomarkers of Type 2 inflammation (blood eosinophils, sputum eosinophils and FeNO) are often suppressed by OCS. If possible, therefore, these tests should be performed before starting OCS (a short course, or maintenance treatment), or at least 1–2 weeks after a course of OCS, or on the lowest possible OCS dose.

The above criteria are suggested for initial assessment; those for blood eosinophils and FeNO are based on the lowest levels associated with response to some biologics. They are not the criteria for eligibility for Type 2-targeted biologic therapy, which may differ - see section 8 and local criteria.

Consider repeating blood eosinophils and FeNO up to 3 times (e.g. when asthma worsens, before giving OCS, or at least 1–2 weeks after a course of OCS, or on the lowest possible OCS dose), before assuming asthma is non-Type 2. One study of patients with uncontrolled asthma taking medium-high dose ICS-LABA found that 65% had a shift in their blood eosinophil category over 48–56 weeks.[515]

Why is the inflammatory phenotype assessed on high dose ICS?

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

7.1. CONSIDER OTHER TREATMENTS IF THERE IS NO EVIDENCE OF TYPE 2 INFLAMMATION

If the patient has no evidence of persistent Type 2 inflammation (section 6):

- Review the basics for factors that may be contributing to symptoms or exacerbations: differential diagnosis, inhaler technique, adherence, comorbidities, medication side-effects (Section 2).
- Recommend avoidance of relevant exposures (tobacco smoke, pollution, allergens if sensitized and there is evidence of benefit from withdrawal, irritants, infections). Ask about exposures at home and at work.
- Consider additional diagnostic investigations (if available and not already done): sputum induction to confirm inflammatory phenotype, high resolution chest CT, bronchoscopy to exclude unusual comorbidities or alternative diagnoses such as tracheobronchomalacia or sub-glottic stenosis; functional laryngoscopy for inducible laryngeal obstruction.
- Consider a trial of add-on treatment if available and not already tried:
  - LAMA
  - Low dose azithromycin (adults),[259,516] but first check sputum for atypical mycobacteria, check ECG for long QTc (and re-check after a month on treatment), and consider potential for antibiotic resistance.
  - Anti-IL4R*[1] if taking maintenance OCS (see section 8 for more details)

[1] Asterisk indicates to check local eligibility and payer criteria for specific biologic therapies, as they may vary from those listed

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Anti-TSLP* (thymic stromal lymphopoietin) (but insufficient evidence in patients taking maintenance OCS ; see section 8 for more details)

As a last resort, consider add-on low dose OCS, but implement strategies such as alternate-day treatment to minimize side-effects.

- Consider bronchial thermoplasty, with registry enrollment. However, the evidence for efficacy and long-term safety is limited.[113,315]
- Stop ineffective add-on therapies.
- Continue to optimize treatment, including inhaler technique, adherence, non-pharmacologic strategies and treating comorbidities (see sections 3 and 10)

7.2 CONSIDER NON-BIOLOGIC OPTIONS IF THERE IS EVIDENCE OF TYPE 2 INFLAMMATION

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

- **Assess adherence objectively** by monitoring of prescribing or dispensing records, blood prednisone levels,[517] or electronic inhaler monitoring.[393] In one study, suppression of high FeNO after 5 days of directly observed therapy was an indicator of past poor adherence.[518]
- **Consider increasing the ICS dose** for 3-6 months, and review again.
- **Consider add-on non-biologic treatment for specific Type 2 clinical phenotypes** (see Chapter 3D, p.94). For example, for aspirin-exacerbated respiratory disease (AERD), consider add-on leukotriene modifier and possibly aspirin desensitization (p.102). For allergic bronchopulmonary aspergillosis (ABPA), consider add-on OCS ± anti-fungal agent (p.103). For chronic rhinosinusitis and/or nasal polyposis, consider intensive intranasal corticosteroids; surgical advice may be needed (p.96). For patients with atopic dermatitis, topical steroidal or non-steroidal therapy may be helpful.

7.3 IS TYPE 2-TARGETED BIOLOGIC THERAPY AVAILABLE AND AFFORDABLE?

If NOT:

- Consider higher dose ICS-LABA, if not used
- Consider other add-on therapy, e.g. LAMA, LM/LTRA, low dose azithromycin if not used
- As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies
- Continue to optimize treatment, including inhaler technique, adherence, non-pharmacologic strategies and treating comorbidities (see sections 3 and 10)

8 CONSIDER ADD-ON BIOLOGIC TYPE 2-TARGETED TREATMENTS

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

An asterisk (*) means to always check local criteria for eligibility and funding, as they may vary from those listed.

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

- Does the patient satisfy local payer eligibility criteria?
- Type 2 comorbidities such as atopic dermatitis, nasal polyposis

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

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- Predictors of asthma response (see below)
- Cost
- Dosing frequency
- Delivery route (IV or SC; potential for self-administration)
- Patient preference

Local payer eligibility criteria for biologic therapy may vary substantially. **For any biologic therapy,** ensure that the manufacturer's and/or regulator's instructions for storage, administration and the duration of monitoring post-administration are followed.

Provide the patient with advice about what to do if they experience any adverse effects, including hypersensitivity reactions. GINA suggests that the first dose of asthma biologic therapy should not be given on the same day as a COVID-19 vaccine, so that adverse effects of either can be more easily distinguished.

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

Add-on anti-IgE for severe allergic asthma

Currently approved:* omalizumab for ages ≥6 years, given by SC injection every 2-4 weeks, with dose based on weight and serum IgE. May also be indicated for nasal polyposis and chronic spontaneous (idiopathic) urticaria. Self-administration may be an option.

Mechanism: binds to Fc part of free IgE, preventing binding of IgE to FcεR1 receptors, reducing free IgE and down-regulating receptor expression.

*Eligibility criteria** (in addition to criteria for severe asthma) vary between payers, but usually include:

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

Outcomes: RCTs in severe allergic asthma: 44% decrease in severe exacerbations[519] improved quality of life.[261] No double blind randomized controlled trials of OCS-sparing effect. In a meta-analysis of observational studies in patients with severe allergic asthma, there was a 59% reduction in exacerbation rate,[520,521] a 41% reduction in the proportion of patients receiving maintenance OCS, and a significant improvement in symptom control.[520,521] In patients with nasal polyposis, omalizumab improved subjective and objective outcomes.[456] Registry study of omalizumab in pregnancy found no increased risk of congenital malformations.

Potential predictors of good asthma response to omalizumab:

- Baseline IgE level does not predict likelihood of response[520]
- In one observational study, a greater decrease in exacerbations was observed (cf. placebo) with blood eosinophils ≥260/μl[522,523] or FeNO ≥20 ppb[522] (these criteria representing their median value in that study) but in two large observational studies, exacerbations were reduced with both low or high blood eosinophils[521,524,525] or with both low or high FeNO.[525]
- Childhood-onset asthma
- Clinical history suggesting allergen-driven symptoms

Adverse effects: injection site reactions; anaphylaxis in ~0.2% patients[261]

Suggested initial trial: at least 4 months

*Check local regulatory and payer criteria, as they may differ from those shown

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

*Currently approved**: For ages ≥12 years: mepolizumab (anti-IL5), 100mg by SC injection every 4 weeks, or benralizumab (anti-IL5 receptor α), 30mg by SC injection every 4 weeks for 3 doses then every 8 weeks. For ages ≥18 years: reslizumab (anti-IL5), 3mg/kg by IV infusion every 4 weeks. For ages 6–11 years, mepolizumab (anti-IL5), 40mg by SC injection every 4 weeks. Mepolizumab may also be indicated for eosinophilic granulomatosis with polyangiitis (EGPA), hypereosinophilic syndrome and chronic rhinosinusitis with nasal polyps. Self-administration may be an option.

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

*Eligibility criteria** (in addition to criteria for severe asthma): these vary by product and between payers, but usually include:

- More than a specified number of severe exacerbations in the last year, and
- Blood eosinophils above locally specified level (e.g. ≥150 or ≥300/µl). There is sometimes a different eosinophil cut-point for patients taking OCS.

Outcomes: RCTs in severe asthma patients with exacerbations in the last year, with varying eosinophil criteria: anti-IL5 and anti-IL5R led to 47–54% reduction in severe exacerbations. Improvements in quality of life, lung function and symptom control were significant but less than the clinically important difference.[267] All reduced blood eosinophils; almost completely with benralizumab.[267] In post hoc analyses, clinical outcomes with mepolizumab or benralizumab were similar in patients with and without an allergic phenotype. In patients taking OCS, median OCS dose was able to be reduced by ~50% with mepolizumab[526] or benralizumab[266] compared with placebo. Efficacy data for mepolizumab in children are limited to one very small uncontrolled open label study.[268] In patients with nasal polyposis, mepolizumab improved subjective and objective outcomes and reduced the need for surgery.[457,458]

Potential predictors of good asthma response to anti-IL5 or anti-IL5R:

- Higher blood eosinophils (strongly predictive)[527]
- Higher number of severe exacerbations in previous year (strongly predictive)[527]
- Adult-onset asthma[528]
- Nasal polyposis[529]
- Maintenance OCS at baseline[529]
- Low lung function (FEV_1 <65% predicted in one study)[530]

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

Suggested initial trial: at least 4 months

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

*Currently approved**: For ages ≥12 years: dupilumab (anti-IL4 receptor α), 200mg or 300mg by SC injection every 2 weeks for severe eosinophilic/Type 2 asthma; 300mg by SC injection every 2 weeks for OCS-dependent severe asthma or if there is concomitant moderate/severe atopic dermatitis. For children 6–11 years with severe eosinophilic/Type 2 asthma by SC injection with dose and frequency depending on weight. May also be indicated for treatment of moderate-to-severe atopic dermatitis and for chronic rhinosinusitis with nasal polyposis. Self-administration may be an option.

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

*Eligibility criteria** (in addition to criteria for severe asthma): these vary between payers, but usually include:

- More than a specified number of severe exacerbations in the last year, and
- Type 2 biomarkers above a specified level (e.g. blood eosinophils ≥150/µl and ≤1500/µl; or FeNO ≥25 ppb); OR requirement for maintenance OCS

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Lemiere C, Taillé C, Lee JK, et al. Impact of baseline clinical asthma characteristics on the response to mepolizumab: a post hoc meta-analysis of two Phase III trials. Respir Res 2021; 22: 184.
FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. Lancet Respir Med 2018; 6: 51-64.

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Outcomes: RCTs in patients with uncontrolled severe asthma (ACQ-5 ≥1.5) and at least one exacerbation in the last year: anti-IL4R led to ~~56%~~ reduction in severe exacerbations,* ~~improvements in quality of life, symptom control and lung function~~ were significant~~, but less than the clinically important difference~~.[269,271] ~~In a post hoc analysis, clinical outcomes were similar in patients with allergic and non-allergic phenotype at baseline.~~ In patients with OCS-dependent severe asthma, without minimum requirements for blood eosinophil count or FeNO, treatment with anti-IL4R reduced mean OCS dose by ~30% versus placebo.[531] In children 6–11 years with eosinophilic/Type 2 asthma, dupilumab reduced severe exacerbation rate by 41% and increased lung function by 5.2 percentage points; Children taking maintenance OCS were excluded.~~ Dupilumab is also indicated for treatment of moderate-severe atopic dermatitis.[532] In patients with chronic rhinosinusitis with nasal polyposis, dupilumab reduced the size of nasal polyps, improved nasal symptoms and reduced the need for OCS or sinus surgery.[459,533]

Potential predictors of good asthma response to dupilumab:

- Higher blood eosinophils (strongly predictive)[269]
- Higher FeNO (strongly predictive)[269]

Adverse effects: injection-site reactions; transient blood eosinophilia; rare cases of eosinophilic granulomatosis with polyangiitis (EGPA). Anti-IL4R is not suggested for patients with baseline or historic blood eosinophils >1,500 cells/μL because of limited evidence (such patients were excluded from Phase III trials).

Suggested initial trial: at least 4 months

Add-on anti-TSLP for severe asthma

Currently approved:* For ages ≥12 years: tezepelumab (anti-TSLP), 210 mg by SC injection every 4 weeks

Mechanism: tezepelumab binds circulating TSLP, a bronchial epithelial cell-derived alarmin implicated in multiple downstream processes involved in asthma pathophysiology.

*Eligibility criteria** (in addition to criteria for severe asthma):* these vary between payers, but usually include:

- Severe exacerbations in the last year.

Anti-TSLP may also be considered in patients with no elevated T2 markers (section 7.1)

Outcomes: in RCTs in severe asthma patients with severe exacerbations in the last year anti-TSLP led to 30–70% reduction in severe exacerbations, and improved quality of life, lung function and symptom control, irrespective of allergic status. There was a clear correlation between higher baseline blood eosinophils or FeNO and better clinical outcomes. In patients taking maintenance OCS, anti-TSLP did not lead to a reduced OCS dose compared with placebo. As yet there is no evidence that tezepelumab also has an impact on extrapulmonary comorbidities.

Potential predictors of good asthma response to anti-TSLP:

- Higher blood eosinophils (strongly predictive)
- Higher FeNO levels (strongly predictive)

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

Suggested initial trial: at least 4 months

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

- At present, there are no well-defined criteria for a good response, but consider exacerbations, symptom control, lung function, side-effects, treatment intensity (including OCS dose), and patient satisfaction
- If the response is unclear, consider extending the trial to 6–12 months
- If there is no response, stop the biologic therapy, and consider switching to a trial of a different Type 2-targeted therapy, if available and the patient is eligible;[521,534] review response as above

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Commented [A158]: Added 2022: Bacharier LB, Maspero JF, Katelaris CH, et al., Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma. N. Engl. J. Med., 2021. 385: 2230-2240.

Commented [A159]: Added 2022: Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. N Engl J Med 2017; 377: 936-946.
Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med 2021; 384: 1800-1809.

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MANAGE AND MONITOR SEVERE ASTHMA TREATMENT

9. REVIEW RESPONSE AND IMPLICATIONS FOR TREATMENT

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

- Asthma: symptom control, e.g. Asthma Control Test, Asthma Control Questionnaire (ACQ-5); frequency and severity of exacerbations (e.g. were OCS needed), lung function
- Type 2 comorbidities, e.g. nasal polyposis, atopic dermatitis
- Medications: treatment intensity, including dose of OCS, side-effects, affordability
- Patient satisfaction

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

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

For oral treatments, consider gradually decreasing or stopping OCS first, because of their significant adverse effects. Tapering in severe asthma may be supported by internet-based monitoring of symptom control and FeNO.[535] Monitor patients for risk of adrenal insufficiency, and provide patient and GP with advice about the need for extra corticosteroid doses during injury, illness or surgery for up to 6 months after cessation of long-term OCS. Continue to assess for presence of osteoporosis, and review need for preventative strategies including bisphosphonates.[276]

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

For biologic treatments, current consensus advice is that, generally, for a patient with a good response, a trial of withdrawal of the biologic should not be considered until after at least 12 months of treatment, and only if asthma remains well-controlled on medium dose ICS therapy, and (for allergic asthma) there is no further exposure to a previous well-documented allergic trigger. There are few studies of cessation of biologic therapy,[536,537] in these studies, symptom control worsened and/or exacerbations recurred for many (but not all) patients after cessation of the biologic.

