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GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION

UPDATED 2012

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Global Strategy for Asthma Management and Prevention
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Global Strategy for Asthma Management and Prevention 2012 (update)

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*Disclosures for members of GINA Board of Directors and Science Committees can be found at http://www.ginasthma.org

PREFACE

Asthma is a serious global health problem. People of all ages in countries throughout the world are affected by this chronic airway disorder that, when uncontrolled, can place severe limits on daily life and is sometimes fatal. The prevalence of asthma is increasing in most countries, especially among children. Asthma is a significant burden, not only in terms of health care costs but also of lost productivity and reduced participation in family life.

During the past two decades, we have witnessed many scientific advances that have improved our understanding of asthma and our ability to manage and control it effectively. However, the diversity of national health care service systems and variations in the availability of asthma therapies require that recommendations for asthma care be adapted to local conditions throughout the global community. In addition, public health officials require information about the costs of asthma care, how to effectively manage this chronic disorder, and education methods to develop asthma care services and programs responsive to the particular needs and circumstances within their countries.

In 1993, the National Heart, Lung, and Blood Institute collaborated with the World Health Organization to convene a workshop that led to a Workshop Report: Global Strategy for Asthma Management and Prevention. This presented a comprehensive plan to manage asthma with the goal of reducing chronic disability and premature deaths while allowing patients with asthma to lead productive and fulfilling lives.

At the same time, the Global Initiative for Asthma (GINA) was implemented to develop a network of individuals, organizations, and public health officials to disseminate information about the care of patients with asthma while at the same time assuring a mechanism to incorporate the results of scientific investigations into asthma care. Publications based on the GINA Report were prepared and have been translated into languages to promote international collaboration and dissemination of information. To disseminate information about asthma care, a GINA Assembly was initiated, comprised of asthma care experts from many countries to conduct workshops with local doctors and national opinion leaders and to hold seminars at national and international meetings. In addition, GINA initiated an annual World Asthma Day (in 2001) which has gained increasing attention each year to raise awareness about the burden of asthma, and to initiate activities at the local/national level to educate families and health care professionals about effective methods to manage and control asthma.

In spite of these dissemination efforts, international surveys provide direct evidence for suboptimal asthma control in many countries, despite the availability of effective therapies. It is clear that if recommendations contained within this report are to improve care of people with asthma, every effort must be made to encourage health care leaders to assure availability of and access to medications, and develop means to implement effective asthma management programs including the use of appropriate tools to measure success.

In 2002, the GINA Report stated that "It is reasonable to expect that in most patients with asthma, control of the disease can, and should be achieved and maintained." To meet this challenge, in 2005, Executive Committee recommended preparation of a new report not only to incorporate updated scientific information but to implement an approach to asthma management based on asthma control, rather than asthma severity. Recommendations to assess, treat and maintain asthma control are provided in this document. The methods used to prepare this document are described in the Introduction.

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It is a privilege for me to acknowledge the work of the many people who participated in this update project, as well as to acknowledge the superlative work of all who have contributed to the success of the GINA program.

The GINA program has been conducted through unrestricted educational grants from Almirall, AstraZeneca, Boehringer-Ingelheim, Chiesi, CIPLA, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Quintiles, Takeda. The generous contributions of these companies assured that Committee members could meet together to discuss issues and reach consensus in a constructive and timely manner. The members of the GINA Committees are, however, solely responsible for the statements and conclusions presented in this publication.

GINA publications are available through the Internet (http://www.ginasthma.org).

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Methodology and Summary of New Recommendations Global Strategy for Asthma Management and Prevention: 2012 Update[1]

Background: When the Global Initiative for Asthma (GINA) program was initiated in 1993, the primary goal was to produce recommendations for the management of asthma based on the best scientific information available. Its first report, *NHLBI/WHO Workshop Report: Global Strategy for Asthma Management and Prevention* was issued in 1995 and revised in 2002 and 2006. In 2002 and in 2006 revised documents were prepared based on published research.

The GINA Science Committee[2] was established in 2002 to review published research on asthma management and prevention, to evaluate the impact of this research on recommendations in the GINA documents related to management and prevention, and to post yearly updates on the GINA website. Its members are recognized leaders in asthma research and clinical practice with the scientific credentials to contribute to the task of the Committee, and 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 from diverse geographic regions.

Updates of the 2006 report have been issued in December of each year with each update based on the impact of publications from July 1 of the previous year through June 30 of the year the update was completed. Posted on the website along with the updated documents is a list of all the publications reviewed by the Committee.

Process: To produce the updated documents a Pub Med search is done using search fields established by the Committee: 1) *asthma, All Fields, All ages, only items with abstracts, Clinical Trial, Human, sorted by Authors;* and 2) *asthma AND systematic, All fields, ALL ages, only items with abstracts, Human, sorted by author.* The first search includes publications for July 1-December 30 for review by the Committee during the ATS meeting. The second search includes publications for January 1 – June 30 for review by the Committee during the ERS meeting. (Publications that appear after June 30 are considered in the first phase of the following year.) To ensure publications in peer review journals not captured by this search methodology are not missed, the respiratory community is invited to submit papers to the Chair, GINA Science Committee, providing an abstract and the full paper are submitted in (or translated into) English.

All members of the Committee receive a summary of citations and all abstracts. Each abstract is assigned to at least two Committee members, although all members are offered the opportunity to provide an opinion on all abstracts. Members evaluate the abstract or, up to her/his judgment, the full publication, and answer four specific written questions from a short questionnaire, and to indicate if the scientific data presented impacts on recommendations in the GINA report. If so, the member is asked to specifically identify modifications that should be made.

The entire GINA Science Committee meets twice yearly to discuss each publication that was considered by at least 1 member of the Committee to potentially have an impact on the management of asthma. The full Committee then reaches a consensus on whether to include it in the report, either as a reference supporting current recommendations, or to change the report. In the absence of consensus, disagreements are decided by an open vote of the full Committee. Recommendations by the Committee for use of any medication are based on the best evidence available from the literature and not on labeling directives from government regulators. The Committee does not make recommendations for therapies that have not been approved by at least one regulatory agency.

For the 2012 update, between July 1, 2011 and June 30, 2012, 386 articles met the search criteria. Of the 386, 19 papers were identified to have an impact on the GINA report. The changes prompted by these publications were posted on the website in December 2012. These were either: A) modifying, that is, changing the text or introducing a concept requiring a new recommendation to the report; or B) confirming, that is, adding to or replacing an existing reference.

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[1]The Global Strategy for Asthma Management and Prevention (updated 2012), the updated Pocket Guides and the complete list of references examined by the Committee are available on the GINA website www.ginasthma.org.

[2]Members (2011-2012): H. Reddel, Chair; P. Barnes, N. Barnes, E. Bateman, A. Becker, E. Bel, J. DeJongste, J. Drazen, M. FitzGerald, R. Lemanske, P. O'Byrne, K. Ohta, S. Pedersen, E. Pizzichini, S. Wenzel.

SUMMARY OF RECOMMENDATIONS IN THE 2013 UPDATE

A. Additions to the text:

Page 33, right column, insert new paragraph: Tiotropium, a long-acting inhaled anticholinergic bronchodilator, has been studied in adults with uncontrolled asthma and compared with salmeterol, doubling the dose of inhaled glucocorticosteroid and as add-on to inhaled glucocorticosteroids and salmeterol[231,233]. One study showed comparable bronchodilator effects with no significant changes on asthma control[232]. Another study showed that adding tiotropium to patients not controlled on inhaled glucocorticosteroids and long-acting $ß_2$-agonists improved lung function but not symptoms[233]. The studies have been relatively short-term and no effect on exacerbations has so far been reported. There are no data about these medications in children.

Reference 231: Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT *et al.* National Heart, Lung, and Blood Institute Asthma Clinical Research Network. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010;363:1715-26.

Reference 232: Kerstjens HA, Disse B, Schroder-Babo W, Bantje TA, Gahlemann M, Sigmund R, Engel M, van Noord JA. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. *J Allergy Clin Immunol*. 2011 Aug;128(2):308-14.

Reference 233: Bateman ED, Kornmann O, Schmidt P, Pivovarova A, Engel M, Fabbri LM. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. *J Allergy Clin Immunol.* 2011 Aug;128(2):315-22.

Page 34, right column, insert line 15: …. although this was not confirmed in all studies[235].

Reference 235: Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Internal Med* 2011;154:573-82.

Page 38, left column, first paragraph, add sentence and reference: A systematic review of yoga interventions for asthma found no convincing evidence of benefit; the quality of studies was generally poor[236].

Reference 236. Posadzki P, Ernst E. Yoga for asthma? A systematic review of randomized clinical trials. *J Asthma.* 2011 Aug;48(6):632-9.

Page 38, right column, last paragraph, add statement and reference: although spacer devices or face masks differ in their drug delivery, and therefore may not be interchangeable[237].

Reference 237. Lavorini F, Fontana GA. Targeting drugs to the airways: The role of spacer devices. *Expert Opin Drug Deliv* 2009;6:91-102.

Page 40, left column, first paragraph replace with: The clinical benefits of intermittent systemic or inhaled glucocorticosteroids for children with intermittent, viral-induced wheeze remain controversial. A one-year study of intermittent treatment with inhaled glucocorticosteroids was equally effective as daily treatment, and reduced the total glucocorticosteroid dose threefold in preschool children with frequent wheezing and a high asthma predictive index[238]. Some studies in older children found small benefits while another study in young children found no effects on wheezing symptoms[139]. There is no evidence to support the use of maintenance low-dose inhaled glucocorticosteroids for preventing early transient wheezing[136, 139, 199].

Reference 238: Zeiger RS, Mauger D, Bacharier LB, Guilbert TW, Martinez FD, Lemanske RF Jr, et al; CARE Network of the National Heart, Lung, and Blood Institute. Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med*. 2011 Nov 24;365(21):1990-2001

Page 40, Figure 3-5, bullet 6: Modify age range to 2-10 years; add reference in figure title.

Reference 239: Guilbert TW, Mauger DT, Allen DB, Zeiger RS, Lemanske RF Jr, Szefler SJ, et al; Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. Growth of preschool children at high risk for asthma 2 years after discontinuation of fluticasone. *J Allergy Clin Immunol*. 2011 Nov;128(5):956-63.

Page 71, right column, replace second bullet and add reference: Investigate and confirm adherence with treatment. Incorrect or inadequate use of medications and inhalers[405] remains the most common reason for failure to achieve good control. In patients with difficult-to-treat asthma, improved adherence and improved health outcomes can be achieved with a comprehensive concordance intervention[416].

Reference 416: Gamble J, Stevenson M, Heaney LG. A study of a multi-level intervention to improve non-adherence in difficult to control asthma. *Respir Med.* 2011 Sep;105(9):1308-15.

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Page 72, left column insert in last paragraph: Extended follow-up on a small number of patients has provided some additional support for long-term safety of bronchial thermoplasty[417]. However, longer-term follow-up of larger number of control and active patients is needed to assess effectiveness and caution should be used in selecting patients for this procedure.

Reference 417: Castro M, Rubin A, Laviolette M, Hanania NA, Armstrong B, Cox G; AIR2 Trial Study Group. Persistence of effectiveness of bronchial thermoplasty in patients with severe asthma. *Ann Allergy Asthma Immunol.* 2011 Jul;107(1):65-70.

Page 77, left column replace paragraph on oxygen: To achieve arterial oxygen saturation of 90% (95% in children), oxygen should be administered by nasal cannulae, by mask, or rarely by head box in some infants. For severe asthma exacerbations, controlled oxygen therapy using pulse oximetry to maintain oxygen saturation at 90 – 93% is associated with better physiological outcomes, compared to high flow 100% oxygen therapy[218, 419]. Oxygen therapy should be titrated against pulse oximetry to maintain a satisfactory oxygen saturation[219]. However, oxygen should not be withheld if oximetry is not available.

Reference 419. Perrin K, Wijesinghe M, Healy B, Wadsworth K, Bowditch R, Bibby S, Baker T, Weatherall M, Beasley R. Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. *Thorax*. 2011 Nov;66(11):937-41.

Page 78, left column, end of first paragraph, insert text and reference: Two days of oral dexamethasone can also be used to treat asthma exacerbations, but there are concerns about metabolic side-effects if dexamethasone is continued beyond two days[420]. Evidence suggests that there is no benefit to tapering the dose of oral glucocorticosteroids, either in the short-term[245] or over several weeks, as long as the patient is on maintenance inhaled glucocorticosteroids[246] (**Evidence B**).

Reference 420: Kravitz J, Dominici P, Ufberg J, Fisher J, Giraldo P. Two days of dexamethasone versus 5 days of prednisone in the treatment of acute asthma: a randomized controlled trial. *Ann Emerg Med.* 2011 Aug;58(2):200-4.

Page 82, right column, paragraph 2, insert in line 4: …in adults[392-394] or in children[422].

Reference 422. Holbrook JT, Wise RA, Gold BD, Blake K, Brown ED, Castro M, Dozor AJ, et al. Writing Committee for the American Lung Association Asthma Clinical Research Centers. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. *JAMA.* 2012 Jan 25;307(4):373-81.