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

Stop the biologic therapy

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

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

Reassess treatment options (if not already done), such as:

- Add-on low-dose azithromycin (adults only; first check sputum for atypical mycobacteria and check ECG for long QTc (and re-check after a month on treatment); consider potential for antibiotic resistance)
- As last resort, consider add-on low-dose maintenance OCS, but implement strategies such as alternate- day therapy and add-on bisphosphonates to minimize side-effects, and alert patient to the need for additional corticosteroid therapy during illness or surgery.
- Consider bronchial thermoplasty (+ registry)

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Brusselle GG, Vanderstichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. Thorax 2013; 68: 322-329.

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

10. CONTINUE COLLABORATIVE OPTIMIZATION OF PATIENT CARE

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

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

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

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

Communicate regularly about:

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

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Chapter 4.

Management of worsening asthma and exacerbations

KEY POINTS

Terminology

- Exacerbations represent an acute or sub-acute worsening in symptoms and lung function from the patient's usual status, or in some cases, a patient may present for the first time during an exacerbation.
- The terms 'episodes', 'attacks' and 'acute severe asthma' are also often used, but they have variable meanings. The term 'flare-up' is preferable for use in discussions with most patients.
- Patients who are at increased risk of asthma-related death should be identified, and flagged for more frequent review.

Written asthma action plans

- All patients should be provided with a written (i.e. printed, digital or pictorial) asthma action plan appropriate for their level of asthma control and health literacy, so they know how to recognize and respond to worsening asthma.
- On the action plan, state when and how to change reliever and controller medications, use oral corticosteroids, and access medical care if symptoms fail to respond to treatment.
- Advise patients who have a history of rapid deterioration to go to an acute care facility or see their doctor immediately their asthma starts to worsen.
- Base the action plan on changes in symptoms or (only in adults) peak expiratory flow (PEF).

Management of exacerbations in a primary care or acute care facility

- Assess exacerbation severity from the degree of dyspnea, respiratory rate, pulse rate, oxygen saturation and lung function, while starting short-acting beta$_2$-agonist (SABA) and oxygen therapy. Infection control procedures should be followed.
- Arrange immediate transfer to an acute care facility if there are signs of severe exacerbation, or to intensive care if the patient is drowsy, confused, or has a silent chest. During transfer, give inhaled SABA and ipratropium bromide, controlled oxygen and systemic corticosteroids.
- Start treatment with repeated administration of SABA (in most patients, by pressurized metered dose inhaler and spacer), early introduction of oral corticosteroids, and controlled flow oxygen if available. Review response of symptoms, oxygen saturation and lung function after 1 hour. Give ipratropium bromide only for severe exacerbations. Consider intravenous magnesium sulfate for patients with severe exacerbations not responding to initial treatment.
- Do not routinely request a chest X-ray, and do not routinely prescribe antibiotics for asthma exacerbations.
- Decide about hospitalization based on the patient's clinical status, lung function, response to treatment, recent and past history of exacerbations, and ability to manage at home.

Discharge management

- Arrange ongoing treatment before the patient goes home. This should include starting inhaled corticosteroid (ICS)-containing controller treatment or stepping up the dose of existing controller treatment for 2–4 weeks, and reducing reliever medication to as-needed use.
- Arrange early follow-up after any exacerbation, regardless of where it was managed. At follow-up:
  - Review the patient's symptom control and risk factors for further exacerbations.
  - Prescribe ICS-containing controller therapy to reduce the risk of further exacerbations. If already taking controller therapy, continue increased doses for 2–4 weeks.
  - Provide a written asthma action plan and, where relevant, advice about avoiding exacerbation triggers
- Check inhaler technique and adherence.

For management of asthma exacerbations in children 5 years and younger, see Chapter 6, p.168.

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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.[20] Exacerbations may occur in patients with a pre-existing diagnosis of asthma or, occasionally, as the first presentation of asthma.

What triggers asthma exacerbations?

Exacerbations usually occur in response to exposure to an external agent (e.g. viral upper respiratory tract infection, pollen or pollution) and/or poor adherence with controller medication; however, a subset of patients present more acutely and without exposure to known risk factors.[538,539] Severe exacerbations can occur in patients with mild or well-controlled asthma symptoms.[14,193] Box 2-2B (p.36) lists factors that increase a patient's risk of exacerbations, independent of their level of symptom control.

Common exacerbation triggers include:

- Viral respiratory infections[540]
- Allergen exposure e.g. grass pollen,[541] soy bean dust,[542] fungal spores
- Food allergy[87]
- Outdoor air pollution[92,538]
- Seasonal changes and/or returning to school in fall (autumn)[543]
- Poor adherence with ICS[544]
- Epidemics of severe asthma exacerbations may occur suddenly, putting high pressure on local health system responses. Such epidemics have been reported in association with springtime thunderstorms and either rye grass pollen or fungal spores,[545] and with environmental exposure to soy bean dust.[542]

Identifying patients at risk of asthma-related death

In addition to factors known to increase the risk of asthma exacerbations (Box 2-2, p.36), 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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Commented [A165]: Reference added 2022: Zheng XY, Orellano P, Lin HL, et al. Short-term exposure to ozone, nitrogen dioxide, and sulphur dioxide and emergency department visits and hospital admissions due to asthma: A systematic review and meta-analysis. Environ Int 2021; 150: 106435.

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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[546]
- Hospitalization[546,547] or emergency care visit for asthma in the past year
- Currently using or having recently stopped using oral corticosteroids (a marker of event severity)[546]
- Not currently using inhaled corticosteroids[83,546]
- Over-use of SABAs, especially use of more than one canister of salbutamol (or equivalent) monthly[82,100,548]
- Poor adherence with ICS-containing medications and/or poor adherence with (or lack of) a written asthma action plan[93]
- A history of psychiatric disease or psychosocial problems[93]
- Food allergy in a patient with asthma[445,549]
- Several comorbidities including pneumonia, diabetes and arrhythmias were independently associated with an increased risk of death after hospitalization for an asthma exacerbation.[[547]

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.[550,551] 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.[550,551] In pediatric literature, the term 'episode' is commonly used, but understanding of this term by parent/carers is not known.

DIAGNOSIS OF EXACERBATIONS

Exacerbations represent a change in symptoms and lung function from the patient's usual status.[20] 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),[552] 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.[553]

A minority of patients perceive airflow limitation poorly and can experience a significant decline in lung function without a change in symptoms.[125,126,134] This especially affects patients with a history of near-fatal asthma and also appears to be more common in males. Regular PEF monitoring may be considered for such patients.

Severe exacerbations are potentially life threatening and their treatment requires careful assessment and close monitoring. Patients with severe exacerbations should be advised to see their 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.87), including monitoring of symptoms and/or lung function, a written asthma action plan, and regular review by a health professional.[419] (For children 5 years and younger, see Chapter 6, p.151). A written (i.e. documented) asthma action plan may be printed, digital, or pictorial, to suit the patient's needs and literacy. A sample written asthma action plan template is included in the GINA toolbox, available from the GINA website at www.ginasthma.org/gina-implementation-guide/.

Commented [A166]: Reference added 2022: Barnes PJ, Szefler SJ, Reddel HK, et al. Symptoms and perception of airway obstruction in asthmatic patients: Clinical implications for use of reliever medications. J Allergy Clin Immunol 2019; 144: 1180-1186.

Commented [A167]: Reference deleted 2022: Rosi E, Stendardi L, Binazzi B, Scano G. Perception of airway obstruction and airway inflammation in asthma: a review. Lung 2006;184:251-8.

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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 maintenance-only 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.[424]

Inhaled reliever medication (ICS-formoterol or SABA)

For patients with mild asthma prescribed as-needed combination low dose ICS-formoterol (see Box 3-5A, p.60), increasing the as-needed doses of ICS-formoterol when asthma worsens reduces the risk of severe exacerbations requiring OCS by two-thirds compared with SABA-only treatment,[161] and is non-inferior for progression to severe exacerbation compared with daily ICS plus as-needed SABA.[161,162] After a day of even small increased doses of ICS-formoterol, the risk of severe exacerbation in the following 3 weeks is reduced compared with the same doses of SABA alone.[185] Based on product information, the maximum recommended dose of ICS-formoterol in a single day is a total of 48 mcg formoterol for beclometasone-formoterol (36 mcg delivered dose), and 72 mcg formoterol for budesonide-formoterol (54 mcg delivered dose).

For patients prescribed an inhaled short-acting beta$_2$-agonist (SABA) bronchodilator as their reliever, repeated SABA dosing provides temporary relief until the cause of the worsening symptoms passes or increased controller treatment has had time to take effect. However, use of SABA reliever is less effective in preventing progression to severe exacerbation requiring OCS than use of low dose ICS-formoterol reliever, either with[166] or without[161,162] daily maintenance controller (see Chapter 3).

The need for repeated doses of SABA over more than 1–2 days signals the need to review, and possibly increase, controller treatment if this has not already been done. This is particularly important if there has been a lack of response to increased use of beta$_2$-agonist therapy.

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

The combination of rapid-onset LABA (formoterol) and low dose ICS (budesonide or beclometasone) in a single inhaler as both the controller and the reliever medication is effective in improving asthma symptom control,[165] and it reduces exacerbations requiring OCS, and hospitalizations[166,217-220] compared with the same or higher dose of controller with as-needed SABA reliever (Evidence A). The recommended maximum total dose of formoterol in 24 hours with budesonide-formoterol is 72 mcg (delivered dose 54 mcg) and with beclometasone-formoterol is 48 mcg (delivered dose 36 mcg). The benefit of this regimen in preventing exacerbations appears to be due to intervention at a *very early stage* of worsening asthma.[282,283] This regimen was also effective in reducing exacerbations in children aged 4–11 years,[238] (Evidence B). This approach should not be attempted with other combination ICS-LABA controller therapies with a slower-onset LABA, or that lack evidence of efficacy and safety with a maintenance and reliever regimen.

Other ICS and ICS-LABA maintenance controller regimens

In a systematic review of self-management studies, action plans in which the ICS dose was at least doubled were associated with improved asthma outcomes and reduced health care utilization[424] (Evidence A). In placebo-controlled trials, temporarily doubling the dose of ICS was not effective[554] (Evidence A); however, the delay before increasing the ICS dose (mean 5–7 days[555,556]) may have contributed. Some studies in adults[557] and young children[558] have reported that higher ICS doses might help prevent worsening asthma progressing to a severe exacerbation. In a randomized controlled trial in primary care with patients aged ≥16 years, those who quadrupled their ICS dose (to average of 2000 mcg/day BDP equivalent) after their PEF fell were significantly less likely to require OCS.[559] In an open-label primary care randomized controlled trial of adult and adolescent patients using ICS with or without LABA, early quadrupling of ICS dose (to average 3200 mcg/day BDP equivalent) was associated with a modest reduction in prescribing of OCS.[560] However, a double-blind placebo-controlled study in children 5–11 years with high adherence to low dose ICS found no

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difference in the rate of severe exacerbations requiring OCS if maintenance ICS was quintupled (to 1600 mcg BDP equivalent) versus continuing maintenance low dose therapy.[561]

Given the shape of the ICS dose-response curve, little benefit may be seen from increasing maintenance ICS when background adherence is high, as in this study. In addition, in several of the above studies (e.g.), a pre-specified level of deterioration in symptoms (± lung function) had to be reached before the extra ICS could be started. These factors may help to explain the greater reduction in severe exacerbations seen with maintenance and reliever therapy with ICS-formoterol, where there is no lag between when symptoms appear and when the doses of both ICS and formoterol are increased through as-needed use of the combination inhaler for symptom relief.

In adult patients with an acute deterioration, high dose ICS for 7–14 days (500–1600 mcg BDP-HFA equivalent) had an equivalent benefit to a short course of OCS[557] (Evidence A). For adults taking combination ICS-LABA as a maintenance controller medication, the ICS dose may be increased by adding a separate ICS inhaler[557,560] (Evidence D). More research is needed to standardize this strategy.

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Harrison TW, Oborne J, Newton S, Tattersfield AE. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. Lancet 2004;363:271-5.
Jackson DJ, Bacharier LB, Mauger DT, et al. Quintupling inhaled glucocorticoids to prevent childhood asthma exacerbations. N Engl J Med 2018;378:891-901.

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Leukotriene receptor antagonists

For patients with mild asthma 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,[557] 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 prednisone is 1–2 mg/kg/day to a maximum of 40 mg/day (Evidence B), usually for 3–5 days. Patients should be advised about common side-effects, including sleep disturbance, increased appetite, reflux, and mood changes.[562] 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, but preferably before ceasing oral corticosteroids if prescribed), for assessment of symptom control and additional risk factors for exacerbations (Box 2-2, p.36), and to identify the potential cause of the exacerbation.

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This visit provides an opportunity for additional asthma education by a trained asthma educator or trained lay health care worker.

The written asthma action plan should be reviewed to see if it met the patient's needs. Maintenance controller treatment can generally be reduced to previous levels 2–4 weeks after the exacerbation (Evidence D), unless the history suggests that the exacerbation occurred on a background of long-term poorly controlled asthma. In this situation, provided inhaler technique and adherence have been checked, a step up in treatment may be indicated (Box 3-5, p.60).

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Adult and adolescent patients with more than 1–2 exacerbations per year despite Step 4-5 therapy should be referred to a specialist center for assessment (see decision tree in Chapter 3E, p.104).

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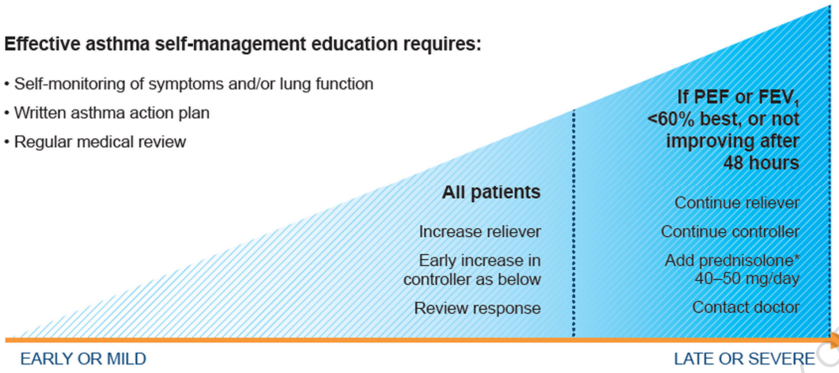
Box 4-2. Self-management of worsening asthma in adults and adolescents with a written asthma action plan



Medication	Short-term change (1–2 weeks) for worsening asthma	Evidence level
Increase usual reliever:		
Low dose ICS-formoterol †	Increase frequency of as-needed ICS-formoterol †	A
Short-acting beta$_2$-agonist (SABA)	Increase frequency of SABA use For pMDI, add spacer	A A
Increase usual controller:		
Maintenance and reliever ICS-formoterol †	Continue maintenance ICS-formoterol and increase reliever ICS-formoterol as needed. †	A
Maintenance ICS with SABA as reliever	In adults and adolescents, quadruple ICS dose. In children with high adherence, 5x increase in ICS dose is not effective.	B
Maintenance ICS-formoterol with SABA as reliever †	Quadruple maintenance ICS-formoterol. †	B
Maintenance ICS plus other LABA with SABA as reliever	Step up to higher dose formulation of ICS plus other LABA In adults, consider adding a separate ICS inhaler to quadruple ICS dose.	B D
Add oral corticosteroids (OCS) and contact doctor; review before ceasing		
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. Once started, morning dosing is preferable.	A
	Adults: prednisolone 40-50mg/day, usually for 5–7 days. *Children 6–11 years*: 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 in each section are listed in order of evidence.

* or equivalent dose of prednisone.

† ICS-formoterol as-needed for relief of symptoms in mild asthma, or as part of maintenance and reliever regimen with low dose budesonide or beclometasone with formoterol. Based on product information, the maximum recommended dose of ICS-formoterol in a single day is a total of 48 mcg formoterol for beclometasone-formoterol (36 mcg delivered dose), and 72 mcg formoterol for budesonide-formoterol (54 mcg delivered dose).

MANAGEMENT OF ASTHMA EXACERBATIONS IN PRIMARY CARE (ADULTS, ADOLESCENTS, CHLDREN 6–11 YEARS)

Assessing exacerbation severity

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

History

The history should include:

- Timing of onset and cause (if known) of the present exacerbation
- Severity of asthma symptoms, including any limiting exercise or disturbing sleep
- Any symptoms of anaphylaxis
- Any risk factors for asthma-related death (Box 4-1, p.126)
- 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.132) and vital signs (e.g. level of consciousness, temperature, pulse rate, respiratory rate, blood pressure, ability to complete sentences, use of accessory muscles, wheeze).
- Complicating factors (e.g. anaphylaxis, pneumonia, pneumothorax)
- Signs of alternative conditions that could explain acute breathlessness (e.g. cardiac failure, inducible laryngeal obstruction, inhaled foreign body or pulmonary embolism).

Objective measurements

- Pulse oximetry. Saturation levels <90% in children or adults signal the need for aggressive therapy.
- PEF in patients older than 5 years (Box 4-3, p.132)

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.[552] The aim is to rapidly relieve airflow obstruction and hypoxemia, address the underlying inflammatory pathophysiology, and prevent relapse. Infection control procedures should be followed.

Inhaled short-acting beta$_2$-agonists

Currently, inhaled salbutamol (albuterol) is the usual bronchodilator in acute asthma management. For mild to moderate exacerbations, repeated administration of inhaled SABA (up to 4–10 puffs every 20 minutes for the first hour) is an effective and efficient way to achieve rapid reversal of airflow limitation[563] (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). In emergency department studies, the efficacy and safety of formoterol and budesonide-formoterol was similar to that of salbutamol in management of acute asthma.

Delivery of SABA via a pMDI and spacer or a DPI leads to a similar improvement in lung function as delivery via nebulizer[563,564] (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,[565] provided the patient can use this device. Because of static charge, some spacers require pre-washing with detergent before use. The manufacturer's advice should be followed.

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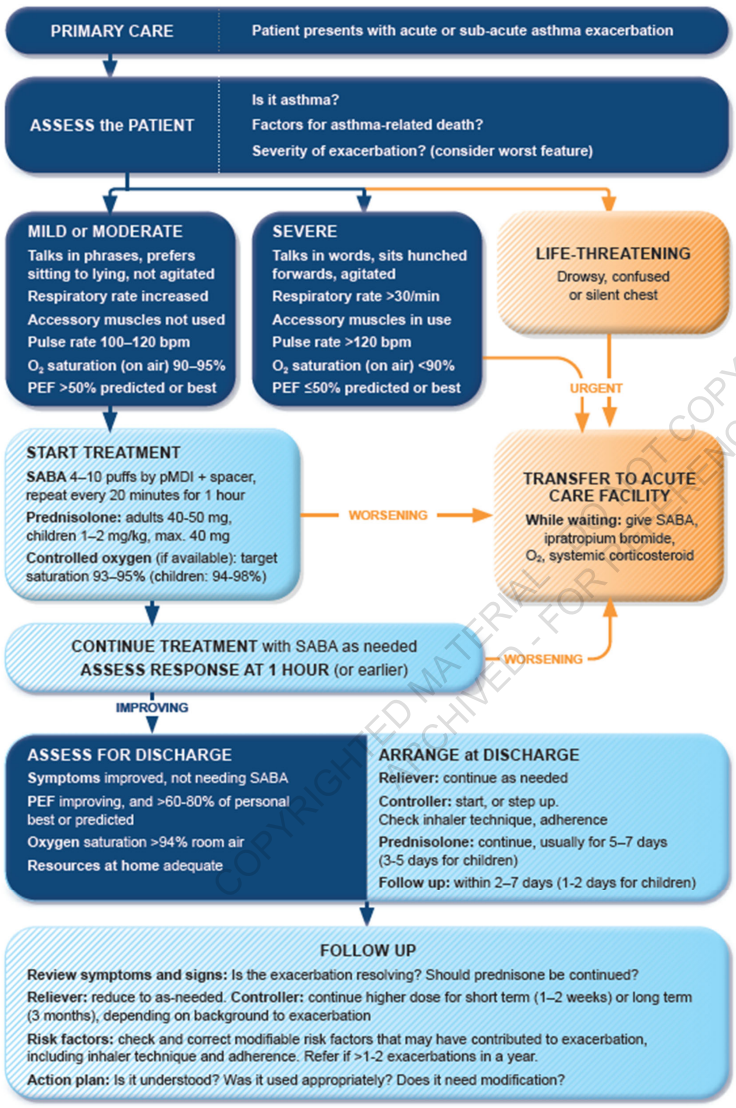
Box 4-3. Management of asthma exacerbations in primary care (adults, adolescents, children 6–11 years)



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). In hospitalized asthma patients, controlled or titrated oxygen therapy is associated with lower mortality and better outcomes than high concentration (100%) oxygen therapy[566-569] (Evidence A). Oxygen should not be withheld if oximetry is not available, but the patient should be monitored for deterioration, somnolence or fatigue because of the risk of hypercapnia and respiratory failure.[566-569] If supplemental oxygen is administered, oxygen saturation should be maintained no higher than 96% in adults.[570]

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 of prednisolone for adults is 1 mg/kg/day or equivalent up to a maximum of 50 mg/day, and 1–2 mg/kg/day for children 6–11 years up to a maximum of 40 mg/day). OCS should usually be continued for 5–7 days in adults[571,572] and 3-5 days in children[573] (Evidence B). Patients should be advised about common side-effects, including sleep disturbance, increased appetite, reflux and mood changes.[562]

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.130). Patients not currently taking controller medication should be commenced on regular ICS-containing therapy, as SABA-only treatment of asthma is no longer recommended. An exacerbation requiring medical care indicates that the patient is at increased risk of future exacerbations (Box 2-2, p.36).

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Antibiotics (not recommended)

Evidence does not support routine use of antibiotics in the treatment of acute asthma exacerbations unless there is strong evidence of lung infection (e.g. fever and purulent sputum or radiographic evidence of pneumonia).[574]

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.132), 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.

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

At the review visit the health care provider should assess whether the flare-up has resolved, and whether OCS can be ceased. They should assess the patient's level of symptom control and risk factors; explore the potential cause of the exacerbation; and review the written asthma action plan (or provide one if the patient does not already have one). Maintenance controller treatment can generally be stepped back to pre-exacerbation levels 2–4 weeks after the exacerbation, unless the exacerbation was preceded by symptoms suggestive of chronically poorly controlled asthma. In this situation, provided inhaler technique and adherence have been checked, a step up in treatment (Box 3-5, p.60) may be indicated.

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MANAGEMENT OF ASTHMA EXACERBATIONS IN THE EMERGENCY DEPARTMENT (ADULTS, ADOLESCENTS, CHILDREN 6–11 YEARS)

Severe exacerbations of asthma are life-threatening medical emergencies, which are most safely managed in an acute care setting e.g. emergency department (Box 4-4). Infection control procedures should be followed. Management of asthma in the intensive care unit is beyond the scope of this report and readers are referred to a comprehensive review.[575]

Assessment

History

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

- Time of onset and cause (if known) of the present exacerbation
- Severity of asthma symptoms, including any limiting exercise or disturbing sleep
- Any symptoms of anaphylaxis
- Risk factors for asthma-related death (Box 4-1, p.126)
- All current reliever and controller medications, including doses and devices prescribed, adherence pattern, any recent dose changes, and response to current therapy.

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Physical examination

The physical examination should assess:

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

Objective assessments

Objective assessments are also needed as the physical examination alone may not indicate the severity of the exacerbation.[576,577] 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[578] (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*:[579] They should be considered for patients with PEF or FEV_1 <50% predicted,[580] or for those who do not respond to initial treatment or are deteriorating. Supplemental controlled oxygen should be continued while blood gases are obtained. During an asthma exacerbation $PaCO_2$ is often below normal (<40 mmHg). Fatigue and somnolence suggest that pCO_2 may be increasing and airway intervention may be needed. PaO_2<60 mmHg (8 kPa) and normal or increased $PaCO_2$ (especially >45 mmHg, 6 kPa) indicate respiratory failure.
- *Chest X-ray (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.[581] 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.[582]

Treatment in acute care settings such as the emergency department

The following treatments are usually administered concurrently to achieve rapid improvement.[583]

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 concentration (100%) oxygen therapy[566-568] (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[563,565] (Evidence A). Evidence is less robust in severe and near-fatal asthma. Systematic reviews of intermittent versus continuous SABA in acute asthma, which mostly used nebulized SABA, provide conflicting results. Use of nebulizers can disseminate aerosols and potentially contribute to spread of respiratory viral infections.[584] Currently, inhaled albuterol is the usual bronchodilator in acute asthma management. Similar efficacy and safety have been reported from emergency department studies with formoterol and in one study of budesonide-formoterol. More studies of ICS-formoterol in emergency department management are needed.

Current evidence does not support the routine use of intravenous beta$_2$-agonists in patients with severe asthma exacerbations[585] (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 in acute care settings should be utilized in all but the mildest exacerbations in adults, adolescents and children 6–11 years.[586-588] (Evidence A). Where possible, systemic corticosteroids should be administered to the patient within 1 hour of presentation.[587,589] 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.[590,591] For children, a liquid formulation is preferred to tablets. OCS require at least 4 hours to produce a clinical improvement. Intravenous corticosteroids can be administered when patients are too dyspneic to swallow; if the patient is vomiting; or when patients require non-invasive ventilation or intubation. In patients discharged from the emergency department, an intramuscular corticosteroid may be an alternative to a course of OCS for preventing relapse,[592] especially if there are concerns about adherence with oral therapy.[593] However, current evidence does not demonstrate a benefit of intramuscular over oral corticosteroids.[588]

(See over for dosage and duration of systemic corticosteroid treatment)

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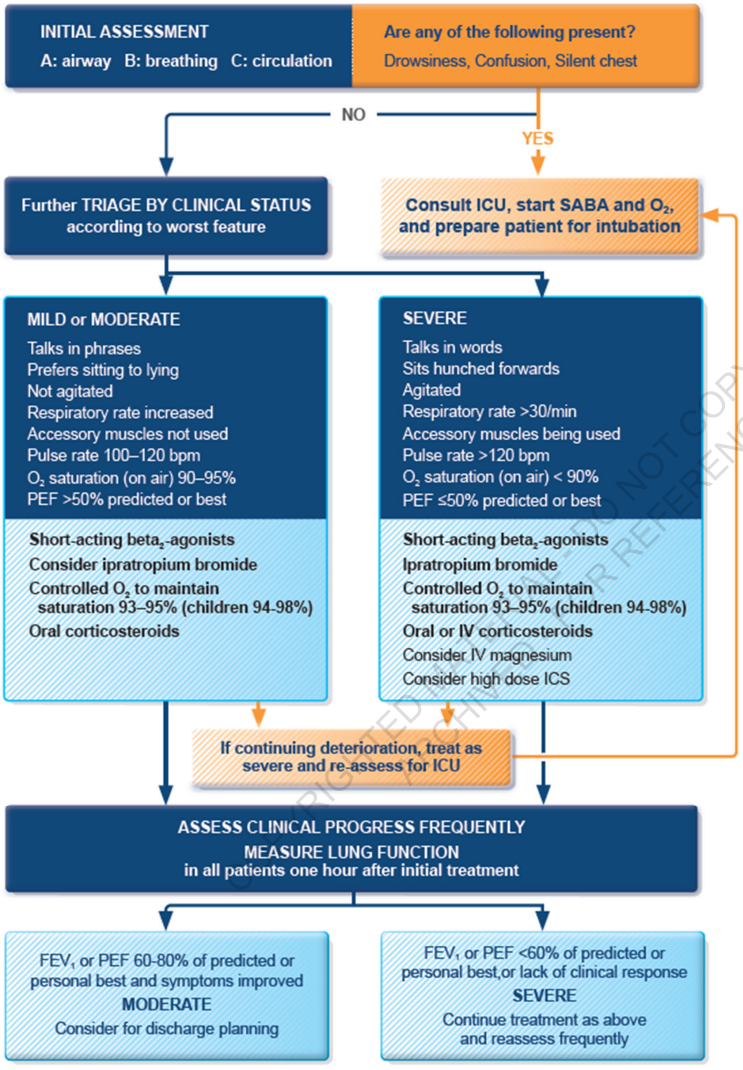
Box 4-4. Management of asthma exacerbations in acute care facility, e.g. emergency department



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

Dosage: daily doses of OCS equivalent to 50 mg prednisolone as a single morning dose, or 200 mg hydrocortisone in divided doses, are typically used for adults. For children, a prednisolone dose of 1–2 mg/kg up to a maximum of 40 mg/day is suggested.[594]

Duration: 5- and 7-day courses in adults have been found to be as effective as 10- and 14-day courses respectively[571,572] (Evidence B), and a 3–5-day course in children is usually considered sufficient for most. A small number of studies examined oral dexamethasone 0.6mg/kg, given once daily for 1-2 days in children and adults; the relapse rate was similar to that with prednisolone for 3–5 days, with a lower risk of vomiting.[595-597]. Oral dexamethasone should not be continued beyond 2 days because of concerns about metabolic side-effects. If there is a failure of resolution, or relapse of symptoms, consideration should be given to switching to prednisolone. 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[598] or over several weeks[599] (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[589] (Evidence A). When added to systemic corticosteroids, evidence is conflicting in adults.[600] In children, administration of ICS with or without concomitant systemic corticosteroids within the first hours of attendance to the emergency department might reduce the risk of hospital admission and need for systemic corticosteroids[600] (Evidence B). Overall, add-on ICS are well tolerated; however, cost may be a significant factor, and the agent, dose and duration of treatment with ICS in the management of asthma in the emergency department remain unclear. Patients admitted to hospital for an asthma exacerbation should continue on, or be prescribed, ICS-containing therapy.