B. References that provided confirmation or update of previous recommendations.

Page 6, right column, first sentence in paragraph four, add reference 136.

Reference 136: Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, Britton JR, McKeever TM. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics.* 2012 Apr;129(4):735-44.

Page 33, right column, insert reference 234 after reference 215.

Reference 234: Kemp J, Armstrong L, Wan Y, Alagappan VK, Ohlssen D, Pascoe S. Safety of formoterol in adults and children with asthma: a meta-analysis. *Ann Allergy Asthma Immunol.* 2011 Jul;107(1):71-8.

Page 41, right column, line 10, insert reference 234 after reference 75, and in line 17, after reference 169.

Reference 234: Kemp J, Armstrong L, Wan Y, Alagappan VK, Ohlssen D, Pascoe S. Safety of formoterol in adults and children with asthma: a meta-analysis. *Ann Allergy Asthma Immunol.* 2011 Jul;107(1):71-8.

Page 57, right column, last paragraph, insert reference 414 after reference 22.

Reference 414: Shah S, Sawyer SM, Toelle BG, Mellis CM, Peat JK, Lagleva M, Usherwood TP, Jenkins CR. Improving paediatric asthma outcomes in primary health care: a randomised controlled trial. *Med J Aust.* 2011 Oct 3;195(7):405-9.

Page 61, right column, paragraph 2 insert reference:

Reference 415: Gehring U, de Jongste JC, Kerkhof M, Oldewening M, Postma D, van Strien RT, et al. The 8-year follow-up of the PIAMA intervention study assessing the effect of mite-impermeable mattress covers. *Allergy.* 2012 Feb;67(2):248-56

Page 73, right column end of first paragraph insert reference 418 after reference 349.

Reference 418: Ortega H, Miller DP, Li H. Characterization of asthma exacerbations in primary care using cluster analysis. *J Asthma.* 2012 Mar;49(2):158-69.

Page 81, right column, last sentence under section on Occupational Asthma, insert insert (See also reference 421).

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Reference 421: Fishwick D, Barber CM, Bradshaw LM, Ayres JG, Barraclough R, Burge S, et al. Standards of care for occupational asthma: an update. *Thorax.* 2012 Mar;67(3):278-80.

C. Inserts to add clarification or additional information

Page 20, left column, insert new paragraph: In early life, the presence of sensitization to common allergens, atopy, is a major risk factor for subsequent development of asthma. In addition, atopy also predicts that asthma may be more severe when it does develop.

Page 32, left column last paragraph: correct dose to 1000 ug/day

Page 64, under heading of obesity, insert: ...including by bariatric surgery

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INTRODUCTION

Asthma is a serious public health problem throughout the world, affecting people of all ages. When uncontrolled, asthma can place severe limits on daily life, and is sometimes fatal.

In 1993, the Global Initiative for Asthma (GINA) was formed. Its goals and objectives were described in a 1995 NHLBI/WHO Workshop Report, *Global Strategy for Asthma Management and Prevention.* This Report (revised in 2002 and 2006), and its companion documents, have been widely distributed and translated into many languages. A network of individuals and organizations interested in asthma care has been created and several country-specific asthma management programs have been initiated. Yet much work is still required to reduce morbidity and mortality from this chronic disease.

In 2006, the *Global Strategy for Asthma Management and Prevention* was revised to emphasize asthma management based on clinical control, rather than classification of the patient by severity. This important paradigm shift for asthma care reflected the progress made in pharmacologic care of patients. Many asthma patients are receiving, or have received, some asthma medications. The role of the health care professional is to establish each patient's current level of treatment and control, then adjust treatment to gain and maintain control. Asthma patients should experience no or minimal symptoms (including at night), have no limitations on their activities (including physical exercise), have no (or minimal) requirement for rescue medications, have near normal lung function, and experience only very infrequent exacerbations.

The recommendations for asthma care based on clinical control described in the 2006 report have been updated annually. This 2011 update reflects a number of modifications, described in "Methodology and Summary of New Recommendations." As with all previous GINA reports, levels of evidence (**Table A**) are assigned to management recommendations where appropriate in Chapter 4, the Five Components of Asthma Management. Evidence levels are indicated in boldface type enclosed in parentheses after the relevant statement—e.g., (**Evidence A**).

FUTURE CHALLENGES

In spite of laudable efforts to improve asthma care over the past decade, a majority of patients have not benefited from advances in asthma treatment and many lack even the rudiments of care. A challenge for the next several years is to work with primary health care providers and public health officials in various countries to design, implement, and evaluate asthma care programs to meet local needs. The GINA Board of Directors recognizes that this is a difficult task and, to aid in this work, has formed several groups of global experts, including: a Dissemination and Implementation Committee; the GINA Assembly, a network of individuals who care for asthma patients in many different health care settings; and two regional programs, GINA Mesoamerica and GINA Mediterranean. These efforts aim to enhance communication with asthma specialists, primary-care health professionals, other health care workers, and patient support organizations. The Board of Directors continues to examine barriers to implementation of the asthma management recommendations, especially the challenges that arise in primary-care settings and in developing countries.

While early diagnosis of asthma and implementation of appropriate therapy significantly reduce the socioeconomic burdens of asthma and enhance patients' quality of life, medications continue to be the major component of the cost of asthma treatment. For this reason, the pricing of asthma medications continues to be a topic for urgent need and a growing area of research interest, as this has important implications for the overall costs of asthma management. Moreover, a large segment of the world's population lives 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.

As the GINA Board of Directors expand their work, every effort will be made to interact with patient and physician groups at national, district, and local levels, and in multiple health care settings, to continuously examine new and innovative approaches that will ensure the delivery of the best asthma care possible. GINA is a partner organization in a program launched in March 2006 by the World Health Organization, the Global Alliance Against Chronic Respiratory Diseases (GARD). Through the work of the GINA Board of Directors, and in cooperation with GARD, progress toward better care for all patients with asthma should be substantial in the next decade.

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

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CHAPTER

1

DEFINITION

AND

OVERVIEW

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KEY POINTS:

- Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.
- Clinical manifestations of asthma can be controlled with appropriate treatment. When asthma is controlled, there should be no more than occasional flare-ups and severe exacerbations should be rare.
- Asthma is a problem worldwide, with an estimated 300 million affected individuals.
- Although from the perspective of both the patient and society the cost to control asthma seems high, the cost of not treating asthma correctly is even higher.
- A number of factors that influence a person's risk of developing asthma have been identified. These can be divided into host factors (primarily genetic) and environmental factors.
- The clinical spectrum of asthma is highly variable, and different cellular patterns have been observed, but the presence of airway inflammation remains a consistent feature.

This chapter covers several topics related to asthma, including definition, burden of disease, factors that influence the risk of developing asthma, and mechanisms. It is not intended to be a comprehensive treatment of these topics, but rather a brief overview of the background that informs the approach to diagnosis and management detailed in subsequent chapters. Further details are found in the reviews and other references cited at the end of the chapter.

DEFINITION

Asthma is a disorder defined by its clinical, physiological, and pathological characteristics. The predominant feature of the clinical history is episodic shortness of breath, particularly at night, often accompanied by cough.

Wheezing appreciated on auscultation of the chest is the most common physical finding.

The main physiological feature of asthma is episodic airway obstruction characterized by expiratory airflow limitation. The dominant pathological feature is airway inflammation, sometimes associated with airway structural changes.

Asthma has significant genetic and environmental components, but since its pathogenesis is not clear, much of its definition is descriptive. Based on the functional consequences of airway inflammation, an operational description of asthma is:

> *Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.*

Because there is no clear definition of the asthma phenotype, researchers studying the development of this complex disease turn to characteristics that can be measured objectively, such as atopy (manifested as the presence of positive skin-prick tests or the clinical response to common environmental allergens), airway hyperresponsiveness (the tendency of airways to narrow excessively in response to triggers that have little or no effect in normal individuals), and other measures of allergic sensitization. Although the association between asthma and atopy is well established, the precise links between these two conditions have not been clearly and comprehensively defined.

There is now good evidence that the clinical manifestations of asthma—symptoms, sleep disturbances, limitations of daily activity, impairment of lung function, and use of rescue medications—can be controlled with appropriate treatment. When asthma is controlled, there should be no more than occasional recurrence of symptoms and severe exacerbations should be rare[1].

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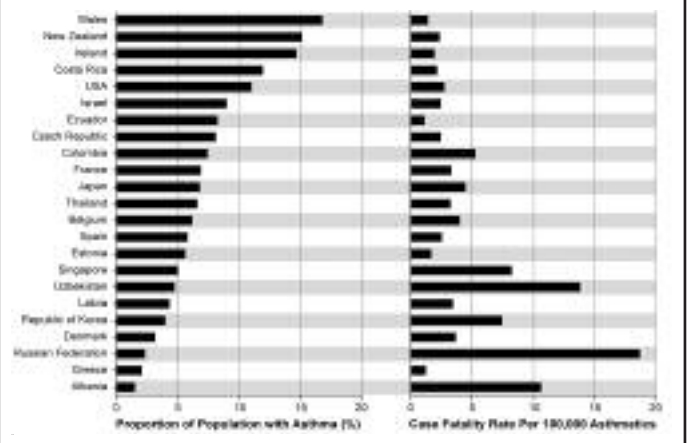
THE BURDEN OF ASTHMA

Prevalence, Morbidity, and Mortality

Asthma is a problem worldwide, with an estimated 300 million affected individuals[2,3]. Despite hundreds of reports on the prevalence of asthma in widely differing populations, the lack of a precise and universally accepted definition of asthma makes reliable comparison of reported prevalence from different parts of the world problematic. Nonetheless, based on the application of standardized methods to measure the prevalence of asthma and wheezing illness in children[4] and adults, it appears that the global prevalence of asthma ranges from 1% to 18% of the population in different countries (**Figure 1-1**)[2,3]. There is good evidence that international differences in asthma symptom prevalence have been reduced, particularly in the 13-14 year age group, with decreases in prevalence in North America and Western Europe and increases in prevalence in regions where prevalence was previously low. Although there was little change in the overall prevalence of current wheeze, the percentage of children reported to have had asthma increased significantly, possibly reflecting greater awareness of this condition and/or changes in diagnostic practice. The increases in asthma symptom prevalence in Africa, Latin America and parts of Asia indicate that the global burden of asthma is continuing to rise, but the global prevalence differences are lessening[118]. The World Health Organization has estimated that 15 million disability-adjusted life years (DALYs) are lost annually due to asthma, representing 1% of the total global disease burden[2]. Annual worldwide deaths from asthma have been estimated at 250,000 and mortality does not appear to correlate well with prevalence (**Figure 1-1**)[2,3]. There are insufficient data to determine the likely causes of the described variations in prevalence within and between populations.

Figure 1-1. Asthma Prevalence and Mortality[2, 3]



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Social and Economic Burden

Social and economic factors are integral to understanding asthma and its care, whether viewed from the perspective of the individual sufferer, the health care professional, or entities that pay for health care. Absence from school and days lost from work are reported as substantial social and economic consequences of asthma in studies from the Asia-Pacific region, India, Latin America, the United Kingdom, and the United States[9-12].

The monetary costs of asthma, as estimated in a variety of health care systems including those of the United States[13-15] and the United Kingdom[16] are substantial. In analyses of economic burden of asthma, attention needs to be paid to both direct medical costs (hospital admissions and cost of medications) and indirect, non-medical costs (time lost from work, premature death)[17]. For example, asthma is a major cause of absence from work in many countries[4-6], including Australia, Sweden, the United Kingdom, and the United States[2,3,18,19]. Comparisons of the cost of asthma in different regions lead to a clear set of conclusions:

- The costs of asthma depend on the individual patient's level of control and the extent to which exacerbations are avoided.
- Emergency treatment is more expensive than planned treatment.
- Non-medical economic costs of asthma are substantial. Guideline-determined asthma care can be cost effective.Families can suffer from the financial burden of treating asthma.

Although from the perspective of both the patient and society the cost to control asthma seems high, the cost of not treating asthma correctly is even higher[119]. Proper treatment of the disease poses a challenge for individuals, health care professionals, health care organizations, and governments. There is every reason to believe that the substantial global burden of asthma can be dramatically reduced through efforts by individuals, their health care providers, health care organizations, and local and national governments to improve asthma control.

Detailed reference information about the burden of asthma can be found in the report Global Burden of Asthma*. Further studies of the social and economic burden of asthma and the cost effectiveness of treatment are needed in both developed and developing countries.

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*(http://www.ginasthma.org/ReportItem.asp?l1=2&l2=2&intId=94

FACTORS INFLUENCING THE DEVELOPMENT AND EXPRESSION OF ASTHMA

Factors that influence the risk of asthma can be divided into those that cause the development of asthma and those that trigger asthma symptoms; some do both. The former include host factors (which are primarily genetic) and the latter are usually environmental factors (**Figure 1-2**)[21]. However, the mechanisms whereby they influence the development and expression of asthma are complex and interactive. For example, genes likely interact both with other genes and with environmental factors to determine asthma susceptibility[22,23]. In addition, developmental aspects—such as the maturation of the immune response and the timing of infectious exposures during the first years of life—are emerging as important factors modifying the risk of asthma in the genetically susceptible person.