On discharge home: patients should be prescribed ongoing ICS-containing treatment since the occurrence of a severe exacerbation is a risk factor for future exacerbations (Evidence B) (Box 2-2, p.36), and ICS-containing medications significantly reduce the risk of asthma-related death or hospitalization[195] (Evidence A). SABA-only treatment of asthma is no longer recommended. For short-term outcomes such as relapse requiring admission, symptoms, and quality of life, a systematic review found no significant differences when ICS were added to systemic corticosteroids after discharge.[601] There was some evidence, however, that post-discharge ICS were as effective as systemic corticosteroids for milder exacerbations, but the confidence limits were wide.[601] (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.[601]

Other treatments

Ipratropium bromide

For adults and children with moderate-severe exacerbations, treatment in the emergency department with both SABA and ipratropium, a short-acting anticholinergic, was associated with fewer hospitalizations (Evidence A for adults[602]/adolescents; Evidence B for children[603]) and greater improvement in PEF and FEV_1 compared with SABA alone.[602-604] (Evidence A, adults/adolescents) For children hospitalized for acute asthma, no benefits were seen from adding ipratropium to SABA, including no reduction in length of stay,[603] but the risk of nausea and tremor was reduced.[603]

Aminophylline and theophylline (not recommended)

Intravenous aminophylline and theophylline should not be used in the management of asthma exacerbations, in view of their poor efficacy and safety profile, and the greater effectiveness and relative safety of SABA.[605] Nausea and/or vomiting are more common with aminophylline.[603,605] 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.[605]

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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[606-608] (Evidence A). Randomized, controlled trials that excluded patients with more severe asthma showed no benefit with the addition of intravenous or nebulized magnesium compared with placebo in the routine care of asthma exacerbations in adults and adolescents[609-611] or children.[610,612] (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.[613]

Leukotriene receptor antagonists (LTRAs)

There is limited evidence to support a role for oral or intravenous LTRAs in acute asthma. Small studies have demonstrated improvement in lung function[614,615] but the clinical role and safety 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,[616] but more studies are needed. Another study examined addition of salmeterol to OCS for hospitalized patients, but was not adequately powered to support a recommendation.[617]

Antibiotics (not recommended)

Evidence does not support the routine use of antibiotics in the treatment of acute asthma exacerbations unless there is strong evidence of lung infection (e.g. fever or purulent sputum or radiographic evidence of pneumonia).[574]

Sedatives (must be avoided)

Sedation should be strictly avoided during exacerbations of asthma because of the respiratory depressant effect of anxiolytic and hypnotic drugs. An association between the use of these drugs and avoidable asthma deaths has been reported.[618,619]

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.[620] Two studies found no difference in need for endotracheal intubation but one study identified fewer admissions in the NIV group. No deaths were reported in either study. Given the small size of the studies, no recommendation is offered. If NIV is tried, the patient should be monitored closely (Evidence D). It should not be attempted in agitated patients, and patients should not be sedated in order to receive NIV (Evidence D).

Reviewing response

Clinical status and oxygen saturation should be re-assessed frequently, with further treatment titrated according to the patient's response (Box 4-4, p.136). 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.

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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.[621,622]

Spirometric criteria proposed for consideration for admission or discharge from the emergency department include:[623]

- 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.126) 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:[624-626]

- Female sex, older age and non-white race
- Use of more than eight $beta_2$-agonist puffs in the previous 24 hours
- Severity of the exacerbation (e.g. need for resuscitation or rapid medical intervention on arrival, respiratory rate >22 breaths/minute, oxygen saturation <95%, final PEF <50% predicted)
- Past history of severe exacerbations (e.g. intubations, asthma admissions)
- Previous unscheduled office and emergency department visits requiring use of OCS.

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

Discharge planning

Prior to discharge from the emergency department or hospital to home, arrangements should be made for a follow-up appointment within 2–7 days (1–2 days for children), and strategies to improve asthma management including medications, inhaler skills and written asthma action plan, should be addressed (Box 4-5).[280]

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.[280]

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.75)
- The patient's understanding of the purposes and correct uses of medications, including ICS-containing controller
- 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[144]) are cost effective and have shown significant improvement in asthma outcomes[280] (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.[280]

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

Medications

Inhaled corticosteroids (ICS)

Initiate ICS prior to discharge, if not previously prescribed (Box 3-4,A-D, p.54 – p.58). Patients currently prescribed ICS-containing medication should generally have their treatment stepped up for 2–4 weeks (Box 4-2, p.130) and should be reminded about the importance of adherence with daily use.

Oral corticosteroids (OCS)

To reduce the risk of relapse, prescribe at least a 5–7 day course of OCS for adults (prednisolone or equivalent 40-50 mg/day)[601]and 3–5 days for children (1–2 mg/kg/day to a maximum of 40 mg/day)[627] (Evidence A). Review progress before ceasing OCS. If the OCS is dexamethasone, treatment is only for total 1-2 days,[595] but if there is failure of resolution, or relapse of symptoms, consideration should be given to switching to prednisolone. For patients considered at risk of poor adherence, intramuscular corticosteroids may be considered[588] (Evidence B).

Reliever medication – return to as-needed rather than regular use

Transfer patients back to **as-needed rather than regular reliever medication use**, based on symptomatic and objective improvement. Regular use of SABA for even 1–2 weeks leads to beta-receptor down-regulation, increased airway hyperresponsiveness and increased eosinophilic inflammation, with reduced bronchodilator response. If ipratropium bromide was used in the emergency department or hospital, it may be quickly discontinued, as it is unlikely to provide ongoing benefit. Patients prescribed ICS–formoterol as their reliever should return to this after an ED presentation.

Risk factors and triggers that contributed to the exacerbation

Identify factors that may have contributed to the exacerbation and implement strategies to reduce modifiable risk factors (Box 3-8, p.75). An exacerbation severe enough to require hospitalization may follow irritant or allergen exposure, viral respiratory infections, inadequate long-term treatment, problems with adherence, and/or lack of a written asthma action plan. Handwashing, masks and social/physical distancing is associated with a reduced risk of acquiring viral respiratory infections, including influenza.

Self-management skills and written asthma action plan

- Review inhaler technique (Box 3-12, p.88).
- Review technique with PEF meter if used.
- Provide a written asthma action plan (Box 4-2, p.130) 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.[628]
- 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.[628,629]
- 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 (1–2 days for children) 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 adults with features of asthma, COPD or both ('asthma-COPD overlap')

KEY POINTS

Asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous and overlapping conditions

- 'Asthma' and 'COPD' are umbrella labels for heterogeneous conditions characterized by chronic airway and/or lung disease. Asthma and COPD each include several different clinical phenotypes, and are likely to have several different underlying mechanisms, some of which may be common to both asthma and COPD.
- Symptoms of asthma and COPD may be similar, and the diagnostic criteria overlap.

Why are the labels 'asthma' and 'COPD' still important?

- There are extremely important differences in evidence-based treatment recommendations for asthma and COPD: treatment with LABA and/or LAMA alone (i.e. without inhaled corticosteroids [ICS]) is recommended as initial treatment in COPD but contraindicated in asthma due to the risk of severe exacerbations and death.
- These risks are also seen in patients who have diagnoses of both asthma and COPD, making it important to identify adult patients who, for safety, should not be treated with long-acting bronchodilators alone.
- In COPD, high dose ICS should not be used because of the risk of pneumonia.

Many patients have features of both asthma and COPD

- Distinguishing asthma from COPD can be difficult, particularly in smokers and older adults, and some patients may have features of both asthma and COPD.
- The terms 'asthma-COPD overlap' (ACO) or 'asthma+COPD' are simple descriptors for patients who have features of both asthma and COPD.
- These terms do *not* refer to a single disease entity. They include patients with several clinical phenotypes that are likely caused by a range of different underlying mechanisms.
- More research is needed to better define these phenotypes and mechanisms, but in the meantime, safety of pharmacologic treatment is a high priority.

Diagnosis

- Diagnosis in patients with chronic respiratory symptoms involves a stepwise approach, first recognizing that the patient is likely to have chronic airways disease, then syndromic categorization as characteristic asthma, characteristic COPD, with features of both or having other conditions such as bronchiectasis.
- Lung function testing is essential for confirming persistent airflow limitation, but variable airflow obstruction can be detected with serial peak flow measurements and/or measurements before and after bronchodilator.

Initial treatment for safety and clinical efficacy

- ***For asthma***: ICS are essential either alone or in combination with a long-acting bronchodilator (LABA), to reduce the risk of severe exacerbations and death. Do not treat with LABA and/or long-acting muscarinic antagonist (LAMA) alone without ICS.
- ***For patients with features of both asthma and COPD***, treat as asthma. ICS-containing therapy is important to reduce the risk of severe exacerbations and death. Do not give LABA and/or LAMA alone without ICS.
- ***For COPD***: Treat according to current GOLD 2021[50] recommendations, i.e. initial treatment with LAMA and/or LABA, with as-needed SABA; add ICS for patients with hospitalizations, ≥2 exacerbations/year requiring OCS, or blood eosinophils ≥300/μl.
- ***All patients*** should be provided with structured education especially focusing on inhaler technique and adherence as well as being assessed for, and receive appropriate treatment for, other clinical problems, including advice about smoking cessation, immunizations, physical activity, and management of comorbidities.
- Specialist referral for additional investigations is encouraged, as patients with asthma+COPD often have worse outcomes than those with asthma or COPD alone.

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OBJECTIVES

The objectives of this section of the GINA report are:

- To assist primary care clinicians to identify typical asthma and typical COPD and to recognize when patients have features of both. This is particularly relevant in older patients (40 years or above)
- To provide advice about safe and effective initial treatment
- To provide guidance on indications for referral for specialist assessment.

BACKGROUND TO DIAGNOSING ASTHMA AND/OR COPD IN ADULT PATIENTS

Why are the labels 'asthma' and 'COPD' still important?

Asthma and COPD are heterogeneous conditions characterized by airway obstruction. Each of these 'umbrella' labels includes several different patterns of clinical features (phenotypes) that may overlap. Each may also include different inflammatory patterns and different underlying mechanisms, some of which may be common to both asthma and COPD.[630]

The most easily recognized phenotypes of asthma and COPD such as allergic asthma in children/young adults and emphysema in older smokers are clearly distinguishable. Regulatory studies of pharmacotherapy in asthma and COPD are largely restricted to patients with very clearly defined asthma or COPD. However, in the community, the features of asthma and COPD may overlap, especially in older adults.

There are extremely important differences in treatment recommendations for asthma and COPD. In particular, treatment with long-acting bronchodilators alone (i.e. without ICS) is recommended for initial treatment in COPD[631] but is contraindicated in asthma due to the risk of severe exacerbations and death. [114,203,632,633] Several studies have also shown that patients with diagnoses of both asthma and COPD are at increased risk of hospitalization or death if they are treated with LABA compared with ICS-LABA.[634-636]

Challenges in clinical diagnosis of asthma and COPD

Although asthma is characterized by variable expiratory airflow limitation, at least initially (Box 1-2, p.23), and COPD is characterized by persistent airflow limitation,[631] the definitions of asthma and COPD are not mutually exclusive (Box 5-1, p.144). This means that clinical features are also important in making a diagnosis.

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In children and young adults with chronic or recurrent respiratory symptoms, the differential diagnosis is different from that in older adults. Once infectious disease and nonpulmonary conditions (e.g. congenital heart disease, inducible laryngeal obstruction) have been excluded, the most likely chronic airway disease in children and young adults is asthma.

However, in adults with a history of long-standing asthma,[637,638] persistent airflow limitation may be found [639-643] Distinguishing these from patients with COPD is problematic, especially if they are smokers or have other risk factors for COPD.[644-647] On the other hand, patients with COPD may show evidence of reversible airflow obstruction when a rapid-acting bronchodilator is administered, a feature more strongly associated with asthma. In medical records, such patients often are assigned both diagnoses.[52,648]

In keeping with common usage of the term "overlap" in other contexts, e.g. for the association between COPD with sleep disorders, and in overlap syndromes of collagen vascular disease, the descriptive term 'asthma-COPD overlap' is often used. Another common descriptor is 'asthma+COPD'. However, to date there are no generally agreed more specific terms or defining features for patients with this combination of diagnoses.

'Asthma-COPD overlap' is a descriptor for patients often seen in clinical practice, who comprise a heterogeneous group. It does not mean a single disease entity.

Prevalence and morbidity of asthma-COPD overlap

In epidemiological studies, reported prevalence rates for asthma-COPD overlap have ranged between 9% and 55% of those with either diagnosis, with variation by gender and age;[642,649-651] the wide range reflects the different criteria that have been used by different investigators. Concurrent doctor-diagnosed asthma and COPD has been reported in between 15 and 32% of patients with one or other diagnosis.[648,652,653]

There is broad agreement that patients with features of both asthma and COPD have a greater burden of symptoms,[654] experience frequent exacerbations,[52,640,654] have poor quality of life,[52,649,654] a more rapid decline in lung function,[654] higher mortality,[640,648] and greater use of healthcare resources[52,655] compared with patients with asthma or COPD alone.

ASSESSMENT AND MANAGEMENT OF PATIENTS WITH CHRONIC RESPIRATORY SYMPTOMS

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 2021]
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 and influenced by host factors including abnormal lung development. [GOLD 2021][50]
Asthma-COPD overlap, also called asthma+COPD
'Asthma-COPD overlap' and 'asthma +COPD' are terms used to collectively describe patients who have persistent airflow limitation together with clinical features that are consistent with both asthma and COPD. This is not a definition of a single disease entity, but a descriptive term for clinical use that includes several different clinical phenotypes reflecting different underlying mechanisms.

1. History and clinical assessment to establish the following:

- The nature and pattern of respiratory symptoms (variable and/or persistent)
- History of asthma diagnosis; childhood and/or current
- Exposure history: smoking and/or other exposures to risk factors for COPD

The features that are *most helpful* in identifying and distinguishing asthma from COPD, and the features that should prompt a patient to be treated as asthma to reduce the risk of severe exacerbations and death, are shown in Box 5-2.

Caution: Consider alternative diagnoses: Other airways diseases, such as bronchiectasis and chronic bronchitis, and other forms of lung disease such as interstitial lung disease may present with some of the above features. The approach to diagnosis provided here does not replace the need for a full assessment of patients presenting with respiratory symptoms, to first exclude non-respiratory diagnoses such as heart failure.[12] Physical examination may provide supportive information.

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Box 5-2. Approach to initial treatment in patients with asthma and/or COPD

CLINICAL PHENOTYPE - ADULTS WITH CHRONIC RESPIRATORY SYMPTOMS (dyspnea, cough, chest tightness, wheeze)

HIGHLY LIKELY TO BE ASTHMA if several of the following features TREAT AS ASTHMA	FEATURES OF BOTH ASTHMA + COPD TREAT AS ASTHMA	LIKELY TO BE COPD if several of the following features TREAT AS COPD
HISTORY • Symptoms vary over time and in intensity - Triggers may include laughter, exercise, allergens, seasonal - Onset before age 40 years - Symptoms improve spontaneously or with bronchodilators (minutes) or ICS (days to weeks) • Current asthma diagnosis, or asthma diagnosis in childhood **LUNG FUNCTION** • Variable expiratory airflow limitation • Persistent airflow limitation may be present	**HISTORY** • Symptoms intermittent or episodic - May have started before or after age 40 • May have a history of smoking and/or other toxic exposures, or history of low birth weight or respiratory illness such as tuberculosis • Any of asthma features at left (e.g. common triggers; symptoms improve spontaneously or with bronchodilators or ICS; current asthma diagnosis or asthma diagnosis in childhood) **LUNG FUNCTION** • Persistent expiratory airflow limitation • With or without bronchodilator reversibility	**HISTORY** • Dyspnea persistent (most days) - Onset after age 40 years - Limitation of physical activity - May have been preceded by cough/sputum - Bronchodilator provides only limited relief • History of smoking and/or other toxic exposure, or history of low birth weight or respiratory illness such as tuberculosis • No past or current diagnosis of asthma **LUNG FUNCTION** • Persistent expiratory airflow limitation • With or without bronchodilator reversibility
INITIAL PHARMACOLOGICAL TREATMENT (as well as treating comorbidities and risk factors. See Box 3-5A)		
• **ICS-CONTAINING TREATMENT IS ESSENTIAL to reduce risk of severe exacerbations and death.** See Box 3-5A - As-needed low dose ICS-formoterol may be used as reliever. See Box 3-5A • **DO NOT GIVE LABA and/or LAMA without ICS** • Avoid maintenance OCS	• **ICS-CONTAINING TREATMENT IS ESSENTIAL to reduce risk of severe exacerbations and death.** See Box 3-5A • Add-on LABA and/or LAMA usually also needed • Additional COPD treatments as per GOLD • **DO NOT GIVE LABA and/or LAMA without ICS** • Avoid maintenance OCS	• **TREAT AS COPD (see GOLD report)** - Initially LAMA and/or LABA - Add ICS as per GOLD for patients with hospitalizations, ≥2 exacerbations/year requiring OCS, or blood eosinophils ≥300/µl • Avoid high dose ICS, avoid maintenance OCS • Reliever containing ICS is not recommended

REVIEW PATIENT AFTER 2-3 MONTHS. REFER FOR EXPERT ADVICE IF DIAGNOSTIC UNCERTAINTY OR INADEQUATE RESPONSE

GOLD: Global Initiative for Obstructive Lung Disease; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist

2; Lung function testing is essential to confirm the following:

- The presence of persistent expiratory airflow limitation
- Variable expiratory airflow limitation

Spirometry is preferably performed at the initial assessment. In cases of clinical urgency it may be delayed to a subsequent visit, but confirmation of diagnosis may be more difficult once patients are started on ICS-containing therapy (see Box 1-3, p.26). Early confirmation (or exclusion) of the presence of persistent expiratory airflow limitation may avoid needless trials of therapy, or delays in initiating other investigations. Spirometry can confirm both persistent airflow limitation and reversibility (Box 5-2, p.145, Box 5-3, p.146).

Measurement of peak expiratory flow (PEF), if performed repeatedly on the same meter over a period of 1–2 weeks, may help to confirm reversible airflow limitation and the diagnosis of asthma by demonstrating excessive variability (Box 1-2, p.23). However, PEF is not as reliable as spirometry, and a normal PEF does not rule out either asthma or COPD.

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Box 5-3. Spirometric measures in asthma and COPD

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

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

3. Selecting initial treatment (See Box 5-2, p.145)

For asthma

Commence treatment as described in Chapter 3 (Box 3-4,A-D, p.54 – p.58). Pharmacotherapy is based on ICS to reduce the risk of severe exacerbations and death and to improve symptom control, with add-on treatment as required, e.g. add-on LABA and/or LAMA. As-needed low dose ICS-formoterol may be used as the reliever, on its own in mild asthma or in addition to maintenance ICS-formoterol in patients with moderate-severe asthma prescribed maintenance and reliever therapy (see Box 3-5A, p.60). Inhaled therapy should be optimized to minimize the need for oral corticosteroids (OCS).

For COPD

Commence treatment as in the current GOLD strategy report.[50] Pharmacotherapy starts with symptomatic treatment with long-acting bronchodilators (LABA and/or LAMA). ICS may be added as per GOLD for patients with hospitalizations, ≥2 exacerbations/year requiring OCS, or blood eosinophils ≥300/μL, but is not used alone as monotherapy without LABA and/or LAMA. Inhaled therapy should be optimized to reduce the need for OCS. In patients with features of COPD, high dose ICS should be avoided because of the risk of pneumonia.[656,657]

For patients with features of asthma and COPD

Start treatment as for asthma (Box 3-4,A-D, p.54 – p.58) until further investigations have been performed.

ICS play a pivotal role 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.[658] For patients with asthma+COPD, ICS should be used initially in a low or medium dose (see Box 3-6, p.62), depending on level of symptoms and risk of adverse effects, including pneumonia.

Patients with features or diagnosis of both asthma and COPD will usually also require add-on treatment with LABA and/or LAMA to provide adequate symptom control.

Patients with any features of asthma should not be treated with LABA and/or LAMA alone, without ICS. A large case-control study in community patients with newly diagnosed COPD found that those who also had a diagnosis of asthma had a lower risk of COPD hospitalizations and death if treated with combination ICS-LABA than with LABA alone.[634] In another large retrospective longitudinal population cohort study of patients aged ≥66 years, those recorded as having asthma with COPD had lower morbidity and hospitalizations if they received ICS treatment; a similar benefit was seen in those with COPD plus concurrent asthma.[636]

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 recommend referral for further diagnostic procedures at relevant points in patient management (see below). This may be particularly important for patients with features of both asthma and COPD, given that this is associated with worse outcomes and greater health care utilization.

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4: Referral for specialized investigations (if necessary)

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Referral for expert advice and further diagnostic evaluation is advised 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 investigated.
- 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 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 ongoing management of asthma, COPD or asthma-COPD overlap, as outlined in the GINA and GOLD strategy reports.

Box 5-4 (p.148) summarizes specialized investigations that are sometimes used to distinguish asthma and COPD.

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Box 5-4. 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		
A positive test for atopy (specific IgE and/or skin prick test to aeroallergens)	Increases probability of allergic asthma; not essential for diagnosis of asthma	Conforms to background prevalence; does not rule out COPD
FeNO	A high level (>50 ppb) in non-smokers is moderately associated with eosinophilic airway inflammation.	Usually normal Low in current smokers
Blood eosinophilia	Supports diagnosis of eosinophilic airway inflammation	May be present in COPD including during exacerbations
Sputum inflammatory cell analysis	Role in differential diagnosis is not established in large populations.	

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

FUTURE RESEARCH

There is an urgent need for more research on this topic, in order to guide better recognition and safe and effective treatment. Patients who do not have 'classical' features of asthma or of COPD, or who have features of both, have generally been excluded from randomized controlled trials of most therapeutic interventions for airways disease, and from many mechanistic studies.

Future research should include study of clinical and physiological characteristics, biomarkers, outcomes and underlying mechanisms, among broad populations of patients with respiratory symptoms or with chronic airflow limitation. In the meantime, the present chapter provides interim advice about diagnosis and initial treatment, for the perspective of clinicians, particularly those in primary care and nonpulmonary specialties. Further research is needed to inform evidence-based definitions and a more detailed classification of patients who present overlapping features of asthma and COPD, and to encourage the development of specific interventions for clinical use.

Chapter 6.

Diagnosis and management of asthma in children 5 years and younger

PART A. DIAGNOSIS

KEY POINTS

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

ASTHMA AND WHEEZING IN YOUNG CHILDREN

Asthma is the most common chronic disease of childhood and the leading cause of childhood morbidity from chronic disease as measured by school absences, emergency department visits and hospitalizations.[659] Asthma often begins in early childhood; in up to half of people with asthma, symptoms commence during childhood.[660] Onset of asthma is earlier in males than females.[661-663]

No intervention has yet been shown to prevent the development of asthma or modify its long-term natural course. Atopy is present in the majority of children with asthma who are over 3 years old, and allergen-specific sensitization (and particularly multiple early-life sensitizations) is one of the most important risk factors for the development of asthma.[664]

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.[665] Some viral infections (respiratory syncytial virus and rhinovirus) are associated with recurrent wheeze throughout childhood. Wheezing in this age group is a highly heterogeneous condition, and not all wheezing indicates asthma. A large proportion of wheezing episodes in young children is virally induced whether the child has asthma or not. Therefore, deciding when wheezing with a respiratory infection is truly an isolated event or represents a recurrent clinical presentation of childhood asthma may be difficult.[663,666] In children aged under 1 year, bronchiolitis may present with wheeze. It is usually accompanied by other chest signs such as crackles on auscultation.

Wheezing phenotypes

In the past, two main classifications of wheezing (called 'wheezing phenotypes') were proposed:

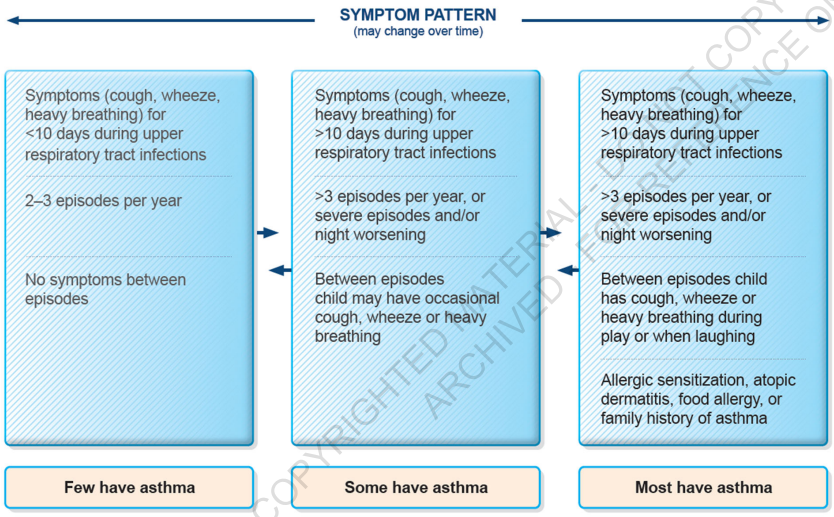
- *Symptom-based classification*: [667] this was based on whether the child had only *episodic wheeze* (wheezing during discrete time periods, often in association with URTI, with symptoms absent between episodes) or *multiple-trigger wheeze* (episodic wheezing with symptoms also occurring between these episodes, e.g. during sleep or with triggers such as activity, laughing, or crying).
- *Time trend-based classification*: this system was initially based on retrospective analysis of data from a cohort study.[663] It included *transient wheeze* (symptoms began and ended before the age of 3 years); *persistent wheeze* (symptoms began before the age of 3 years and continued beyond the age of 6 years), and *late-onset wheeze* (symptoms began after the age of 3 years). These general patterns have been confirmed in subsequent studies using unsupervised statistical approaches.[668,669]

However, prospective allocation of individual children to these phenotypes has been challenging in 'real-life' clinical situations, and the clinical usefulness of these, and other, classification and asthma prediction systems remain a subject of active investigation. For example, one study conducted in a research setting with high medication adherence found that daily ICS treatment reduced exacerbations in pre-school children characterized as 'sensitization with indoor pet exposure' or 'multiple sensitization with eczema', but not among those characterized as 'minimal sensitization' or 'sensitization with tobacco smoke exposure'.[670]

CLINICAL DIAGNOSIS OF ASTHMA

It may be challenging to make a confident diagnosis of asthma in children 5 years and younger, because episodic respiratory symptoms such as wheezing and cough are also common in children without asthma, particularly in those 0–2 years old,[671,672] and it is not possible to routinely assess airflow limitation or bronchodilator responsiveness in this age group. A probability-based approach, based on the pattern of symptoms during and between viral respiratory infections,[673] may be helpful for discussion with parents/carers (Box 6-1 & 2). This allows individual decisions to be made about whether to give a trial of controller treatment. It is important to make decisions for each child individually, to avoid either over- or under-treatment.

Box 6-1. Probability of asthma diagnosis in children 5 years and younger



Symptoms suggestive of asthma in children 5 years and younger

As shown in Box 6-1 and Box 6-2/2A an asthma diagnosis in children 5 years and younger can often be based on:

- Symptom patterns (recurrent episodes of wheeze, cough, breathlessness (typically manifested by activity limitation), and nocturnal symptoms or awakenings)
- Presence of risk factors for development of asthma, such as family history of atopy, allergic sensitization, allergy or asthma, or a personal history of food allergy or atopic dermatitis
- Therapeutic response to controller treatment.
- Exclusion of alternate diagnoses.

Box 6-1 is a schematic figure showing the estimated probability of an asthma diagnosis[674,675] in children aged 5 years or younger who have viral-induced cough, wheeze or heavy breathing, based on the pattern of symptoms.

Many young children wheeze with viral infections and deciding when a child should be given controller treatment may be difficult. The frequency and severity of wheezing episodes and the temporal pattern of symptoms (only with viral colds or also in response to other triggers) should be taken into account. Any controller treatment should be viewed as a treatment trial, with follow up scheduled after 2–3 months to review the response. Review is also important since the pattern of symptoms tends to change over time in a large proportion of children.

A diagnosis of asthma in young children is therefore based largely on recurrent symptom patterns combined with a careful clinical assessment of family history and physical findings with careful consideration of the differential diagnostic possibilities. A positive family history of allergic disorders, or the presence of atopy or allergic sensitization provide additional predictive support, as early allergic sensitization increases the likelihood that a wheezing child will develop persistent asthma.[664]

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 wheezing and breathing difficulties • Cough occurring with exercise, laughing, crying or exposure to tobacco smoke, particularly in the absence of an apparent respiratory infection
Wheezing	• Recurrent wheezing, including during sleep or with triggers such as activity, laughing, crying or exposure to tobacco smoke or air pollution
Difficult or heavy breathing or shortness of breath	• Occurring with exercise, laughing, or crying
Reduced activity	• Not running, playing or laughing at the same intensity as other children; tires earlier during walks (wants to be carried)
Past or family history	• Other allergic disease (atopic dermatitis or allergic rhinitis, food allergy). Asthma in first-degree relative(s)
Therapeutic trial with low dose ICS (Box 6-5, p.165), and as-needed SABA	• Clinical improvement during 2–3 months of controller treatment and worsening when treatment is stopped

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

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Box 6-2A. Questions that can be used to elicit features suggestive of asthma

- Does your child have wheezing? Wheezing is a high-pitched noise which comes from the chest and not the throat. Use of a video questionnaire,[676] or asking a parent to record an episode on a smartphone if available can help to confirm the presence of wheeze and differentiate from upper airway abnormalities.
- Does your child wake up at night because of coughing, wheezing, or 'difficult breathing', 'heavy breathing', or 'breathlessness?
- Does your child have to stop running, or play less hard, because of coughing, wheezing or 'difficult breathing', 'heavy breathing', or 'shortness of breath'?
- Does your child cough, wheeze or get 'difficult breathing', 'heavy breathing', or 'shortness of breath' when laughing, crying, playing with animals, or when exposed to strong smells or smoke?
- Has your child ever had eczema, or been diagnosed with allergy to foods?
- Has anyone in your family had asthma, hay fever, food allergy, eczema, or any other disease with breathing problems?

Wheeze

Wheeze is the most common and specific symptom associated with asthma in children 5 years and younger. Wheezing occurs in several different patterns, but a wheeze that occurs recurrently, during sleep, or with triggers such as activity, laughing, or crying, is consistent with a diagnosis of asthma. Clinician confirmation is important, as parents may describe any noisy breathing as 'wheezing'.[677] Some cultures do not have a word for wheeze.

Wheezing may be interpreted differently based on:

- Who observes it (e.g. parent/carer versus the health care provider)
- The environmental context (e.g. high income countries versus areas with a high prevalence of parasites that involve the lung)
- The cultural context (e.g. the relative importance of certain symptoms can differ between cultures, as can the diagnosis and treatment of respiratory tract diseases in general).

Cough

Cough due to asthma is generally non-productive, recurrent and/or persistent, and is usually accompanied by wheezing episodes and breathing difficulties. Allergic rhinitis may be associated with cough in the absence of asthma. A nocturnal cough (when the child is asleep) or a cough that occurs with exercise, laughing or crying, in the absence of an apparent respiratory infection, supports a diagnosis of asthma. The common cold and other respiratory illnesses are also associated with coughing. Prolonged cough in infancy, and cough without cold symptoms, are associated with later parent-reported physician-diagnosed asthma, independent of infant wheeze. Characteristics of cough in infancy may be early markers of asthma susceptibility, particularly among children with maternal asthma.[678]

Breathlessness

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

Activity and social behavior

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

TESTS TO ASSIST IN DIAGNOSIS

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

Therapeutic trial

A trial of treatment for at least 2–3 months with as-needed short-acting 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 allergic sensitization

Sensitization to allergens can be assessed using either skin prick testing or allergen-specific immunoglobulin E. Allergic sensitization is present in the majority of children with asthma once they are over 3 years of age; however, absence of sensitization to common aeroallergens does not rule out a diagnosis of asthma. Allergic sensitization is the best predictor for development of persistent asthma.[679]

Chest X-ray

Radiographs are rarely indicated; however, if there is doubt about the diagnosis of asthma in a wheezing or coughing child, a plain chest X-ray may help to exclude structural abnormalities (e.g. congenital lobar emphysema, vascular ring) chronic infections such as tuberculosis, an inhaled foreign body, or other diagnoses. Other imaging investigations may be appropriate, depending on the condition being considered.