Figure 1-2. Factors Influencing the Development and Expression of Asthma

HOST FACTORS
- Genetic, e.g.,
  - Genes pre-disposing to atopy
  - Genes pre-disposing to airway hyperresponsiveness
- Obesity
- Sex

ENVIRONMENTAL FACTORS
- Allergens
  - Indoor: Domestic mites, furred animals (dogs, cats, mice), cockroach allergen, fungi, molds, yeasts
  - Outdoor: Pollens, fungi, molds, yeasts
- Infections (predominantly viral)
- Occupational sensitizers
- Tobacco smoke
  - Passive smoking
  - Active smoking
- Outdoor/Indoor Air Pollution
- Diet

Additionally, some characteristics have been linked to an increased risk for asthma, but are not themselves true causal factors. The apparent racial and ethnic differences in the prevalence of asthma reflect underlying genetic variances with a significant overlay of socioeconomic and environmental factors. In turn, the links between asthma and socioeconomic status—with a higher prevalence of asthma in developed than in developing nations, in poor compared to affluent populations in developed nations, and in affluent compared to poor populations in developing nations—likely reflect lifestyle differences such as exposure to allergens, access to health care, etc.

Much of what is known about asthma risk factors comes from studies of young children. Risk factors for the development of asthma in adults, particularly *de novo* in adults who did not have asthma in childhood, are less well defined.

The lack of a clear definition for asthma presents a significant problem in studying the role of different risk factors in the development of this complex disease, because the characteristics that define asthma (e.g., airway hyperresponsiveness, atopy, and allergic sensitization) are themselves products of complex gene-environment interactions and are therefore both features of asthma and risk factors for the development of the disease.

Host Factors

Genetic. Asthma has a heritable component, but it is not simple. Current data show that multiple genes may be involved in the pathogenesis of asthma[24,25], and different genes may be involved in different ethnic groups. The search for genes linked to the development of asthma has focused on four major areas: production of allergen-specific IgE antibodies (atopy); expression of airway hyperresponsiveness; generation of inflammatory mediators, such as cytokines, chemokines, and growth factors; and determination of the ratio between Th1 and Th2 immune responses (as relevant to the hygiene hypothesis of asthma)[26]. Family studies and case-control association analyses have identified a number of chromosomal regions associated with asthma susceptibility. For example, a tendency to produce an elevated level of total serum IgE is co-inherited with airway hyperresponsiveness, and a gene (or genes) governing airway hyperresponsiveness is located near a major locus that regulates serum IgE levels on chromosome 5q[27]. However, the search for a specific gene (or genes) involved in susceptibility to atopy or asthma continues, as results to date have been inconsistent[24,25].

In addition to genes that predispose to asthma there are genes that are associated with the response to asthma treatments. For example, variations in the gene encoding the beta-adrenoreceptor have been linked to differences in subjects' responses to β_2-agonists[28]. Other genes of interest modify the responsiveness to glucocorticosteroids[29] and leukotriene modifiers[30]. These genetic markers will likely become important not only as risk factors in the pathogenesis of asthma but also as determinants of responsiveness to treatment[28,30-33].

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Obesity. Asthma is more frequently observed in obese subjects (Body Mass Index > 30 kg/m^2) and is more difficult to control[124-127,134]. Obese people with asthma have lower lung function and more co-morbidities compared with normal weight people with asthma[131]. The use of systemic glucocorticosteroids and a sedentary lifestyle may promote obesity in severe asthma patients, but in most instances, obesity precedes the development of asthma.

How obesity promotes the development of asthma is still uncertain but it may result from the combined effects of various factors. It has been proposed that obesity could influence airway function due to its effect on lung mechanics, development of a pro-inflammatory state, in addition to genetic, developmental, hormonal or neurogenic influences[35,129,130]. In this regard, obese patients have a reduced expiratory reserve volume, a pattern of breathing that may possibly alter airway smooth muscle plasticity and airway function[34]. Furthermore, the release by adipocytes of various pro-inflammatory cytokines and mediators such as interleukin-6, tumor necrosis factor (TNF)-α, eotaxin, and leptin, combined with a lower level of anti-inflammatory adipokines in obese subjects can favor a systemic inflammatory state although it is unknown how this could influence airway function[131,132].

Sex. Male sex is a risk factor for asthma in children. Prior to the age of 14, the prevalence of asthma is nearly twice as great in boys as in girls[36]. As children get older the difference between the sexes narrows, and by adulthood the prevalence of asthma is greater in women than in men. The reasons for this sex-related difference are not clear. However, lung size is smaller in males than in females at birth[37] but larger in adulthood.

Environmental Factors

There is some overlap between environmental factors that influence the risk of developing asthma, and factors that cause asthma symptoms—for example, occupational sensitizers belong in both categories. However, there are some important causes of asthma symptoms—such as air pollution and some allergens—which have not been clearly linked to the development of asthma. Risk factors that cause asthma symptoms are discussed in detail in **Chapter 4.2.**

Allergens. Although indoor and outdoor allergens are well known to cause asthma exacerbations, their specific role in the development of asthma is still not fully resolved. Birth-cohort studies have shown that sensitization to house dust mite allergens, cat dander, dog dander[38,39], and Aspergillus mold[40] are independent risk factors for asthma-like symptoms in children up to 3 years of age. However, the relationship between allergen exposure and sensitization in children is not straightforward. It depends on the allergen, the dose, the time of exposure, the child's age, and probably genetics as well.

For some allergens, such as those derived from house dust mites and cockroaches, the prevalence of sensitization appears to be directly correlated with exposure[38,41]. However, although some data suggest that exposure to house dust mite allergens may be a causal factor in the development of asthma[42], other studies have questioned this interpretation[43,44]. Cockroach infestation has been shown to be an important cause of allergic sensitization, particularly in inner-city homes[45].

In the case of dogs and cats, some epidemiologic studies have found that early exposure to these animals may protect a child against allergic sensitization or the development of asthma[46-48], but others suggest that such exposure may increase the risk of allergic sensitization[47,49-51]. This issue remains unresolved.

The prevalence of asthma is reduced in children raised in a rural setting, which may be linked to the presence of endotoxin in these environments[52].

Infections. During infancy, a number of viruses have been associated with the inception of the asthmatic phenotype. Respiratory syncytial virus (RSV) and parainfluenzavirus produce a pattern of symptoms including bronchiolitis that parallel many features of childhood asthma[53,54]. A number of long-term prospective studies of children admitted to the hospital with documented RSV have shown that approximately 40% will continue to wheeze or have asthma into later childhood[53]. On the other hand, evidence also indicates that certain respiratory infections early in life, including measles and sometimes even RSV, may protect against the development of asthma[55,56]. The data do not allow specific conclusions to be drawn. Parasite infections do not in general protect against asthma, but infection with hookworm may reduce the risk[120].

The "hygiene hypothesis" of asthma suggests that exposure to infections early in life influences the development of a child's immune system along a "nonallergic" pathway, leading to a reduced risk of asthma and other allergic diseases. Although the hygiene hypothesis continues to be investigated, this mechanism may explain observed associations between family size, birth order, day-care attendance, and the risk of asthma. For example, young children with older siblings and those who attend day care are at increased risk of infections, but enjoy protection against the development of allergic diseases, including asthma later in life[57-59].

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The interaction between atopy and viral infections appears to be a complex relationship[60], in which the atopic state can influence the lower airway response to viral infections, viral infections can then influence the development of allergic sensitization, and interactions can occur when individuals are exposed simultaneously to both allergens and viruses.

Occupational sensitizers. Over 300 substances have been associated with occupational asthma[61-65], which is defined as asthma caused by exposure to an agent encountered in the work environment. These substances include highly reactive small molecules such as isocyanates, irritants that may cause an alteration in airway responsiveness, known immunogens such as platinum salts, and complex plant and animal biological products that stimulate the production of IgE (**Figure 1-3**).

Figure 1-3. Examples of Agents Causing Asthma in Selected Occupations*

Occupation/occupational field	Agent
	Animal and Plant Proteins
Bakers	Flour, amylase
Dairy farmers	Storage mites
Detergent manufacturing	*Bacillus subtilis* enzymes
Electrical soldering	Colophony (pine resin)
Farmers	Soybean dust
Fish food manufacturing	Midges, parasites
Food processing	Coffee bean dust, meat tenderizer, tea, shellfish, amylase, egg proteins, pancreatic enzymes, papain
Granary workers	Storage mites, *Aspergillus*, indoor ragweed, grass
Health care workers	Psyllium, latex
Laxative manufacturing	Ispaghula, psyllium
Poultry farmers	Poultry mites, droppings, feathers
Research workers, veterinarians	Locusts, dander, urine proteins
Sawmill workers, carpenters	Wood dust (western red cedar, oak, mahogany, ebrawood, redwood, Lebanon cedar, African maple, eastern white cedar)
Shipping workers	Grain dust (molds, insects, grain)
Silk workers	Silk worm moths and larvae
	Inorganic chemicals
Beauticians	Persulfate
Plating	Nickel salts
Refinery workers	Platinum salts, vanadium
	Organic chemicals
Automobile painting	Ethanolamine, dissocyanates
Hospital workers	Disinfectants (sulfathiazole, chloramines, formaldehyde, glutaraldehyde), latex
Manufacturing	Antibiotics, piperazine, methyldopa, salbutamol, cimetidine
Rubber processing	Formaldehyde, ethylene diamine, phthalic anhydride
Plastics industry	Toluene dissocyanate, hexamethyl dissocyanate, dephenylmethyl isocyanate, phthalic anhydride, triethylene tetramines, trimellitic anhydride, hexamethyl tetramine, acrylates

**See http://www.bohrf.org.uk for a comprehensive list of known sensitizing agents*

Occupational asthma arises predominantly in adults[66, 67], and occupational sensitizers are estimated to cause about 1 in 10 cases of asthma among adults of working age[68]. Asthma is the most common occupational respiratory disorder in industrialized countries[69]. Occupations associated with a high risk for occupational asthma include farming and agricultural work, painting (including spray painting), cleaning work, and plastic manufacturing[62].

Most occupational asthma is immunologically mediated and has a latency period of months to years after the onset of exposure[70]. IgE-mediated allergic reactions and cell-mediated allergic reactions are involved[71, 72].

Levels above which sensitization frequently occurs have been proposed for many occupational sensitizers. However, the factors that cause some people but not others to develop occupational asthma in response to the same exposures are not well identified. Very high exposures to inhaled irritants may cause “irritant induced asthma” (formerly called the reactive airways dysfunctional syndrome) even in non-atopic persons. Atopy and tobacco smoking may increase the risk of occupational sensitization, but screening individuals for atopy is of limited value in preventing occupational asthma[73]. The most important method of preventing occupational asthma is elimination or reduction of exposure to occupational sensitizers.

Tobacco smoke. Tobacco smoking is associated with accelerated decline of lung function in people with asthma[133], increases asthma severity, may render patients less responsive to treatment with inhaled[121,122] and systemic[74] glucocorticosteroids, and reduces the likelihood of asthma being controlled[75].

Exposure to tobacco smoke both prenatally[135,136] and after birth is associated with measurable harmful effects including a greater risk of developing asthma-like symptoms in early childhood. However, evidence of increased risk of allergic diseases is uncertain[77, 78]. Distinguishing the independent contributions of prenatal and postnatal maternal smoking is problematic[79]. However, studies of lung function immediately after birth have shown that maternal smoking during pregnancy has an influence on lung development[37]. Furthermore, infants of smoking mothers are 4 times more likely to develop wheezing illnesses in the first year of life[79]. In contrast, there is little evidence (based on metaanalysis) that maternal smoking during pregnancy has an effect on allergic sensitization[78]. Exposure to environmental tobacco smoke (passive smoking) increases the risk of lower respiratory tract illnesses in infancy[80] and childhood[81].

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Outdoor/indoor air pollution. The role of outdoor air pollution in causing asthma remains controversial[82]. Children raised in a polluted environment have diminished lung function[83], but the relationship of this loss of function to the development of asthma is not known.

Outbreaks of asthma exacerbations have been shown to occur in relationship to increased levels of air pollution, and this may be related to a general increase in the level of pollutants or to specific allergens to which individuals are sensitized[84-86]. However, the role of pollutants in the development of asthma is less well defined. Similar associations have been observed in relation to indoor pollutants, e.g., smoke and fumes from gas and biomass fuels used for heating and cooling, molds, and cockroach infestations.

Diet. The role of diet, particularly breast-feeding, in relation to the development of asthma has been extensively studied and, in general, the data reveal that infants fed formulas of intact cow's milk or soy protein have a higher incidence of wheezing illnesses in early childhood compared with those fed breast milk[87].

Some data also suggest that certain characteristics of Western diets, such as increased use of processed foods and decreased antioxidant (in the form of fruits and vegetables), increased n-6 polyunsaturated fatty acid (found in margarine and vegetable oil), and decreased n-3 polyunsaturated fatty acid (found in oily fish) intakes have contributed to the recent increases in asthma and atopic disease[88].