Lung function testing

Due to the inability of most children 5 years and younger to perform reproducible expiratory maneuvers, lung function testing, bronchial provocation testing, and other physiological tests do not have a major role in the diagnosis of asthma at this age. However, by 5 years of age, many children are capable of performing reproducible spirometry if coached by an experienced technician and with visual incentives.

Exhaled nitric oxide

Measurement of fractional concentration of exhaled nitric oxide (FeNO) is not widely available for most children in this age group and currently remains primarily a research tool. FeNO can be measured in young children with tidal breathing, and normal reference values have been published for children aged 1–5 years.[680] In pre-school children with recurrent coughing and wheezing, an elevated FeNO recorded 4 weeks from any URTI predicted physician-diagnosed asthma at school age,[681] and increased the odds for wheezing, asthma and ICS use by school age, independent of clinical history and presence of specific IgE.[682]

Risk profiles

A number of risk profile tools aimed at identifying which wheezing children aged 5 years and younger are at high risk of developing persistent asthma symptoms have been evaluated for use in clinical practice. However, these tools have shown limited performance for clinical practice. Only three prediction tools have been externally validated (Asthma Predictive Index[683] from Tucson, USA, PIAMA index[675] from the Netherlands, and Leicester tool[684] from the UK), and a systematic review has shown that these tools have poor predictive accuracy, with variation in sensitivity and positive predictive value.[685] Larger predictive studies using more advanced statistical methods, and with objective measurements for asthma diagnosis, are probably needed to propose a practical tool in clinical care to predict persistent asthma in recurrent wheezers in infancy and pre-school age. The role of these tools is to help identify children at greater risk of

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developing persistent asthma symptoms, not as criteria for the diagnosis of asthma in young children. Each tool demonstrates different performance characteristics with varying criteria used to identify risk.[686]

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).[671]

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

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

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

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

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

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 (SABA), regardless of whether the diagnosis of asthma has been made. However, for initial episodes of wheeze in children <1 year in the setting of infectious bronchiolitis, SABAs are generally ineffective.
- A trial of controller therapy should be given if the symptom pattern suggests asthma, alternative diagnoses have been excluded and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe.
- Response to treatment should be reviewed before deciding whether to continue it. If the response is absent or incomplete, reconsider alternative diagnoses.
- The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered dose inhaler and spacer, with face mask for <3 years and mouthpiece for most 3–5 year-olds. Children should be switched from a face mask to mouthpiece as soon as they are able to demonstrate good technique.
- Review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children.

GOALS OF ASTHMA MANAGEMENT

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

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

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

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

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

Education of parent/carer, and child (depending on the child's age)

- Skills training for effective use of inhaler devices and encouragement of good adherence
- Monitoring of symptoms by parent/carer
- A written personalized asthma action plan.

ASSESSMENT OF ASTHMA

What does 'asthma control' mean?

Asthma control means the extent to which the manifestations of asthma are controlled, with or without treatment.[20,55] It has two components (Box 6-4, p.160): the child's asthma status over the previous four weeks (current symptom control), and how asthma may affect them in the future (future risk). In young children, as in older patients, both symptom control and future risk should be monitored (Evidence D). The rationale for this is described on p.38.

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Assessing asthma symptom control

Defining satisfactory symptom control in children 5 years and younger depends on information derived from family members and carers, who may be unaware either of how often the child has experienced asthma symptoms, or that their respiratory symptoms represent uncontrolled asthma. Few objective measures to assess symptom control have been validated for children <4 years. The Childhood Asthma Control Test can be used for children aged 4–11 years.[72] The Test for Respiratory and Asthma Control in Kids (TRACK) is a validated questionnaire for caregiver completion for preschool aged children with symptoms consistent with asthma; it includes both symptom control and courses of systemic corticosteroids in the previous year.[76]

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☐			
SABA 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 exacerbations (ED attendance, hospitalization, or course of OCS) in previous year
- The start of the child's usual 'flare-up' season (especially if autumn/fall)
- Exposures: tobacco smoke; indoor or outdoor air pollution; indoor allergens (e.g. house dust mite, cockroach, pets, mold), especially in combination with viral infection[687]
- Major psychological or socio-economic problems for child or family
- Poor adherence with controller medication, or incorrect inhaler technique
- Outdoor pollution (NO_2 and particles)[92]

Risk factors for persistent airflow limitation

- Severe asthma with several hospitalizations
- History of bronchiolitis

Risk factors for medication side-effects

- Systemic: Frequent courses of OCS, high dose and/or potent ICS
- 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; SABA: short-acting beta$_2$-agonist; * Excludes reliever taken before exercise

Before stepping up treatment, ensure that the child's symptoms are due to asthma, and that the child has good inhaler technique and good adherence to existing treatment.

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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.160), has not been sufficiently studied in young children. Although exacerbations may occur in children after months of apparently good symptom control, the risk is greater if current symptom control is poor. Preschool children at high risk of asthma (based on modified API) who were treated with daily low dose ICS experienced fewer days with asthma symptoms and a reduced risk of exacerbations than those receiving placebo.[688]

The future risk of harm due to excessive doses of inhaled or systemic corticosteroids must also be avoided. This can be minimized by ensuring that the prescribed treatment is appropriate and reduced to the lowest dose that maintains satisfactory symptom control and minimizes exacerbations. The child's height should be measured and recorded at least yearly, as growth velocity may be lower in the first 1–2 years of ICS treatment,[111] and poorly controlled asthma can affect growth.[110] The minimum effective dose of ICS to maintain good asthma control should be used. If decreased growth velocity is seen, other factors should be considered, including poorly controlled asthma, frequent use of oral corticosteroids, and poor nutrition, and referral should be considered.

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

MEDICATIONS FOR SYMPTOM CONTROL AND RISK REDUCTION

Choosing medications for children 5 years and younger

Good control of asthma can be achieved in the overwhelming majority of young children with a pharmacological intervention strategy.[689] 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.48).

- 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. Studies suggest that consideration of factors such as allergic sensitization and/or peripheral blood count may help to better identify which children are more likely to have a short-term response to ICS.[690] However, further studies are needed to assess the applicability of these findings in a wider range of settings, particularly in areas where blood eosinophilia may reflect helminth infection rather than asthma or atopy.
- How does this particular child differ from other children with asthma, in terms of:
  - Response to previous treatment
  - Parental preference (goals, beliefs and concerns about medications)
  - Practical issues (cost, inhaler technique and adherence)?

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

A stepwise treatment approach is recommended (Box 6-5, p.165), 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.167).

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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 until symptoms disappear, usually within 1 to 7 days. Further treatment of the acute wheezing episodes themselves is described below (see *Acute asthma exacerbations in children 5 years and younger*, p.168). However, uncertainty surrounds the addition of other drugs in these children, especially when the nature of the episode is unclear. In general, the following principles apply.

- *If the history and symptom pattern suggest a diagnosis of asthma* (Box 6-2, p.154; Box 6-2A, p.155) and respiratory symptoms are uncontrolled (Box 6-4, p.160) 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.165) and the response evaluated (Evidence D). Regular controller treatment may also be indicated in a child with less frequent, but more severe episodes of viral- induced wheeze (Evidence D).
- *If the diagnosis of asthma is in doubt*, and inhaled SABA therapy or courses of antibiotics need to be repeated frequently, e.g. more than every 6–8 weeks, a trial of regular controller treatment should be considered to confirm whether the symptoms are due to asthma (Evidence D). Referral for specialist opinion should also be considered at this stage.

It is important to discuss the decision to prescribe controller treatment and the choice of treatment with the child's parents or carers. They should be aware of both the relative benefits and risks of the treatments, and the importance of maintaining normal activity levels for their child's normal physical and social development. Although effects of ICS on growth velocity are seen in pre-pubertal children in the first 1-2 years of treatment, this is not progressive or cumulative, and the one study that examined long-term outcomes showed a difference of only 0.7% in adult height.[111,691] Poorly controlled asthma itself adversely affects adult height.[110] For more detail see Appendix Chapter 5B.

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

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

Before considering a step-up of controller treatment

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

- Confirm that the symptoms are due to asthma rather than a concomitant or alternative condition (Box 6-3, p.105). Refer for expert assessment if the diagnosis is in doubt.
- Check and correct inhaler technique.
- Confirm good adherence with the prescribed dose.
- Consider trial of one of the other treatment options for that step, as many children may respond to one of the options.
- Enquire about risk factors such as allergen or tobacco smoke exposure (Box 6-4, p.160).

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ASTHMA TREATMENT STEPS FOR CHILDREN AGED 5 YEARS AND YOUNGER

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.167) for choice of inhaler device. Use of SABA for the relief of symptoms on average more than twice a week over a one month period indicates the need for a trial of controller medication. Initial episodes of wheeze in children <1 year often occur in the setting of infectious bronchiolitis, and this should be managed according to local bronchiolitis guidelines. SABAs are generally ineffective for bronchiolitis.[692]

Other options

Oral bronchodilator therapy is not recommended due to its slower onset of action and higher rate of side-effects compared with inhaled SABA (Evidence D).

For children with intermittent viral-induced wheeze and no interval symptoms, particularly those with underlying atopy (positive mAPI) in whom inhaled SABA medication is not sufficient, intermittent high dose ICS may be considered[558,693,694] (see *Management of worsening asthma and exacerbations*, p.168), 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.166) is recommended as the preferred initial treatment to control asthma in children 5 years and younger (Evidence A).[688,695-697] 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.[698] However, for young children with recurrent viral- induced wheezing, a review concluded that neither regular nor intermittent LTRA reduces OCS-requiring exacerbations (Evidence A).[699] A further systematic review found that in pre-schoolers with asthma or recurrent wheezing, daily ICS was more effective in improving symptom control and reducing exacerbations than regular LTRA monotherapy.[700] Parents should be counselled about the potential adverse effects of montelukast on sleep and behavior, and health professionals should consider the benefits and risks of side effects before prescribing; the FDA has required a boxed warning about these problems.[208]

For pre-school children with asthma characterized by frequent viral-induced wheezing and interval asthma symptoms, as-needed (prn)[701] or episodic ICS[702] may be considered, but a trial of regular daily low dose ICS should be undertaken first. The effect on exacerbation risk seems similar for regular daily low dose and episodic high dose ICS.[697] See also *Initial home management of asthma exacerbations*, p.169.

If good asthma control is not achieved with a given therapy, trials of the alternative Step 2 therapies are recommended prior to moving to Step 3.

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STEP 3: Additional controller treatment, plus as-needed SABA and consider specialist referral

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

- Confirm that the symptoms are due to asthma rather than a concomitant or alternative condition (Box 6-3, p.158).
- Check and correct inhaler technique. Consider alternative delivery systems if indicated.
- Confirm good adherence with the prescribed dose.
- Enquire about risk factors such as allergen or tobacco smoke exposure (Box 6-4, p.160).

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

Doubling the initial low dose of ICS may be the best option (Evidence C). Assess response after 3 months. The child should be referred for expert assessment if symptom control remains poor and/or flare-ups persist, or if side-effects of treatment are observed or suspected.

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Other options

Addition of a LTRA to low dose ICS may be considered, based on data from older children (Evidence D). The relative cost of different treatment options in some countries may be relevant to controller choices for children. See note above about the FDA warning for montelukast.[208]

Not recommended

There are insufficient data about the efficacy and safety of ICS-LABA in children <4 years old to recommend their use. A short-term (8 week) placebo-controlled study did not show any significant difference in symptoms between combination fluticasone propionate-salmeterol vs fluticasone propionate alone; no additional safety signals were noted in the group receiving LABA.[703]

STEP 4: Continue controller treatment and refer for expert assessment

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

If doubling the initial dose of ICS fails to achieve and maintain good asthma control, carefully reassess inhaler technique and medication adherence as these are common problems in this age group. In addition, reassess and address control of environmental factors where relevant, and reconsider the asthma diagnosis.

Other options

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

- Further increase the dose of ICS for a few weeks until the control of the child's asthma improves (Evidence D). Monitor for side-effects.
- Add LTRA (data based on studies in older children, Evidence D). Benefits, and risks of side effects, should be considered, as described previously.[208]
- Add long acting beta agonist (LABA) in combination with ICS; data based on studies in children ≥4 years of age
- Add a low dose of oral corticosteroid (for a few weeks only) until asthma control improves (Evidence D); monitor for side-effects.
- Add intermittent high dose ICS at onset of respiratory illnesses 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.