MECHANISMS OF ASTHMA

Asthma is an inflammatory disorder of the airways, which involves several inflammatory cells and multiple mediators that result in characteristic pathophysiological changes[89]. In ways that are still not well understood, this pattern of inflammation is strongly associated with airway hyper-responsiveness and asthma symptoms.

Airway Inflammation In Asthma

The clinical spectrum of asthma is highly variable, and different cellular patterns have been observed, but the presence of airway inflammation remains a consistent feature. The airway inflammation in asthma is persistent even though symptoms are episodic, and the relationship between the severity of asthma and the intensity of inflammation is not clearly established[90,91]. The inflammation affects all airways including in most patients the upper respiratory tract and nose but its physiological effects are most pronounced in medium-sized bronchi.

Figure 1-4: Inflammatory Cells in Asthmatic Airways

Mast cells: Activated mucosal mast cells release bronchoconstrictor mediators (histamine, cysteinyl leukotrienes, prostaglandin D_2)[92]. These cells are activated by allergens through high-affinity IgE receptors, as well as by osmotic stimuli (accounting for exercise-induced bronchoconstriction). Increased mast cell numbers in airway smooth muscle may be linked to airway hyperresponsiveness[93].

Eosinophils, present in increased numbers in the airways, release basic proteins that may damage airway epithelial cells. They may also have a role in the release of growth factors and airway remodeling[94].

T lymphocytes, present in increased numbers in the airways, release specific cytokines, including IL-4, IL-5, IL-9, and IL-13, that orchestrate eosinophilic inflammation and IgE production by B lymphocytes[95]. An increase in Th2 cell activity may be due in part to a reduction in regulatory T cells that normally inhibit Th2 cells. There may also be an increase in inKT cells, which release large amounts of T helper 1 (Th1) and Th2 cytokines[96].

Dendritic cells sample allergens from the airway surface and migrate to regional lymph nodes, where they interact with regulatory T cells and ultimately stimulate production of Th2 cells from na ve T cells[97].

Macrophages are increased in number in the airways and may be activated by allergens through low-affinity IgE receptors to release inflammatory mediators and cytokines that amplify the inflammatory response[98].

Neutrophil numbers are increased in the airways and sputum of patients with severe asthma and in smoking asthmatics, but the pathophysiological role of these cells is uncertain and their increase may even be due to glucocorticosteroid therapy[99] .

Figure 1-5: Airway Structural Cells Involved in the Pathogenesis of Asthma

Airway epithelial cells sense their mechanical environment, express multiple inflammatory proteins in asthma, and release cytokines, chemokines, and lipid mediators. Viruses and air pollutants interact with epithelial cells.

Airway smooth muscle cells express similar inflammatory proteins to epithelial cells[100].

Endothelial cells of the bronchial circulation play a role in recruiting inflammatory cells from the circulation into the airway.

Fibroblasts and myofibroblasts produce connective tissue components, such as collagens and proteoglycans, that are involved in airway remodeling.

Airway nerves are also involved. Cholinergic nerves may be activated by reflex triggers in the airways and cause bronchoconstriction and mucus secretion. Sensory nerves, which may be sensiti ed by inflammatory stimuli including neurotrophins, cause reflex changes and symptoms such as cough and chest tightness, and may release inflammatory neuropeptides[101].

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Figure 1-6: Key Mediators of Asthma

Chemokines are important in the recruitment of inflammatory cells into the airways and are mainly expressed in airway epithelial cells[102]. Eotaxin is relatively selective for eosinophils, whereas thymus and activation-regulated chemokines (TARC) and macrophage-derived chemokines (MDC) recruit Th2 cells.

Cysteinyl leukotrienes are potent bronchoconstrictors and proinflammatory mediators mainly derived from mast cells and eosinophils. They are the only mediator whose inhibition has been associated with an improvement in lung function and asthma symptoms[103].

Cytokines orchestrate the inflammatory response in asthma and determine its severity[104]. Key cytokines include IL-1β and TNF-α, which amplify the inflammatory response, and GM-CSF, which prolongs eosinophil survival in the airways. Th2-derived cytokines include IL-5, which is required for eosinophil differentiation and survival; IL-4, which is important for Th2 cell differentiation; and IL-13, needed for IgE formation.

Histamine is released from mast cells and contributes to bronchoconstriction and to the inflammatory response.

Nitric oxide (NO), a potent vasodilator, is produced predominantly from the action of inducible nitric oxide synthase in airway epithelial cells[105]. Exhaled NO is increasingly being used to monitor the effectiveness of asthma treatment, because of its reported association with the presence of inflammation in asthma[106].

Prostaglandin D_2 is a bronchoconstrictor derived predominantly from mast cells and is involved in Th2 cell recruitment to the airways.

Figure 1-7: Structural Changes in Asthmatic Airways

Subepithelial fibrosis results from the deposition of collagen fibers and proteoglycans under the basement membrane and is seen in all asthmatic patients, including children, even before the onset of symptoms but may be influenced by treatment. Fibrosis occurs in other layers for the airway wall, with deposition of collagen and proteoglycans.

Airway smooth muscle increases, due both to hypertrophy (increased size of individual cells) and hyperplasia (increased cell division), and contributes to the increased thickness of the airway wall[109]. This process may relate to disease severity and is caused by inflammatory mediators, such as growth factors.

Blood vessels in airway walls proliferate the influence of growth factors such as vascular endothelial growth factor (VEGF) and may contribute to increased airway wall thickness.

Mucus hypersecretion results from increased numbers of goblet cells in the airway epithelium and increased size of submucosal glands.

The pattern of inflammation in the airways appears to be similar in all clinical forms of asthma, whether allergic, non-allergic, or aspirin-induced, and at all ages.

Inflammatory cells. The characteristic pattern of inflammation found in allergic diseases is seen in asthma, with activated mast cells, increased numbers of activated eosinophils, and increased numbers of T cell receptor

Figure 1-8: Airway Narrowing in Asthma

Airway smooth muscle contraction in response to multiple bronchoconstrictor mediators and neurotransmitters is the predominant mechanism of airway narrowing and is largely reversed by bronchodilators.

Airway edema is due to increased microvascular leakage in response to inflammatory mediators. This may be particularly important during acute exacerbations.

Airway thickening due to structural changes, often termed "remodeling," may be important in more severe disease and is not fully reversible by current therapy.

Mucus hypersecretion may lead to luminal occlusion ("mucus plugging") and is a product of increased mucus secretion and inflammatory exudates.

invariant natural killer T cells and T helper 2 lymphocytes (Th2), which release mediators that contribute to symptoms (**Figure 1-4**). Structural cells of the airways also produce inflammatory mediators, and contribute to the persistence of inflammation in various ways (**Figure 1-5**). Inflammatory mediators. Over 100 different mediators are now recognized to be involved in asthma and mediate the complex inflammatory response in the airways (**Figure 1-6**).

Structural changes in the airways. In addition to the inflammatory response, there are characteristic structural changes, often described as airway remodeling, in the airways of asthma patients (**Figure 1-7**). Some of these changes are related to the severity of the disease and may result in relatively irreversible narrowing of the airways[107,108]. These changes may represent repair in response to chronic inflammation.

Pathophysiology

Airway narrowing is the final common pathway leading to symptoms and physiological changes in asthma. Several factors contribute to the development of airway narrowing in asthma[109-111](**Figure 1-8**).

Airway hyperresponsiveness. Airway hyperresponsiveness, the characteristic functional abnormality of asthma, results in airway narrowing in a patient with asthma in response to a stimulus that would be innocuous in a normal person. In turn, this airway narrowing leads to variable airflow limitation and intermittent symptoms. Airway hyperresponsiveness is linked to both inflammation and repair of the airways and is partially reversible with therapy. Its mechanisms (**Figure 1-9**) are incompletely understood.

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Figure 1-9: Mechanisms of Airway Hyperresponsiveness

Excessive contraction of airway smooth muscle may result from increased volume and/or contractility of airway smooth muscle cells[112].

Uncoupling of airway contraction as a result of inflammatory changes in the airway wall may lead to excessive narrowing of the airways and a loss of the maximum plateau of contraction found in normal airways when bronchoconstrictor substances are inhaled.

Thickening of the airway wall by edema and structural changes amplifies airway narrowing due to contraction of airway smooth muscle for geometric reasons[112].

Sensory nerves may be sensitized by inflammation, leading to exaggerated bronchoconstriction in response to sensory stimuli.

Special Mechanisms

Acute exacerbations. Transient worsening of asthma may occur as a result of exposure to risk factors for asthma symptoms[113], or "triggers," such as exercise, air pollutants, and even certain weather conditions, e.g., thunderstorms[86]. More prolonged worsening is usually due to viral infections of the upper respiratory tract (particularly rhinovirus and respiratory syncytial virus)[114] or allergen exposure which increase inflammation in the lower airways (acute or chronic inflammation) that may persist for several days or weeks.

Nocturnal asthma. The mechanisms accounting for the worsening of asthma at night are not completely understood but may be driven by circadian rhythms of circulating hormones such as epinephrine, cortisol, and melatonin and neural mechanisms such as cholinergic tone. An increase in airway inflammation at night has been reported. This might reflect a reduction in endogenous anti-inflammatory mechanisms[115].

Irreversible airflow limitation. Some patients with severe asthma develop progressive airflow limitation that is not fully reversible with currently available therapy. This may reflect the changes in airway structure in chronic asthma[116].

Difficult-to-treat asthma. The reasons why some patients develop asthma that is difficult to manage and relatively insensitive to the effects of glucocorticosteroids are not well understood. Common associations are poor compliance with treatment and psychological and psychiatric disorders. However, genetic factors may contribute in some. Many of these patients have difficult-to-treat asthma from the onset of the disease, rather than progressing from milder asthma. In these patients airway closure leads to air trapping and hyperinflation. Although the pathology appears broadly similar to other forms of asthma, there is an increase in neutrophils, more small airway involvement, and more structural changes.

Smoking and asthma. Tobacco smoking makes asthma more difficult to control, results in more frequent exacerbations and hospital admissions, and produces a more rapid decline in lung function and an increased risk of death[117]. Asthma patients who smoke may have a neutrophil-predominant inflammation in their airways and are poorly responsive to glucocorticosteroids[121,122].

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CHAPTER

2

DIAGNOSIS AND CLASSIFICATION

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KEY POINTS:

- A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough, and chest tightness.
- Measurements of lung function (spirometry or peak expiratory flow) provide an assessment of the severity of airflow limitation, its reversibility, and its variability, and provide confirmation of the diagnosis of asthma.
- Measurements of allergic status can help to identify risk factors that cause asthma symptoms in individual patients.
- Extra measures may be required to diagnose asthma in children 5 years and younger and in the elderly, and occupational asthma.
- For patients with symptoms consistent with asthma,but normal lung function, measurement of airway responsiveness may help establish the diagnosis.
- Asthma has been classified by severity in previous reports. However, asthma severity may change over time, and depends not only on the severity of the underlying disease but also its responsiveness to treatment.
- To aid in clinical management, a classification of asthma by level of control is recommended.
- Clinical control of asthma is defined as:

  -No (twice or less/week) daytime symptoms
  -No limitations of daily activities, including exercise
  -No nocturnal symptoms or awakening because of asthma
  -No (twice or less/week) need for reliever treatment
  -Normal or near-normal lung function
  -No exacerbations

INTRODUCTION

A correct diagnosis of asthma is essential if appropriate drug therapy is to be given. Asthma symptoms may be intermittent and their significance may be overlooked by patients and physicians, or, because they are non-specific, they may result in misdiagnosis (for example of wheezy bronchitis, COPD, or the breathlessness of old age). This is particularly true among children, where misdiagnoses include various forms of bronchitis or croup, and lead to inappropriate treatment.

CLINICAL DIAGNOSIS

Medical History

Symptoms. A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough, and chest tightness[1]. Episodic symptoms after an incidental allergen exposure, seasonal variability of symptoms and a positive family history of asthma and atopic disease are also helpful diagnostic guides. Asthma associated with rhinitis may occur intermittently, with the patient being entirely asymptomatic between seasons or it may involve seasonal worsening of asthma symptoms or a background of persistent asthma. The patterns of these symptoms that strongly suggest an asthma diagnosis are variability; precipitation by non-specific irritants, such as smoke, fumes, strong smells, or exercise; worsening at night; and responding to appropriate asthma therapy. In some sensitized individuals, asthma may be exacerbated by seasonal increases in specific aeroallergens[2]. Examples include Alternaria, and birch, grass, and ragweed pollens.

Useful questions to consider when establishing a diagnosis of asthma are described in **Figure 2-1**.

Figure 2-1. Questions to Consider in the Diagnosis of Asthma

- Has the patient had an attack or recurrent attacks of wheezing?
- Does the patient have a troublesome cough at night?
- Does the patient wheeze or cough after exercise?
- Does the patient experience wheezing, chest tightness, or cough after exposure to airborne allergens or pollutants?
- Do the patient's colds “go to the chest” or take more than 10 days to clear up?
- Are symptoms improved by appropriate asthma treatment?

Cough-variant asthma. Patients with cough-variant asthma[3] have chronic cough as their principal, if not only, symptom. It is particularly common in children, and is often more problematic at night; evaluations during the day can be normal. For these patients, documentation of variability in lung function or of airway hyperresponsiveness, and possibly a search for sputum eosinophils, are particularly important[4]. Cough-variant asthma must be distinguished from so-called eosinophilic bronchitis in which patients have cough and sputum eoinophils but normal indices of lung function when assessed by spirometry and airway hyperresponsiveness[5].

Other diagnoses to be considered are cough-induced by angiotensin-converting-enzyme (ACE) inhibitors, gastroesophageal reflux, postnasal drip, chronic sinusitis, and vocal cord dysfunction[6].

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Exercise-induced bronchoconstriction. Physical activity is an important cause of asthma symptoms for most asthma patients, and for some it is the only cause. Exercise-induced bronchoconstriction typically develops within 5-10 minutes after completing exercise (it rarely occurs during exercise). Patients experience typical asthma symptoms, or sometimes a troublesome cough, which resolve spontaneously within 30-45 minutes. Some forms of exercise, such as running, are more potent triggers[7]. Exercise-induced bronchoconstriction may occur in any climatic condition, but it is more common when the patient is breathing dry, cold air and less common in hot, humid climates[8].

Rapid improvement of post-exertion symptoms after inhaled β_2-agonist use, or their prevention by pretreatment with an inhaled β_2-agonist before exercise, supports a diagnosis of asthma. Some children with asthma present only with exercise-induced symptoms. In this group, or when there is doubt about the diagnosis, exercise testing is helpful. An 8-minute running protocol is easily performed in clinical practice and can establish a firm diagnosis of asthma[9].

Physical Examination

Because asthma symptoms are variable, the physical examination of the respiratory system may be normal. The most usual abnormal physical finding is wheezing on auscultation, a finding that confirms the presence of airflow limitation. However, in some people with asthma, wheezing may be absent or only detected when the person exhales forcibly, even in the presence of significant airflow limitation. Occasionally, in severe asthma exacerbations, wheezing may be absent owing to severely reduced airflow and ventilation. However, patients in this state usually have other physical signs reflecting the exacerbation and its severity, such as cyanosis, drowsiness, difficulty speaking, tachycardia, hyperinflated chest, use of accessory muscles, and intercostal recession.

Other clinical signs are only likely to be present if patients are examined during symptomatic periods. Features of hyperinflation result from patients breathing at a higher lung volume in order to increase outward retraction of the airways and maintain the patency of smaller airways (which are narrowed by a combination of airway smooth muscle contraction, edema, and mucus hypersecretion). The combination of hyperinflation and airflow limitation in an asthma exacerbation markedly increases the work of breathing.

Tests for Diagnosis and Monitoring

Measurements of lung function. The diagnosis of asthma is usually based on the presence of characteristic symptoms. However, measurements of lung function, and particularly the demonstration of reversibility of lung function abnormalities, greatly enhance diagnostic confidence. This is because patients with asthma frequently have poor recognition of their symptoms and poor perception of symptom severity, especially if their asthma is long-standing[10] . Assessment of symptoms such as dyspnea and wheezing by physicians may also be inaccurate. Measurement of lung function provides an assessment of the severity of airflow limitation, its reversibility and its variability, and provides confirmation of the diagnosis of asthma. Although measurements of lung function do not correlate strongly with symptoms or other measures of disease control in either adults[11] or children[12], these measures provide complementary information about different aspects of asthma control.

Various methods are available to assess airflow limitation, but two methods have gained widespread acceptance for use in patients over 5 years of age. These are spirometry, particularly the measurement of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), and peak expiratory flow (PEF) measurement.

Predicted values of FEV_1, FVC, and PEF based on age, sex, and height have been obtained from population studies. These are being continually revised, and with the exception of PEF for which the range of predicted values is too wide, they are useful for judging whether a given value is abnormal or not. If precision is needed, for example, in the conduct of a clinical trial, use of a more rigorous definition (lower limit of normal -LLN) should be considered.

The terms **reversibility** and **variability** refer to changes in symptoms accompanied by changes in airflow limitation that occur spontaneously or in response to treatment. The term reversibility is generally applied to rapid improvements in FEV_1 (or PEF), measured within minutes after inhalation of a rapid-acting bronchodilator—for example after 200-400 ug salbutamol (albuterol)[13]—or more sustained improvement over days or weeks after the introduction of effective controller treatment such as inhaled glucocorticosteroids[13] . Variability refers to improvement or deterioration in symptoms and lung function occurring over time. Variability may be experienced over the course of one day (when it is called diurnal variability), from day to day, from month to month, or seasonally. Obtaining a history of variability is an essential component of the diagnosis of asthma. In addition, variability forms part of the assessment of asthma control.

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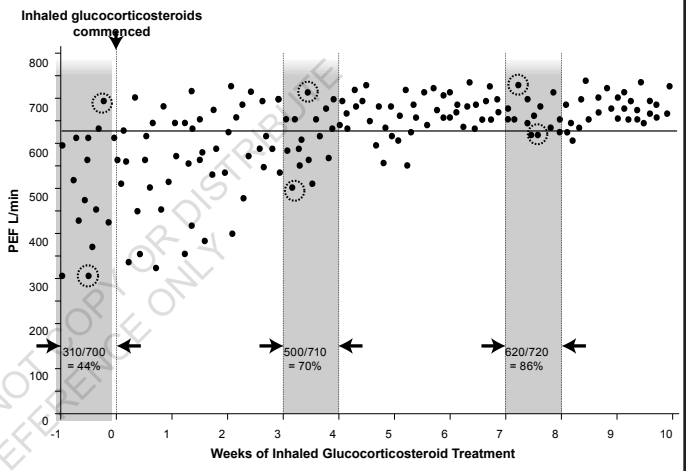
Spirometry is the recommended method of measuring airflow limitation and reversibility to establish a diagnosis of asthma. Measurements of FEV_1 and FVC are undertaken during a forced expiratory maneuver using a spirometer. Recommendations for the standardization of spirometry have been published[13-15]. The degree of reversibility in FEV_1 which indicates a diagnosis of asthma is generally accepted as 12% and 200 ml from the pre-bronchodilator value[13]. However most asthma patients will not exhibit reversibility at each assessment, particularly those on treatment, and the test therefore lacks sensitivity. Repeated testing at different visits is advised.

Spirometry is reproducible, but effort-dependent. Therefore, proper instructions on how to perform the forced expiratory maneuver must be given to patients, and the highest value of three recordings taken. As ethnic differences in spirometric values have been demonstrated, appropriate predictive equations for FEV_1 and FVC should be established for each patient. The normal range of values is wider and predicted values are less reliable in young people (< age 20) and in the elderly (> age 70). Because many lung diseases may result in reduced FEV_1, a useful assessment of airflow limitation is the ratio of FEV_1 to FVC. The FEV_1/FVC ratio is normally greater than 0.75 to 0.80, and possibly greater than 0.90 in children. Any values less than these suggest airflow limitation.

Peak expiratory flow measurements are made using a peak flow meter and can be an important aid in both diagnosis and monitoring of asthma. Modern PEF meters are relatively inexpensive, portable, plastic, and ideal for patients to use in home settings for day-to-day objective measurement of airflow limitation. However, measurements of PEF are not interchangeable with other measurements of lung function such as FEV_1 in either adults[16] or children[17]. PEF can underestimate the degree of airflow limitation, particularly as airflow limitation and gas trapping worsen. Because values for PEF obtained with different peak flow meters vary and the range of predicted values is too wide, PEF measurements should preferably be compared to the patient's own previous best measurements[18] using his/her own peak flow meter. The previous best measurement is usually obtained when the patient is asymptomatic or on full treatment and serves as a reference value for monitoring the effects of changes in treatment.

Careful instruction is required to reliably measure PEF because PEF measurements are effort-dependent. Most commonly, PEF is measured first thing in the morning before treatment is taken, when values are often close to their lowest, and last thing at night when values are usually higher. One method of describing diurnal PEF variability is as the amplitude (the difference between the maximum and the minimum value for the day), expressed as a percentage of the mean daily PEF value, and averaged over 1-2 weeks[19]. Another method of describing PEF variability is the minimum morning pre-bronchodilator PEF over 1 week, expressed as a percent of the recent best (Min%Max) (**Figure 2-2**)[19]. This latter method has been suggested to be the best PEF index of airway lability for clinical practice because it requires only a once-daily reading, correlates better than any other index with airway hyperresponsiveness, and involves a simple calculation.

Figure 2-2. Measuring PEF Variability*



*PEF chart of a 27-year-old man with long-standing, poorly controlled asthma, before and after the start of inhaled glucocorticosteroid treatment. With treatment, PEF levels increased, and PEF variability decreased, as seen by the increase in Min%Max (lowest morning PEF/highest PEF %) over 1 week.

PEF monitoring is valuable in a subset of asthmatic patients and can be helpful:

- *To confirm the diagnosis of asthma.* Although spirometry is the preferred method of documenting airflow limitation, a 60 L/min (or 20% or more of pre-bronchodilator PEF) improvement after inhalation of a bronchodilator[20], or diurnal variation in PEF of more than 20% (with twice daily readings, more than 10% [21]) suggests a diagnosis of asthma.

- *To improve control of asthma, particularly in patients with poor perception of symptoms*[10]. Asthma management plans which include self-monitoring of symptoms or PEF for treatment of exacerbations have been shown to improve asthma outcomes[22]. It is easier to discern the response to therapy from a PEF chart than from a PEF diary, provided the same chart format is consistently used[23].

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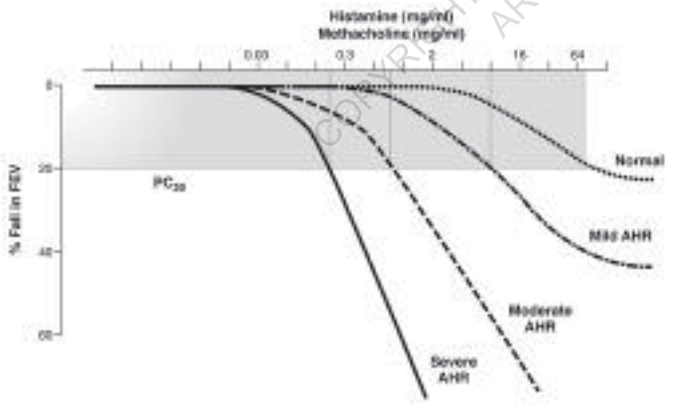
- *To identify environmental (including occupational) causes of asthma symptoms.* This involves the patient monitoring PEF daily or several times each day over periods of suspected exposure to risk factors in the home or workplace, or during exercise or other activities that may cause symptoms, and during periods of non-exposure.

Measurement of airway responsiveness. For patients with symptoms consistent with asthma, but normal lung function, measurements of airway responsiveness to direct airway challenges such as inhaled methacholine and histamine or indirect airway challenges such as inhaled mannitol[83] or exercise challenge may help establish a diagnosis of asthma[24] . Measurements of airway responsiveness reflect the "sensitivity" of the airways to factors that can cause asthma symptoms, sometimes called "triggers," and the test results are usually expressed as the provocative concentration (or dose) of the agonist causing a given fall (often 20%) in FEV_1 (**Figure 2-3**). These tests are sensitive for a diagnosis of asthma, but have limited specificity[25]. This means that a negative test can be useful to exclude a diagnosis of persistent asthma in a patient who is not taking inhaled glucocorticosteroid treatment, but a positive test does not always mean that a patient has asthma[26]. This is because airway hyperresponsiveness has been described in patients with allergic rhinitis[27] and in those with airflow limitation caused by conditions other than asthma, such as cystic fibrosis[28], bronchiectasis, and chronic obstructive pulmonary disease (COPD)[29].

Figure 2-3. Measuring Airway Responsiveness*



*Airway responsiveness to inhaled methacholine or histamine in a normal subject, and in asthmatics with mild, moderate, and severe airway hyperresponsiveness. Asthmatics have an increased sensitivity and an increased maximal broncho- constrictor response to the agonist. The response to the agonist is usually expressed as the provocative concentration causing a 20% decline in FEV_1 (PC_{20}).

Non-invasive markers of airway inflammation. The evaluation of airway inflammation associated with asthma may be undertaken by examining spontaneously produced or hypertonic saline-induced sputum for eosinophilic or neutrophilic inflammation[30]. In addition, levels of exhaled nitric oxide (FeNO)[31] and carbon monoxide (FeCO)[32] have been suggested as non-invasive markers of airway inflammation in asthma. Levels of FeNO are elevated in people with asthma (who are not taking inhaled glucocorticosteroids) compared to people without asthma, yet these findings are not specific for asthma. Neither sputum eosinophilia nor FeNO have been evaluated prospectively as an aid in asthma diagnosis, but these measurements are being evaluated for potential use in determining optimal treatment[33,34,56], although it has been shown that the use of FeNO as a measure of asthma control does not improve control or enable reduction in dose of inhaled glucocorticosteroid[55].