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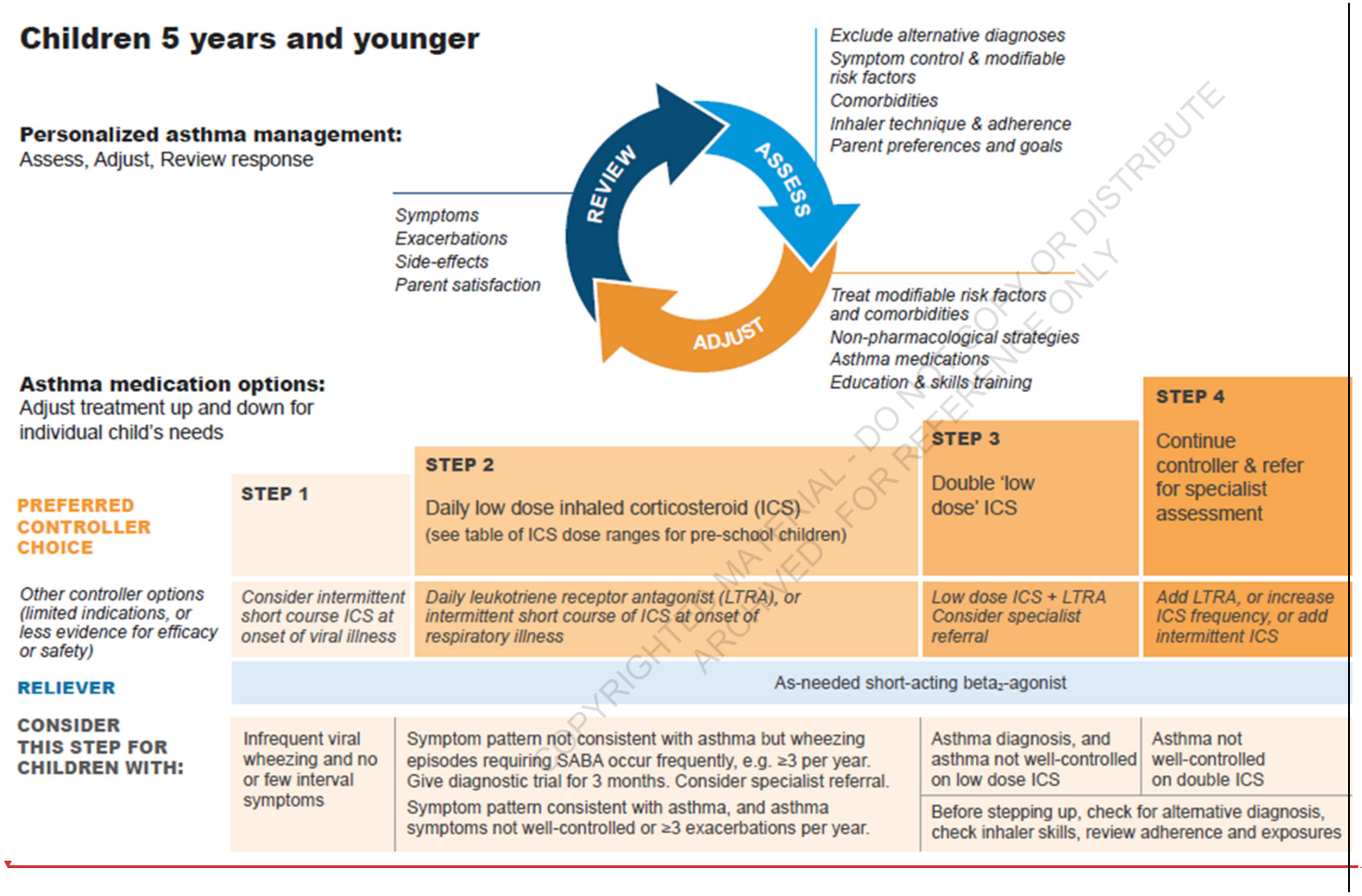
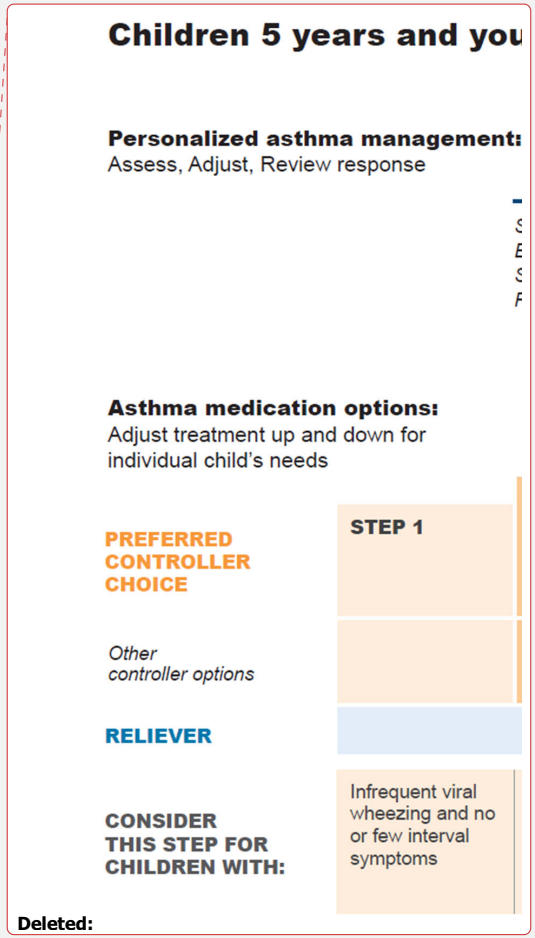
Box 6-5. Personalized management of asthma in children 5 years and younger



ICS: inhaled corticosteroids; LTRA: leukotriene receptor antagonist; SABA: short-acting beta$_2$-agonist



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

This is not a table of equivalence, but instead, suggestions for 'low' total daily doses for the ICS treatment recommendations for children aged 5 years and younger in Box 6.5 (p.165), based on available studies and product information. Data on comparative potency are not readily available, particularly for children, and this table does NOT imply potency equivalence. The doses listed here are the lowest approved doses for which safety and effectiveness have been adequately studied in this age group.

Low dose ICS provides most of the clinical benefit for most children with asthma. Higher doses are associated with an increased risk of local and systemic side-effects, which must be balanced against potential benefits.

Inhaled corticosteroid	Low total daily dose (mcg) (age-group with adequate safety and effectiveness data)
BDP (pMDI, standard particle, HFA)	100 (ages 5 years and older)
BDP (pMDI, extrafine particle, HFA)	50 (ages 5 years and older)
Budesonide nebulized	500 (ages 1 year and older)
Fluticasone propionate (pMDI, standard particle, HFA)	50 (ages 4 years and older)
Fluticasone furoate (DPI)	Not sufficiently studied in children 5 years and younger)
Mometasone furoate (pMDI, standard particle, HFA)	100 (ages 5 years and older)
Ciclesonide (pMDI, extrafine particle, HFA)	Not sufficiently studied in children 5 years and younger

BDP: beclometasone dipropionate; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; pMDI: pressurized metered dose inhaler (non-chlorofluorocarbon formulations); in children, pMDI should always be used with a spacer

REVIEWING RESPONSE AND ADJUSTING TREATMENT

Assessment at every visit should include asthma symptom control and risk factors (Box 6-4, p.160), 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,[704-706] so the need for continued controller treatment should be regularly assessed (e.g. every 3–6 months) (Evidence D). If therapy is stepped-down or discontinued, schedule a follow-up visit 3–6 weeks later to check whether symptoms have recurred, as therapy may need to be stepped-up or reinstituted (Evidence D).

Marked seasonal variations may be seen in symptoms and exacerbations in this age-group. For children with seasonal symptoms whose daily long-term controller treatment is to be discontinued (e.g. 4 weeks after their season ends), the parent/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[707] (Box 6-7, p.167) (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.

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- 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. If a nebulizer is used, follow local infection control procedures.

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).[21]

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,[708] 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 departments and hospitals, ambulance services and emergency pharmacies). Details of treatments that can be initiated at home are provided in the following section, *Part C: Management of worsening asthma and exacerbations in children 5 years and younger*, p.168.

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

KEY POINTS

Symptoms of exacerbation in young children

- 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.

Home management in a written asthma action plan

- Give a written asthma action plan to parents/carers of young children with asthma so they can recognize an impending severe attack, start treatment, and identify when urgent hospital treatment is required.
- Initial treatment at home is with inhaled short-acting $beta_2$-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 no compelling evidence to support parent-initiated oral corticosteroids.

Management of exacerbations in primary care or acute care facility

- 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, has a respiratory rate >40/minute or is cyanosed, if resources are lacking in the home, or if oxygen saturation is <92% on room air.
- Consider oral prednisone/prednisolone 1–2 mg/kg/day for children attending an Emergency Department or admitted to hospital, up to a maximum of 20 mg/day for children aged 0–2 years, and 30 mg/day for children aged 3–5 years, for up to 5 days; or dexamethasone 0.6 mg/kg/day for 2 days. If there is failure of resolution, or relapse of symptoms with dexamethasone, consideration should be given to switching to prednisolone.

Arrange early follow-up after an exacerbation

- Children who have experienced an asthma exacerbation are at risk of further exacerbations. Arrange follow-up within 1–2 days of an exacerbation and again 1–2 months later 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. In pediatric literature, the term ‘episode’ is commonly used, but understanding of this term by parent/carers is not known

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

- Onset of symptoms of respiratory tract infection
- An acute or sub-acute increase in wheeze and shortness of breath
- An increase in coughing, especially while the child is asleep
- Lethargy or reduced exercise tolerance
- Impairment of daily activities, including feeding
- A poor response to reliever medication.

In a study of children aged 2–5 years, the combination of increased daytime cough, daytime wheeze, and night-time beta$_2$-agonist use was a strong predictor at a group level of an imminent exacerbation (1 day later). This combination predicted around 70% of exacerbations, with a low false positive rate of 14%. In contrast, no individual symptom was predictive of an imminent asthma exacerbation.[709]

Upper respiratory symptoms frequently precede the onset of an asthma exacerbation, indicating the important role of viral URTI in precipitating exacerbations in many, although not all, children with asthma. In a randomized controlled trial of acetaminophen versus ibuprofen, given for pain or fever in children with mild persistent asthma, there was no evidence of a difference in the subsequent risk of flare-ups or poor symptom control.[690]

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 be advised to seek medical attention immediately 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.[710-714] Preemptive episodic high dose nebulized ICS may reduce exacerbations in children with intermittent viral triggered wheezing.[697] However, because of the high potential for side-effects, especially if the treatment is continued inappropriately or is given frequently, family-administered high dose ICS should be considered only where the health care provider is confident that the medications will be used appropriately, and the child is closely monitored for side-effects (see p.172).

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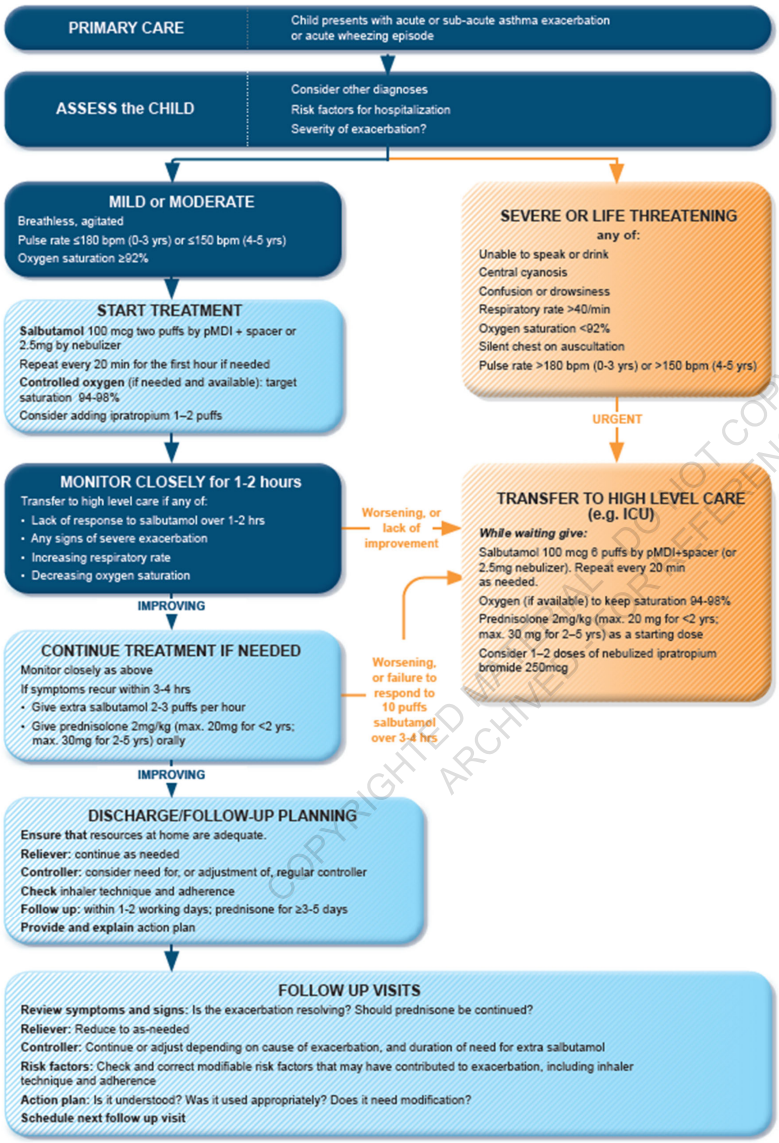
Leukotriene receptor antagonists

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.[715] In contrast another study found no significant effect with LTRA vs placebo 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.[716] Parents should be counseled about the FDA warning about risk of adverse effects on sleep and behavior with montelukast.[208]

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



PRIMARY CARE OR HOSPITAL MANAGEMENT OF ACUTE ASTHMA EXACERBATIONS IN CHILDREN 5 YEARS OR YOUNGER

Assessment of exacerbation severity

Conduct a brief history and examination concurrently with the initiation of therapy (Box 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.[578] 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.[717]

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	>180 beats/minute (0–3 years) >150 beats/minute (4–5 years)
Respiratory rate	≤40/minute	>40/minute
Central cyanosis	Absent	Likely to be present
Wheeze intensity	Variable	Chest may be quiet

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

Indications for immediate transfer to hospital

Children with features of a severe exacerbation that fail to resolve within 1–2 hours despite repeated dosing with inhaled SABA must be referred to hospital for observation and further treatment (Evidence D). Other indications are respiratory arrest or impending arrest; lack of supervision in the home or doctor's office; and recurrence of signs of a severe exacerbation within 48 hours (particularly if treatment with OCS has already been given). In addition, early medical attention should be sought for children with a history of severe life-threatening exacerbations, and those less than 2 years of age as the risk of dehydration and respiratory fatigue is increased (Box 6-10, p.172).

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Emergency treatment and initial pharmacotherapy

Oxygen

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

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

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

- At initial or subsequent assessment

Child is unable to speak or drink
Cyanosis
Respiratory rate >40 per minute
Oxygen saturation <92% when breathing room air
Silent chest on auscultation

- Lack of response to initial bronchodilator treatment

Lack of response to 6 puffs of inhaled SABA (2 separate puffs, repeated 3 times) over 1–2 hours
Persisting tachypnea* despite three administrations of inhaled SABA, even if the child shows other clinical signs of improvement

- Social environment that limits delivery of acute treatment, or parent/carer unable to manage acute asthma at home

During transfer to hospital, continue to give inhaled SABA, oxygen (if available) to maintain saturation 94–98%, and give systemic corticosteroids (see Box 6-8, p.170)

*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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Inhaled bronchodilator therapy

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The initial dose of inhaled 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[718] (Evidence A), and nebulizers can spread infectious particles. 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, and infection control procedures should be followed. The frequency of dosing depends on the response observed over 1–2 hours (see below).

For children with moderate-severe exacerbations and a poor response to initial SABA, nebulized ipratropium bromide may be added every 20 minutes for 1 hour only.[718]

Magnesium sulfate

The role of magnesium sulfate is not established for children 5 years and younger, because there are few studies in this age group. Nebulized isotonic magnesium sulfate may be considered as an adjuvant to standard treatment with nebulized salbutamol and ipratropium in the first hour of treatment for children ≥2 years old with acute severe asthma (e.g. oxygen saturation <92%, Box 6-9, p.171), particularly those with symptoms lasting <6 hours.[719] 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.[720]

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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. Consider adding 1–2 puffs of ipratropium. Failure to respond at 1 hour, or earlier deterioration, should prompt urgent admission to hospital, addition of nebulized ipratropium, 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 department, 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 immediately 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 and/or oral corticosteroids are indicated (Evidence D), as outlined below.

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

Therapy	Dose and administration
Supplemental oxygen	Delivered by face mask (usually 1 L/minute) to maintain oxygen saturation 94–98%
Short-acting beta$_2$-agonist (SABA)	2–6 puffs of salbutamol by spacer, or 2.5 mg of salbutamol by nebulizer, every 20 minutes for first hour*, then reassess severity. If symptoms persist or recur, give an additional 2–3 puffs per hour. Admit to hospital if >10 puffs required in 3–4 hours.
Systemic corticosteroids	Give initial dose of oral prednisolone (1–2 mg/kg up to a maximum 20 mg for children <2 years old; 30 mg for children 2–5 years) OR, intravenous methylprednisolone 1 mg/kg 6-hourly on day 1
Additional options in the first hour of treatment	
Ipratropium bromide	Consider adding 1–2 puffs of ipratropium bromide by pMDI and spacer For children with moderate-severe exacerbations with a poor response to initial SABA, give nebulized ipratropium bromide 250 mcg every 20 minutes for 1 hour only
Magnesium sulfate	Consider nebulized isotonic magnesium sulfate (150 mg) 3 doses in the first hour of treatment for children aged ≥2 years with severe exacerbation (Box 6-9, p.171)

*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[721] (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. If a nebulizer is used, follow infection control procedures.