Measurements of allergic status. Because of the strong association between asthma and allergic rhinitis, the presence of allergies, allergic diseases, and allergic rhinitis in particular, increases the probability of a diagnosis of asthma in patients with respiratory symptoms. Moreover, the presence of allergies in asthma patients (identified by skin testing or measurement of specific IgE in serum) can help to identify risk factors that cause asthma symptoms in individual patients. Deliberate provocation of the airways with a suspected allergen or sensitizing agent may be helpful in the occupational setting, but is not routinely recommended, because it is rarely useful in establishing a diagnosis, requires considerable expertise and can result in life-threatening bronchospasm[35].

Skin tests with allergens represent the primary diagnostic tool in determining allergic status. They are simple and rapid to perform, and have a low cost and high sensitivity. However, when improperly performed, skin tests can lead to falsely positive or negative results. Measurement of specific IgE in serum does not surpass the reliability of results from skin tests and is more expensive. The main limitation of methods to assess allergic status is that a positive test does not necessarily mean that the disease is allergic in nature or that it is causing asthma, as some individuals have specific IgE antibodies without any symptoms and it may not be causally involved. The relevant exposure and its relation to symptoms must be confirmed by patient history. Measurement of total IgE in serum has no value as a diagnostic test for atopy.

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DIAGNOSTIC CHALLENGES AND DIFFERENTIAL DIAGNOSIS

The differential diagnosis in patients with suspected asthma differs among different age groups: infants, children, young adults, and the elderly.

Children 5 years and Younger

In early life, the presence of sensitization to common allergens, atopy, is a major risk factor for subsequent development of asthma. In addition, atopy also predicts that asthma may be more severe when it does develop.

The diagnosis of asthma in early childhood is challenging and has to be based largely on clinical judgment and an assessment of symptoms and physical findings. Since the use of the label "asthma" for wheezing in children has important clinical consequences, it must be distinguished from other causes persistent and recurrent wheeze.

Episodic wheezing and cough is very common even in children who do not have asthma and particularly in those under age 3[36]. Three categories of wheezing have been described in children 5 years and younger:

- *Transient early wheezing,* which is often outgrown in the first 3 years. This is often associated with prematurity and parental smoking.

- *Persistent early-onset wheezing* (before age 3). These children typically have recurrent episodes of wheezing associated with acute viral respiratory infections, have no evidence of atopy[37] and, unlike children in the next category of late onset wheezing/ asthma, have no family history of atopy. The symptoms normally persist through school age and are still present at age 12 in a large proportion of children. The cause of the episode is usually the respiratory syncytial virus in children younger than age 2, while other viruses predominate in older preschool children.

- *Late-onset wheezing/asthma*. These children have asthma which often persists throughout childhood and into adult life[38, 39]. They typically have an atopic background, often with eczema, and airway pathology is characteristic of asthma.

The following categories of symptoms are highly suggestive of a diagnosis of asthma: frequent episodes of wheeze (more than once a month), activity-induced cough or wheeze, nocturnal cough in periods without viral infections, absence of seasonal variation in wheeze, and symptoms that persist after age 3. A simple clinical index based on the presence of a wheeze before the age of 3, and the presence of one major risk factor (parental history of asthma or eczema) or two of three minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis) has been shown to predict the presence of asthma in later childhood[38]. However, treating children at risk with inhaled glucocorticosteroids has not been shown to affect the development of asthma[40].

Alternative causes of recurrent wheezing must be considered and excluded. These include:

- Chronic rhino-sinusitis
- Gastroesophageal reflux
- Recurrent viral lower respiratory tract infections
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Tuberculosis
- Congenital malformation causing narrowing of the intrathoracic airways
- Foreign body aspiration
- Primary ciliary dyskinesia syndrome
- Immune deficiency
- Congenital heart disease

Neonatal onset of symptoms (associated with failure to thrive), vomiting-associated symptoms, or focal lung or cardiovascular signs suggest an alternative diagnosis and indicate the need for further investigations.

A useful method for confirming the diagnosis of asthma in children 5 years and younger is a trial of treatment with short-acting bronchodilators and inhaled glucocorticosteroids. Marked clinical improvement during the treatment and deterioration when treatment is stopped supports a diagnosis of asthma. Use of spirometry and other measures recommended for older children and adults such as airway responsiveness and markers of airway inflammation is difficult and several require complex equipment[41] making them unsuitable for routine use. However, children 4 to 5 years old can be taught to use a PEF meter, but to ensure reliability parental supervision is required[42].

Older Children and Adults

A careful history and physical examination, together with the demonstration of reversible and variable airflow obstruction (preferably by spirometry), will in most instances confirm the diagnosis. The following categories of alternative diagnoses need to be considered:

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- Upper airway obstruction and inhaled foreign bodies[43]
- Vocal cord dysfunction[44]
- Other forms of obstructive lung disease, particularly COPD

- Non-obstructive forms of lung disease (e.g., diffuse parenchymal lung disease)
- Non-respiratory causes of symptoms (e.g., left ventricular failure)

Because asthma is a common disease, it can be found in association with any of the above diagnoses, which complicates the diagnosis as well as the assessment of severity and control. This is particularly true when asthma is associated with hyperventilation, vocal cord dysfunction, or COPD. Careful assessment and treatment of both the asthma and the comorbidity is often necessary to establish the contribution of each to a patient's symptoms.

The Elderly

Undiagnosed asthma is a frequent cause of treatable respiratory symptoms in the elderly, and the frequent presence of comorbid diseases complicates the diagnosis. Wheezing, breathlessness, and cough caused by left ventricular failure is sometimes labeled "cardiac asthma," a misleading term, the use of which is discouraged. The presence of increased symptoms with exercise and at night may add to the diagnostic confusion because these symptoms are consistent with either asthma or left ventricular failure. Use of beta-blockers, even topically (for glaucoma) is common in this age group. A careful history and physical examination, combined with an ECG and chest X-ray, usually clarifies the picture. In the elderly, distinguishing asthma from COPD is particularly difficult, and may require a trial of treatment with bronchodilators and/or oral/inhaled glucocorticosteroids.

Asthma treatment and assessment and attainment of control in the elderly are complicated by several factors: poor perception of symptoms, acceptance of dyspnea as being "normal" in old age, and reduced expectations of mobility and activity.

Occupational Asthma

Asthma acquired in the workplace is a diagnosis that is frequently missed. Because of its insidious onset, occupational asthma is often misdiagnosed as chronic bronchitis or COPD and is therefore either not treated at all or treated inappropriately. The development of new symptoms of rhinitis, cough, and/or wheeze particularly in non-smokers should raise suspicion. Detection of asthma of occupational origin requires a systematic inquiry about work history and exposures. The diagnosis requires a defined history of occupational exposure to known or suspected sensitizing agents; an absence of asthma symptoms before beginning employment; or a definite worsening of asthma after employment. A relationship between symptoms and the workplace (improvement in symptoms away from work and worsening of symptoms on returning to work) can be helpful in establishing a link between suspected sensitizing agents and asthma[45].

Since the management of occupational asthma frequently requires the patient to change his or her job, the diagnosis carries considerable socioeconomic implications and it is important to confirm the diagnosis objectively. This may be achieved by specific bronchial provocation testing[46], although there are few centers with the necessary facilities for specific inhalation testing. Another method is to monitor PEF at least 4 times a day for a period of 2 weeks when the patient is working and for a similar period away from work[47-50]. The increasing recognition that occupational asthma can persist, or continue to deteriorate, even in the absence of continued exposure to the offending agent[51], emphasizes the need for an early diagnosis so that appropriate strict avoidance of further exposure and pharmacologic intervention may be applied. Publications provide an evidence-based approach to the identification of occupational asthma and compare specific inhalation challenge testing with alternative tests for confirming the responsible agents[52].

Distinguishing Asthma from COPD

Both asthma and COPD are major chronic obstructive airways diseases that involve underlying airway inflammation. COPD is characterized by airflow limitation that is not fully reversible, is usually progressive, and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Individuals with asthma who are exposed to noxious agents (particularly cigarette smoking) may develop fixed airflow limitation and a mixture of "asthma-like" inflammation and "COPD-like" inflammation. Thus, even though asthma can usually be distinguished from COPD, in some individuals who develop chronic respiratory symptoms and fixed airflow limitation, it may be difficult to differentiate the two diseases. A symptom-based questionnaire for differentiating COPD and asthma for use by primary health care professionals is available[53,54].

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CLASSIFICATION OF ASTHMA

Etiology

Many attempts have been made to classify asthma according to etiology, particularly with regard to environmental sensitizing agents. However, such a classification is limited by the existence of patients in whom no environmental cause can be identified. Despite this, an effort to identify an environmental cause for asthma (for example, occupational asthma) should be part of the initial assessment to enable the use of avoidance strategies in asthma management. Describing patients as having allergic asthma is usually of little benefit in guiding treatment, unless a single specific trigger agent can be identified.

Phenotype

There is increasing awareness of heterogeneity in the manifestations of asthma and in its response to treatment. This is often described in terms of 'phenotypes'[57,58], the characteristics which result from the interaction between a patient's genetic makeup and their environment. Several different clinical phenotypes are recognized on the basis of cluster analysis of clinical and other features of asthma, e.g. aspirin-induced asthma, exacerbation-prone asthma and the search for distinctive pathological or molecular features that could explain these clinical patterns continues. Most work has been done on inflammatory phenotypes, identified using sputum induction. Patients with eosinophilic and non-eosinophilic phenotypes have been shown to differ in their clinical response to inhaled glucocorticosteroids[59,60], and at a group level, inflammatory markers may be predictive of risk of exacerbation after glucocorticosteroid reduction[61]. Inflammatory phenotypes appear to be moderately stable over time, although data are limited[62,63]. At present, since few clinicians have access to qualified sputum laboratories, identification of the inflammatory phenotype is most likely to be useful for patients with severe asthma or in the context of research.

Asthma Control

Asthma control may be defined in a variety of ways. In lay terms, control may indicate disease prevention, or even cure. However, in asthma, where neither of these are realistic options at present, it refers to control of the manifestations of disease. The aim of treatment should be

Figure 2-4. LEVELS OF ASTHMA CONTROL

A. Assessment of current clinical control (preferably over 4 weeks)

Characteristic	Controlled (All of the following)	Partly Controlled (Any measure present)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma*†
Limitation of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/ rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV_1)‡	Normal	<80% predicted or personal best (if known)	

B. Assessment of Future Risk (risk of exacerbations, instability, rapid decline in lung function, side-effects)

Features that are associated with increased risk of adverse events in the future include:

Poor clinical control, frequent exacerbations in past year*, ever admission to critical care for asthma, low FEV_1, exposure to cigarette smoke, high dose medications

* Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate
† By definition, an exacerbation in any week makes that an uncontrolled asthma week
‡ Without administration of bronchodilator.
Lung function is not a reliable test for children 5 years and younger

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to achieve and maintain control for prolonged periods[64] with due regard to the safety of treatment, potential for adverse effects, and the cost of treatment required to achieve this goal. Therefore, the assessment of asthma control should include not only control of the clinical manifestations (symptoms, night waking, reliever use, activity limitation, lung function), but also control of the expected future risk to the patient such as exacerbations, accelerated decline in lung function, and side-effects of treatment. In general, the achievement of good clinical control of asthma leads to reduced risk of exacerbations[65]. However, certain patients may continue to experience exacerbations in spite of adequate interval control. Smokers are less likely to achieve control and remain at risk of exacerbations[66]. It should be noted that inhaled glucocorticosteroids both improve clinical control and reduce future risk, but some pharmacological agents are more effective in improving features of clinical control, while others are relatively more effective at reducing exacerbations. Thus, for some patient phenotypes, treatment may be selected to address the predominant problem.

Figure 2-4 describes the clinical characteristics of *Controlled, Partly Controlled* and *Uncontrolled* asthma. This is a working scheme based on current opinion and has not been formally validated. However, this classification has been shown to correlate well with the Asthma Control Test[67] and with assessment of asthma control according to the US National Expert Panel Report 3 guidelines[68,69]. In clinical practice, this classification should be used in conjunction with an assessment of the patient's clinical condition and the potential risks and benefits of changing treatment.

Several standardized measures for assessing clinical control of asthma have been developed, which score the goals of treatment as continuous variables and provide numerical values to distinguish different levels of control. Examples of validated instruments are the Asthma Control Questionnaire (ACQ) (www.qoltech.co.uk/Asthma1.htm)[70], the Asthma Control Test (ACT) (www.asthmacontrol.com)[71], the Childhood Asthma Control Test (C-ACT)[72], the Asthma Therapy Assessment Questionnaire (ATAQ) (www.ataqinstrument.com)[73], and the Asthma Control Scoring System[74]. Few of these instruments include a measure of lung function. They are being promoted for use not only in research but for patient care as well, even in the primary care setting. Some are suitable for self-assessment of asthma control by patients[75], and some are available in many languages, on the Internet, and in paper form and may be completed by patients prior to, or during, consultations with their health care provider. They have the potential to improve the assessment of asthma control, providing a reproducible objective measure that may be charted over time (week by week or month by month) and representing an improvement in communication between patient and health care professional. Their value in clinical use, as distinct from research settings, has yet to be demonstrated but will likely become evident in coming years. All of these tools are subject to copyright restrictions, and some have fees associated with their use in research.

There is considerable interest in controlling not only the clinical manifestations of asthma, but also the inflammatory and patho-physiological features of the disease. There is evidence that reducing inflammation with controller therapy achieves good clinical control and reduces the risk of exacerbations. In addition, inflammatory and patho-physiological markers may be predictors of future risk of exacerbations and decline in lung function, independent of the patient's level of clinical control[66,76]. Biomarker-guided treatment appears, primarily, to be of value in asthma phenotypes in which there is dissociation between measures of clinical control and airway inflammation. For example, treatment based on the proportion of eosinophils in sputum has resulted in a reduction of exacerbations or minimization of doses of inhaled glucocorticosteroids in patients with uncontrolled asthma in spite of moderate levels of treatment[77,78].

However, in primary care, because of the cost and/or unavailability of tests such as endobronchial biopsy and measurement of sputum eosinophils and exhaled nitric oxide[30-34], the current recommendation is that treatment should be aimed at controlling the clinical features of disease, including lung function abnormalities.

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Asthma Severity

For patients not receiving inhaled glucocorticosteroid treatment, previous GINA documents subdivided asthma by severity based on the level of symptoms, airflow limitation, and lung function variability into four categories: Intermittent, Mild Persistent, Moderate Persistent, or Severe Persistent, although this classification was often erroneously applied to patients already on treatment[79]. A copy of this classification system is archived at www.ginasthma.org. It is important to recognize, however, that asthma severity involves both the severity of the underlying disease and its responsiveness to treatment[80]. Thus, asthma could present with severe symptoms and airflow obstruction, but become completely controlled with low-dose treatment. In addition, severity is not a static feature of an individual patient's asthma, but may change over months or years. The main limitation of this previous method of classification of asthma severity was its poor value in predicting what treatment would be required and what a patient's response to that treatment might be. For this reason, an assessment of asthma control at initial

presentation and periodically during treatment is more relevant and useful[81] .

In view of these limitations, asthma severity is now by consensus classified on the basis of the intensity of treatment required to achieve good asthma control[79,80]. Mild asthma is asthma that can be well-controlled with low intensity treatment such as low-dose inhaled glucocorticosteroids, leukotriene modifiers or cromones. Severe asthma is asthma that requires high intensity treatment, e.g. GINA Step 4, to maintain good control, or where good control is not achieved despite high intensity treatment[82]. It is recognized that different asthma phenotypes may have different levels of responsiveness to conventional treatment. As phenotype-specific treatment becomes available, asthma previously considered to be severe could become mild.

Terminology around asthma severity is confusing because "severity" is also used to describe the magnitude of airway obstruction or the intensity of symptoms. Patients will often perceive their asthma as severe if they have intense or frequent symptoms, but it is important to convey that this may merely represent inadequate treatment. Because the terms "control" and "severity" are used in other contexts in lay language, it is important that health professionals communicate clearly how the words are used in the context of asthma.

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CHAPTER

3

ASTHMA

TREATMENTS

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KEY POINTS:

- Medications to treat asthma can be classified as controllers or relievers. Controllers are medications taken daily on a long-term basis to keep asthma under clinical control chiefly through their anti-inflammatory effects. Relievers are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve its symptoms.
- Asthma treatment can be administered in different ways—inhaled, orally, or by injection. The major advantage of inhaled therapy is that drugs are delivered directly into the airways, producing higher local concentrations with significantly less risk of systemic side effects.
- Inhaled glucocorticosteroids are the most effective controller medications currently available.
- Rapid-acting inhaled β_2-agonists are the medications of choice for relief of bronchoconstriction and for the pretreatment of exercise-induced bronchoconstriction, in both adults and children of all ages.
- Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates the need to reassess treatment.

INTRODUCTION

The goal of asthma treatment is to achieve and maintain clinical control. Medications to treat asthma can be classified as controllers or relievers. **Controllers** are medications taken daily on a long-term basis to keep asthma under clinical control chiefly through their anti-inflammatory effects. They include inhaled and systemic glucocorticosteroids, leukotriene modifiers, long-acting inhaled β_2-agonists in combination with inhaled glucocorticosteroids, sustained-release theophylline, cromones, and anti-IgE. Inhaled glucocorticosteroids are the most effective controller medications currently available. **Relievers** are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve its symptoms. They include rapid-acting inhaled β_2-agonists, inhaled anticholinergics, short-acting theophylline, and short-acting oral β_2-agonists.

ASTHMA MEDICATIONS: ADULTS

Route of Administration

Asthma treatment for adults can be administered in different ways—inhaled, orally or parenterally (by subcutaneous, intramuscular, or intravenous injection). The major advantage of inhaled therapy is that drugs are delivered directly into the airways, producing higher local concentrations with significantly less risk of systemic side effects.

Inhaled medications for asthma are available as pressurized metered-dose inhalers (MDIs), breath-actuated MDIs, dry powder inhalers (DPIs), soft mist inhalers, and nebulized or "wet" aerosols* . Inhaler devices differ in their efficiency of drug delivery to the lower respiratory tract, depending on the form of the device, formulation of medication, particle size, velocity of the aerosol cloud or plume (where applicable), and ease with which the device can be used by the majority of patients. Individual patient preference, convenience, and ease of use may influence not only the efficiency of drug delivery but also patient adherence to treatment and long-term control.

Pressurized MDIs (pMDIs) require training and skill to coordinate activation of the inhaler and inhalation. Medications in these devices can be dispensed as a suspension in chlorofluorocarbons (CFCs) or as a solution in hydrofluoroalkanes (HFAs). For a pMDI containing CFCs, the use of a spacer (holding chamber) improves drug delivery, increases lung deposition, and may reduce local and systemic side effects[1]. However, CFC inhaler devices are being phased out due to the impact of CFCs upon the atmospheric ozone layer, and are being replaced by HFA devices. For pMDIs containing bronchodilators, the switch from CFC to HFA inhalers does not result in a change in efficacy at the same nominal dose[2]. However, for some glucocorticosteroids, the HFA formulations provide an aerosol of smaller particle size that results in less oral deposition (with associated reduction in oral side effects), and correspondingly greater lung deposition[3-5]. Clinicians are advised to consult the package inserts of each product to confirm the recommended dose equivalent to currently used drugs. Some of these comparisons are provided in **Figure 3-1**.

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*Information on various inhaler devices available can be found on the GINA Website (http://www.ginasthma.org).

Pressurized MDIs may be used by patients with asthma of any severity, including during exacerbations. Breath-actuated aerosols may be helpful for patients who have difficulty using the "press and breathe" pressurized MDI[6]. Soft mist inhalers appear to require less coordination. Dry powder inhalers are generally easier to use, but they require a minimal inspiratory flow rate and may prove difficult for some patients. DPIs differ with respect to the fraction of ex-actuator dose delivered to the lung. For some drugs, the dose may need to be adjusted when switching from an MDI[6] to a DIP[7]. Nebulized aerosols are rarely indicated for the treatment of chronic asthma in adults[8].

CONTROLLER MEDICATIONS

Inhaled glucocorticosteroids*

Role in therapy -Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma. Studies have demonstrated their efficacy in reducing asthma symptoms[9], improving quality of life[9], improving lung function[9], decreasing airway hyperresponsiveness[10], controlling airway inflammation[11], reducing frequency and severity of exacerbations[12], and reducing asthma mortality[13]. However, they do not cure asthma, and when they are discontinued deterioration of clinical control follows within weeks to months in a proportion of patients[14,15].

Inhaled glucocorticosteroids differ in potency and bioavailability, but because of relatively flat dose-response relationships in asthma relatively few studies have been able to confirm the clinical relevance of these differences[191]. **Figure 3-1** lists approximately equipotent doses of different inhaled glucocorticosteroids based upon the available efficacy literature, but the categorization into dosage categories does not imply that clear dose-response relationships have been demonstrated for each drug. The efficacy of some products varies when administered via different inhaler devices[16]. Most of the benefit from inhaled glucocorticosteroids is achieved in adults at relatively low doses, equivalent to 400 ug of budesonide per day[17]. Increasing to higher doses provides little further benefit in terms of asthma control but increases the risk of side effects[17,18]. However, there is marked individual variability of responsiveness to inhaled glucocorticosteroids and because of this and the recognized poor adherence to treatment with inhaled glucocorticosteroids, many patients will require higher doses to achieve full therapeutic benefit. As tobacco smoking reduces the responsiveness to inhaled glucocorticosteroids, higher doses may be required in patients who smoke[240].

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Figure 3-1. Estimated Equipotent Daily Doses of Inhaled Glucocorticosteriods for Adults†

Drug	Low Daily Dose (µg)	Medium Daily Dose (µg)	High Daily Dose (µg)‡
Beclomethasone dipropionate - CFC	200-500	>500-1000	>1000-2000
Beclomethasone dipropionate - HFA	100 - 250	>250 - 500	>500 - 1000
Budesonide*	200-400	>400-800	>800-1600
Ciclesonide*	80-160	>160-320	>320-1280
Flunisolide	500-1000	>1000-2000	>2000
Fluticasone propionate	100-250	>250-500	>500-1000
Mometasone furoate*	200	≥400	≥800
Triamcinolone acetonide	400-1000	>1000-2000	>2000

†Comparisons based on efficacy data
‡Patients considered for high daily doses except for short periods should be referred to a specialist for assessment to consider alternative combinations of controllers. Maximum recommended doses are arbitrary but with prolonged use are associated with increased risk of systemic side effects.
*Approved for once-daily dosing in mild patients

NOTES:

- The most important determinant of approprioate dosing is the clinician's judgement of the patient's response therapy. The clinician must monitor the patient's response in terms of clinical control and adjust the dose accordingly. Once control of asthma is achieved, the dose of medication should carefully be titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effects.
- Designation of low, medium, and high doses is provided from manufacturers' recommendations where possible. Clear demonstration of dose-response relationships is seldom provided or available. The principle is therefore to establish the minimum effective controlling dose in each patient, as higher doses may not be more effective and are likely to be associated with greater potential for adverse effects
- As CFC preparations are taken from the market, medication inserts for HFA preparations should be carefully reviewed by the clinician for the equivalent correct dosage.

**In this section recommendations for doses of inhaled glococorticosteriods are given as "µ/day budesonide or equivalent," because a majority of the clinical literature on these medications uses this standard*

To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of inhaled glucocorticosteroids[211]. There is, however, a clear relationship between the dose of inhaled glucocorticosteroids and the prevention of severe acute exacerbations of asthma[12], although there appear to be differences in response according to symptom/inflammation phenotype[212]. Therefore, some patients with severe asthma may benefit from long-term treatment with higher doses of inhaled glucocorticosteroids.

Side effects: Local adverse effects from inhaled glucocorticosteroids include oropharyngeal candidiasis, dysphonia, and occasionally coughing from upper airway irritation. For pressurized MDIs the prevalence of these effects may be reduced by using certain spacer devices[1]. Mouth washing (rinsing with water, gargling, and spitting out) after inhalation may reduce oral candidiasis. The use of prodrugs that are activated in the lungs but not in the pharynx (e.g., ciclesonide[19] and beclometasone), and new formulations and devices that reduce oropharyngeal deposition, may minimize such effects without the need for a spacer or mouth washing.

Inhaled glucocorticosteroids are absorbed from the lung, accounting for some degree of systemic bioavailability. The risk of systemic adverse effects from an inhaled glucocorticosteroid depends upon its dose and potency, the delivery system, systemic bioavailability, first-pass metabolism (conversion to inactive metabolites) in the liver, and half-life of the fraction of systemically absorbed drug (from the lung and possibly gut)[20]. Therefore, the systemic effects differ among the various inhaled glucocorticosteroids. Several comparative studies have demonstrated that ciclesonide, budesonide, and fluticasone propionate at equipotent doses have less systemic effect[20-23]. Current evidence suggests that in adults, systemic effects of inhaled glucocorticosteroids are not a problem at doses of 400 µg or less budesonide or equivalent daily.

The systemic side effects of long-term treatment with high doses of inhaled glucocorticosteroids include easy bruising[24], adrenal suppression[1,20], and decreased bone mineral density[25,26]. A meta-analysis of case-control studies of non-vertebral fractures in adults using inhaled glucocorticosteroids (BDP or equivalent) indicated that in older adults, the relative risk of non-vertebral fractures increases by about 12% for each 1000 µg/day increase in the dose BDP or equivalent but that the magnitude of this risk was considerably less than other common risk factors for fracture in the older adult[213]. Inhaled glucocorticosteroids have also been associated with cataracts[27,29] and glaucoma in cross-sectional studies[28], but there is no evidence of posterior-subcapsular cataracts in prospective studies[30-32].

One difficulty in establishing the clinical significance of such adverse effects lies in dissociating the effect of high-dose inhaled glucocorticosteroids from the effect of courses of oral glucocorticosteroids taken by patients with severe asthma. There is no evidence that use of inhaled glucocorticosteroids increases the risk of pulmonary infections, including tuberculosis, and inhaled glucocorticosteroids are not contraindicated in patients with active tuberculosis[33].