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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.169). However, the clinical benefit of these interventions – particularly on endpoints such as hospitalizations and longer-term outcomes – has not been impressive.

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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.166) 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

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OCS.[558,693,694,722,723] Addition of ICS to standard care (including OCS) does not reduce risk of hospitalization but reduces length of stay and acute asthma scores in children in the emergency department.[724] However, the potential for side-effects with high dose ICS should be taken into account, especially if used repeatedly, and the child should be monitored closely. For those children already on ICS, doubling the dose was not effective in a small study of mild-moderate exacerbations in children aged 6–14 years,[725] nor was quintupling the dose in children aged 5–11 years with good adherence. This approach should be reserved mainly for individual cases, and should always involve regular follow up and monitoring of adverse effects (Evidence D).

Oral corticosteroids

For children with 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),[726] although several studies have failed to show any benefits when given earlier (e.g. by parents) during periods of worsening wheeze managed in an outpatient setting (Evidence D).[710-713,727,728] A meta-analysis demonstrated a reduced risk of hospitalization when oral corticosteroids were administered in the emergency department, but no clear benefit in risk of hospitalization when given in the outpatient setting.[729] A course of 3–5 days is sufficient in most children of this age, and can be stopped without tapering (Evidence D), but the child must be reviewed after discharge (as below) to confirm they are recovering.

In children discharged from the emergency department, an intramuscular corticosteroid may be an alternative to a course of OCS for preventing relapse.[588] There is insufficient evidence to recommend intramuscular over oral corticosteroids.[588]

Regardless of treatment, the severity of the child's symptoms must be carefully monitored. The sooner therapy is started in relation to the onset of symptoms, the more likely it is that the impending exacerbation may be clinically attenuated or prevented.

Discharge and follow up after an exacerbation

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

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

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

- Instruction on recognition of signs of recurrence and worsening of asthma. The factors that precipitated the exacerbation should be identified, and strategies for future avoidance of these factors implemented.
- A written, individualized action plan, including details of accessible emergency services
- Careful review of inhaler technique
- Further treatment advice explaining that:
  - SABAs should be used on an as-needed basis, but the daily requirement should be recorded to ensure it is being decreased over time to pre-exacerbation levels.
  - ICS has been initiated where appropriate (at twice the low initial dose in Box 6-6 (p.166) for the first month after discharge, then adjusted as needed) or continued, for those previously prescribed controller medication.
- A supply of SABA and, where applicable, the remainder of the course of oral corticosteroid, ICS or LTRA
- A follow-up appointment within 1–2 days and another within 1–2 months, depending on the clinical, social and practical context of the exacerbation

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Chapter 7.

Primary prevention of asthma

KEY POINTS

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

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FACTORS CONTRIBUTING TO THE DEVELOPMENT OF ASTHMA IN CHILDREN

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

'Primary prevention' refers to preventing the onset of disease. This chapter focuses on primary prevention in children. See p.101 and review articles[40] for strategies for preventing occupational asthma.

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FACTORS ASSOCIATED WITH INCREASED OR DECREASED RISK OF ASTHMA IN CHILDREN

Nutrition of mother and baby

Maternal diet

For some time, the mother's diet during pregnancy has been a focus of concern relating to the development of allergy and asthma in the child. There is no firm evidence that ingestion of any specific foods during pregnancy increases the risk for asthma. However, a 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.[730] 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.[731,732] 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.[733-736] Dietary changes during pregnancy are therefore not recommended for prevention of allergies or asthma.

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Maternal obesity and weight gain during pregnancy

Data suggest that maternal obesity and weight gain during pregnancy pose an increased risk for asthma in children. A meta-analysis[737] showed that maternal obesity in pregnancy was associated with higher odds of ever asthma or wheeze or current asthma or wheeze; each 1 kg/m^2 increase in maternal 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.

Breastfeeding

Despite the existence of many studies reporting a beneficial effect of breastfeeding on asthma prevention, results are conflicting,[738] and caution should be taken in advising families that breastfeeding will prevent asthma.[739] Breastfeeding 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, breastfeeding should be encouraged for all of its other positive benefits (Evidence A).

Timing of 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. However, meta-analyses have found no evidence that this practice reduces the risk of allergic disease (including asthma).[740] In the case of peanuts, early introduction may prevent peanut allergy in high risk infants.[740]

Dietary supplements for mothers and/or babies

Vitamin D

Intake of vitamin D may be through diet, dietary supplementation or sunlight. A systematic review of cohort, case control and cross-sectional studies concluded that maternal dietary intake of vitamin D, and of vitamin E, was associated with lower risk of wheezing illnesses in children.[741] This was not confirmed in two randomized controlled trials of vitamin D supplementation in pregnancy comparing standard dose with high dose vitamin D, although a significant effect was not ruled out.[742,743] When the results from these two trials were combined, there was a 25% reduction of risk of asthma/recurrent wheeze at ages 0–3 years.[744] The effect was greatest among women who maintained 25(OH)vitamin D levels of at least 30 ng/ml from the time of study entry through delivery, suggesting that sufficient levels of Vitamin D during early pregnancy may be important in decreasing risk for early life wheezing episodes,[744] although in both trials, no effects of vitamin D supplementation on the development of asthma and recurrent wheeze were evident at the age of 6 years.[745]

Fish oil and long-chain polyunsaturated fatty acids

Systematic reviews of cohort studies about maternal dietary intake of fish or seafood during pregnancy[733,746] and of randomized controlled trials on maternal dietary intake of fish or long-chained polyunsaturated fatty acids during pregnancy[733] showed no consistent effects on the risk of wheeze, asthma or atopy in the child. One study demonstrated decreased wheeze/asthma in pre-school children at high risk for asthma when mothers were given a high dose fish oil supplement in the third trimester;[747] however 'fish oil' is not well defined, and the optimal dosing regimen has not been established.

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Probiotics

A meta-analysis provided insufficient evidence to recommend probiotics for the prevention of allergic disease (asthma, rhinitis, eczema or food allergy).[748]

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,[749,750] the relationship for animal allergen appears to be more complex.[738] Some studies have found that exposure to pet allergens is associated with increased risk of sensitization to these allergens,[751,752] and of asthma and wheezing.[753,754] By contrast, other studies have demonstrated a *decreased* risk of developing allergy with exposure to pets.[755,756] 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.[757] For children at risk of

asthma, dampness, visible mold and mold odor in the home environment are associated with increased risk of developing asthma.[758] 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,[759] the Canadian Asthma Primary Prevention Study,[760] and the Prevention of Asthma in Children study[761] were associated with lower risk of asthma diagnosis in children younger than 5 years.[762] 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.[759,763] The Isle of Wight study has shown a continuing positive benefit for early-life intervention through to 18 years of age;[764] however, exactly which components of the intervention were important and which specific mechanistic changes were induced remain elusive.

Treatment with grass SLIT for 3 years did not reduce the incidence of asthma diagnosis (primary outcome) in a large randomized double-blind placebo-controlled trial in children 5-12 years with grass-allergic rhinoconjunctivitis, but asthma symptoms and asthma medication use were reduced. At present, SLIT for children with grass allergic rhinoconjunctivitis is not recommended for asthma prevention.[765] Additional studies are needed.

Pollutants

Maternal smoking during pregnancy is the most direct route of pre-natal environmental tobacco smoke exposure.[766] 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.[767] Exposure to outdoor pollutants, such as living near a main road, is associated with increased risk of asthma.[768,769] A 2019 study suggested that up to 4 million new pediatric asthma cases (13% of the global incidence) may be attributable to exposure to traffic-related air pollution (TRAP).[770] Prenatal NO_2, SO_2, and PM10 exposures are associated with an increased risk of asthma in childhood,[771] but it is difficult to separate pre- and post-natal exposure.

Microbial effects

The 'hygiene hypothesis', and the more recently coined 'microflora hypothesis' and 'biodiversity hypothesis',[772] 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.[773] The risk of asthma is also reduced in children whose bedrooms have high levels of bacterial-derived lipopolysaccharide endotoxin.[774,775] Similarly, children in homes with ≥2 dogs or cats are less likely to be allergic than those in homes without dogs or cats.[756] Exposure of an infant to the mother's vaginal microflora through vaginal delivery may also be beneficial; the prevalence of asthma is higher in children born by cesarean section than those born vaginally.[776,777] This may relate to differences in the infant gut microbiota according to their mode of delivery.[778]

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.[779] However, there is little evidence to suggest that this effect is sustained. Although the risk of parent-reported asthma with infrequent wheeze was reduced at 6 years, there was no impact on doctor-diagnosed asthma or lung function.[780] Thus, the long-term effect of palivizumab in the prevention of asthma remains uncertain.

Medications and other factors

Antibiotic use during pregnancy and in infants and toddlers has been associated with the development of asthma later in life,[781,782] although not all studies have shown this association.[783] Intake of the analgesic, paracetamol (acetaminophen), may be associated with asthma in both children and adults,[784] although exposure during infancy may be confounded by use of paracetamol for respiratory tract infections.[784] Frequent use of paracetamol by pregnant women has been associated with asthma in their children.[785] There is no evidence that vaccinations increase the risk of a child developing asthma.

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Commented [A177]: Reference added 2022: Baron R, Taye M, der Vaart IB, et al. The relationship of prenatal antibiotic exposure and infant antibiotic administration with childhood allergies: a systematic review. BMC Pediatr 2020; 20: 312.

Commented [A178]: References deleted 2022: Marra F, Marra CA, Richardson K, et al. Antibiotic use in children is associated with increased risk of asthma. Pediatrics 2009;123:1003-10
Stensballe LG, Simonsen J, Jensen SM, Bonnelykke K, Bisgaard H. Use of antibiotics during pregnancy increases the risk of asthma in early childhood. J Pediatr 2013;162:832-8.e3.

Psychosocial factors

The social environment to which children are exposed may also contribute to the development and severity of asthma. Maternal distress during pregnancy[786] or during the child's early years[787] has been associated with an increased risk of the child developing asthma.

Obesity

A meta-analysis of 18 studies found that being either overweight or obese was a risk factor for childhood asthma and wheeze, particularly in girls.[431] In adults, there is evidence suggesting that obesity affects the risk of asthma, but that asthma does not affect the risk of obesity.[788,789]

ADVICE ABOUT PRIMARY PREVENTION OF ASTHMA

Based on the results of cohort and observational studies,[790] and a GRADE-based analysis for the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines,[738] parents enquiring about how to reduce the risk of their children developing asthma can be provided with the advice summarized in Box 7-1.

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

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

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

- Children should not be exposed to environmental tobacco smoke during pregnancy or after birth.
- Identification and correction of Vitamin D insufficiency in women with asthma who are pregnant, or planning pregnancy, may reduce the risk of early life wheezing episodes.
- Vaginal delivery should be encouraged where possible.
- Breastfeeding 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.

SECTION 3. TRANSLATION INTO CLINICAL PRACTICE

Chapter 8.

Implementing asthma management strategies into health systems

KEY POINTS

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

INTRODUCTION

Due to the exponential increase in medical research publications, practical syntheses are needed to guide policy makers and health care professionals in delivering evidence-based care. When asthma care is consistent with evidence-based recommendations, outcomes improve.[155,791,792] 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 ADAPTE[793] 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.[794] Further, there is generally very limited high quality evidence addressing the many decision nodes in comprehensive clinical practice guidelines, particularly in developing countries.

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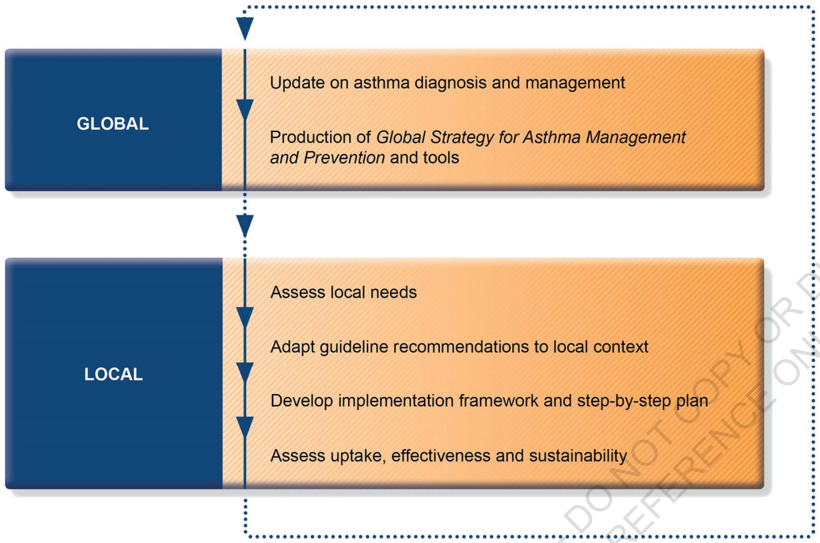
ADAPTING AND IMPLEMENTING ASTHMA CLINICAL PRACTICE GUIDELINES

Implementation of asthma management strategies may be carried out at a national, regional or local level.[795] Ideally, implementation should be a multidisciplinary effort involving many stakeholders, and using cost-effective methods of knowledge translation.[795-797] Each implementation initiative needs to consider the nature of the local health system and its resources (e.g. human, infrastructure, available treatments) (Box 8-1). Moreover, goals and implementation strategies will need to vary from country to country and within countries, based on economics, culture and the physical and social environment. Priority should be given to high-impact interventions.

Specific steps need to be followed before clinical practice recommendations can be embedded into local clinical practice and become the standard of care, particularly in low resource settings. The individual steps are summarized in Box 8-2, and a detailed description of the processes involved in each step can be found in the GINA Appendix Chapter 6, available online at www.ginasthma.org.

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



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

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

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BARRIERS AND FACILITATORS

Many barriers to, and facilitators of, implementation procedures have been described.[797-800] Some of the barriers to implementation of evidence-based asthma management relate to the delivery of care, while others relate to patients' attitudes (see Box 8-3, and examples in Appendix Chapter 6, Box 6-1). Cultural and economic barriers can particularly affect the application of recommendations.

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

Health care providers	Patients
Insufficient knowledge of recommendations	Low health literacy
Lack of agreement with recommendations or expectation that they will be effective	Insufficient understanding of asthma and its management
Resistance to change	Lack of agreement with recommendations
External barriers (organizational, health policies, financial constraints)	Cultural and economic barriers
Lack of time and resources	Peer influence
Medico-legal issues	Attitudes, beliefs, preferences, fears and misconceptions

EXAMPLES OF HIGH IMPACT IMPLEMENTATION INTERVENTIONS

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

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

- Free ICS for patients with a recent hospital admission and/or severe asthma[801]
- Early treatment with ICS, guided self-management, reduction in exposure to tobacco smoke, improved access to asthma education[155]
- Self-inking stamp prompting assessment of asthma control and treatment strategies[802]
- Use of individualized written asthma action plans as part of self-management education[424]
- An evidence-based care process model for acute and chronic pediatric asthma management, implemented at multiple hospitals[803]

ICS: inhaled corticosteroids

EVALUATION OF THE IMPLEMENTATION PROCESS

An important part of the implementation process is to establish a means of evaluating the effectiveness of the program and any improvements in quality of care (see Appendix Chapter 6, Box A6-3). The Cochrane Effective Practice and Organization of Care Group (EPOC) offers suggestions on how to assess the effectiveness of interventions.[804]

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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We can replace refs 10 and 11 with the parent webpage https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines, which provides access to the lists for both adults and children

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