Leukotriene modifiers.

Role in therapy -Leukotriene modifiers include cysteinyl-leukotriene 1 (CysLT1) receptor antagonists (montelukast, pranlukast, and zafirlukast) and a 5-lipoxygenase inhibitor (zileuton). Clinical studies have demonstrated that leukotriene modifiers have a small and variable bronchodilator effect, reduce symptoms including cough[34], improve lung function, and reduce airway inflammation and asthma exacerbations[35-37]. They may be used as an alternative treatment for adult patients with mild persistent asthma[38-40], and some patients with aspirin-sensitive asthma respond well to leukotriene modifiers[41]. However, when used alone as controller, the effect of leukotriene modifiers are generally less than that of low doses of inhaled glucocorticosteroids, and, in patients already on inhaled glucocorticosteroids, leukotriene modifiers cannot substitute for this treatment without risking the loss of asthma control[42,43].

Leukotriene modifiers used as add-on therapy may reduce the dose of inhaled glucocorticosteroids required by patients with moderate to severe asthma[44], and may improve asthma control in patients whose asthma is not controlled with low or high doses of inhaled glucocorticosteroids[43,45-47]. With the exception of one study that demonstrated equivalence in preventing exacerbations[48], several studies have demonstrated that leukotriene modifiers are less effective than long-acting inhaled β_2-agonists as add-on therapy[49-51,192]. A controlled release formulation of zileuton allows this medication to be used on a twice daily basis with effects equivalent to that of standard zileuton used four times a day[203].

Side effects -Leukotriene modifiers are well tolerated, and few if any class-related effects have so far been recognized. Zileuton has been associated with liver toxicity[204], and monitoring of liver tests is recommended during treatment with this medication. No association was found between Churg-Strauss syndrome and leukotriene modifiers after controlling for asthma drug use, although it is not possible to rule out modest associations given that Churg-Strauss syndrome is so rare and so highly correlated with asthma severity[52].

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Long-acting inhaled bronchodilators

Role in therapy - Long-acting inhaled β_2-agonists, including formoterol and salmeterol, should not be used as monotherapy in asthma as these medications do not appear to influence airway inflammation in asthma. They are most effective when combined with inhaled glucocorticosteroids[55,56,193], and this combination therapy is the preferred treatment when a medium dose of inhaled glucocorticosteroid alone fails to achieve control of asthma. The addition of long-acting inhaled β_2-agonists to a daily regimen of inhaled glucocorticosteroids improves symptom scores, decreases nocturnal asthma symptoms, improves lung function, decreases the use of rapid-acting inhaled β_2-agonists[57-59], reduces the number of exacerbations[12,57-62], does not increase the risk of asthma-related hospitalizations[214], and achieves clinical control of asthma in more patients, more rapidly, and at a lower dose of inhaled glucocorticosteroids than inhaled glucocorticosteroids given alone[63].

This greater efficacy of combination treatment has led to the development of fixed combination inhalers that deliver both glucocorticosteroid and long-acting β_2-agonist simultaneously (fluticasone propionate plus salmeterol, budesonide plus formoterol, mometasone plus formoterol, beclometasone plus formoterol). Controlled studies have shown that delivering this therapy in a combination inhaler is as effective as giving each drug separately[64,65]. Fixed combination inhalers are more convenient for patients, may increase compliance[66], and ensure that the long-acting β_2-agonist is always accompanied by a glucocorticosteroid. In addition, combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance. Both components of budesonide-formoterol given as needed contribute to enhanced protection from severe exacerbations in patients receiving combination therapy for maintenance[67,194] and provide improvements in asthma control at relatively low doses of inhaled glucocorticosteroids[67-70]. (See Appendix B, GINA Pocket Guide updated 2009 for information on Asthma Combination Medications For Adults and Children 5 Years and Older.)

Long-acting β_2-agonists when used as a combination medication with inhaled glucocorticosteroids may also be used to prevent exercise-induced bronchospasm, and for this purpose may provide longer protection than rapid-acting inhaled β_2-agonists[71]. Salmeterol and formoterol provide a similar duration of bronchodilation and protection against bronchoconstrictors, but there are pharmacological differences between them. Formoterol has a more rapid onset of action than salmeterol[72, 73], which may make formoterol suitable for symptom relief as well as symptom prevention[68].

Tiotropium, a long-acting inhaled anticholinergic bronchodilator, has been studied in adults with uncontrolled asthma and compared with salmeterol, doubling the dose of inhaled glucocorticosteroid and as add-on to inhaled glucocorticosteroids and salmeterol[231,233]. One study showed comparable bronchodilator effects with no significant changes on asthma control[232]. Another study showed that adding tiotropium to patients not controlled on inhaled glucocorticosteroids and long-acting β_2-agonists improved lung function but not symptoms[233]. The studies have been relatively short-term and no effect on exacerbations has so far been reported. There are no data about these medications in children.

Side effects - Therapy with long-acting inhaled β_2-agonists causes fewer systemic adverse effects—such as cardiovascular stimulation, skeletal muscle tremor, and hypokalemia—than oral therapy. The regular use of rapid-acting β_2-agonists in both short and long acting forms may lead to relative refractoriness to β_2-agonists[74]. Based on data indicating a possible increased risk of asthma-related death associated with the use of salmeterol in a small group of individuals[75] long-acting β_2-agonists should not be used as a substitute for inhaled or oral glucocorticosteroids, and should only be used in combination with an appropriate dose of inhaled glucocorticosteroid as determined by a physician[215,234]. Some meta-analyses of studies of long-acting β_2-agonists have shown numerically very small increases in the number of deaths in patients receiving long-acting β_2-agonists in combination with inhaled glucocorticosteroids, when compared to inhaled glucocorticosteroids alone. Where present, the effect sizes are extremely small and need to be balanced against the benefits in improved asthma control and reduction in exacerbations that these medications bring when combined with inhaled glucocorticosteroids[205,214]. No influence of β_2-adrenergic receptor phenotypes upon the efficacy or safety of long-acting β_2-agonist therapy has been observed when administered in combination with inhaled glucocorticosteroids whether by the single inhaler for maintenance and relief method or at a regular fixed dose in adults[206,220].

Theophylline

Role in therapy -Theophylline is a bronchodilator and, when given in a lower dose, has modest anti-inflammatory properties[77-79]. It is available in sustained-release formulations that are suitable for once-or twice-daily In addition, combination inhalers containing formoterol and dosing. Data on the relative efficacy of theophylline as a long-term controller is lacking. However, available evidence suggests that it has little effect as a first-line controller[80]. It may used as add-on therapy in patients who do not achieve control on inhaled glucocorticosteroids alone[81-83].

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Additionally in such patients the withdrawal of sustained-release theophylline has been associated with deterioration of control[84]. As add-on therapy, theophylline is less effective than long-acting inhaled β_2-agonists[85,86].

Side effects -Side effects of theophylline, particularly at higher doses (10 mg/kg body weight/day or more), are significant and reduce their usefulness. Side effects can be reduced by careful dose selection and monitoring, and generally decrease or disappear with continued use. Adverse effects include gastrointestinal symptoms, loose stools, cardiac arrhythmias, seizures, and even death. Nausea and vomiting are the most common early events. Monitoring is advised when a high dose is started, if the patient develops an adverse effect on the usual dose, when expected therapeutic aims are not achieved, and when conditions known to alter theophylline metabolism exist. For example, febrile illness, pregnancy, and anti-tuberculosis medications[87] reduce blood levels of theophylline, while liver disease, congestive heart failure, and certain drugs including cimetidine, some quinolones, and some macrolides increase the risk of toxicity. Lower doses of theophylline, which have been demonstrated to provide the full anti-inflammatory benefit of this drug[82], are associated with less frequent side effects, and plasma theophylline levels in patients on low-dose therapy need not be measured unless overdose is suspected.

Cromones: sodium cromoglycate and nedocromil sodium.

Role in therapy – The role of sodium cromoglycate and nedocromil sodium in long-term treatment of asthma in adults is limited. Efficacy has been reported in patients with mild persistent asthma and exercise-induced bronchospasm. Their anti-inflammatory effect is weak and they are less effective than a low dose of inhaled glucocorticosteroid[88].

Side effects -Side effects are uncommon and include coughing upon inhalation and sore throat. Some patients find the taste of nedocromil sodium unpleasant.

Long-acting oral β_2-agonists.

Role in therapy -Long acting oral β_2-agonists include slow release formulations of salbutamol, terbutaline, and bambuterol, a prodrug that is converted to terbutaline in the body. They are used only on rare occasions when additional bronchodilation is needed.

Side effects -The side effect profile of long-acting oral β_2-agonists is higher than that of inhaled β_2-agonists, and includes cardiovascular stimulation (tachycardia), anxiety, and skeletal muscle tremor. Adverse cardiovascular reactions may also occur with the combination of oral β_2-agonists and theophylline. Regular use of long-acting oral β_2-agonists as monotherapy is likely to be harmful and these medications must always be given in combination with inhaled glucocorticosteroids.

Anti-IgE*

Role in therapy -Anti-IgE (omalizumab) is a treatment option limited to patients with elevated serum levels of IgE. Its current indication is for patients with severe allergic asthma[89] who are uncontrolled on inhaled glucocorticosteroids, although the dose of concurrent treatment has varied in different studies. Improved asthma control is reflected by fewer symptoms, less need for reliever medications, and fewer exacerbations[90,91], although this was not confirmed in all studies[235]. Further investigations will likely provide additional clarification of the role of anti-IgE in other clinical settings.

Side effects: As indicated by several studies involving asthma patients ages 12 years and older[207], who were already receiving treatment with glucocorticosteroids (inhaled and/or oral) and long-acting β_2-agonists[89], anti-IgE appears to be safe as add-on therapy[92-94] , including patients generally considered to be at high risk for exacerbations[229] . Withdrawal of glucocorticosteroids facilitated by anti-IgE therapy has led to unmasking the presence of Churg-Strauss syndrome in a small number of patients[221]. Clinicians successful in initiating glucocorticosteroid withdrawal using anti-IgE should be aware of this side effect.

Systemic glucocorticosteroids.

Role in therapy -Long-term oral glucocorticosteroid therapy (that is, for periods longer than two weeks as a glucocorticosteroid "burst") may be required for severely uncontrolled asthma, but its use is limited by the risk of significant adverse effects. The therapeutic index (effect/side effect) of long-term inhaled glucocorticosteroids is always more favorable than long-term systemic glucocorticosteroids in asthma[95,96]. If oral glucocorticosteroids have to be administered on a long-term basis, attention must be paid to measures that minimi e the systemic side effects. Oral preparations are preferred over parenteral (intramuscular or intravenous) for long-term therapy because of their lower mineralocorticoid effect, relatively short half-life, and lesser effects on striated muscle, as well as the greater flexibility of dosing that permits titration to the lowest acceptable dose that maintains control.

*Visit GINA website, www.ginasthma.org for GRADE review of question "In adults with asthma, does monoclonal anti-IgE, omalizumab, compared to placebo improve patient outcomes?"

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Figure 3-2. Glucocorticosteroids and Osteoporosis

Asthma patients on high-dose inhaled glucocorticosteroids or oral glucocorticosteroids at any dose are considered at risk of developing osteoporosis and fractures, but it is not certain whether this risk exists for patients on lower doses of inhaled glucocorticosteroids[1]. Physicians should consider monitoring patients who are at risk. The following summarizes monitoring and management but more detailed guidelines for the management of steroid-induced osteoporosis are available[2,3].

Screening - Chest X-rays should be reviewed for the presence of vertebral fractures. Wedging, compressions, and cod-fishing of vertebral bodies are synonymous with fractures, and indicate those who are at the highest risk for future fractures. In men, this may be a better predictor of fracture risk than bone mineral density (BMD). BMD measurements by dual energy X-ray absorptiomety (DXA scan) should be undertaken in:

- Any patient with asthma who has been taking oral glucocorticosteroids for over 6 months duration at a mean daily dose of 7.5 mg prednisone/prednisolone or above.
- Post-menopausal women taking over 5 mg prednisone/prednisolone daily for more than 3 months.
- Any patient with asthma and a history of vertebral or other fractures that may be related to osteoporosis.

Bone density measurements should also be offered to:

- Post-menopausal women taking > 2 mg inhaled BDP or equivalent daily
- Any patient who is receiving frequent short courses of high-dose oral glucocorticosteroids

Osteoporosis is present if the bone density in lumbar spine or femoral neck shows :

- T-score below -2.5 (2.5 standard deviations below the mean value of young normal subjects of the same sex in patients 19-69 years).
- Z-score below -1 (1 standard deviation below the predicted value for age and sex).

Follow-up scanning - Repeat scanning should be done:

- In 2 years in those whose initial scan was not osteoporotic but in whom treatment (as above) with oral glucocorticosteroids continues.
- In 1 year for those with osteoporosis on the first scan who are started on osteoporosis treatment.

Management

- General measures include avoidance of smoking, regular exercise, use of the lowest dose of oral glucocorticosteroid possible, and a good dietary intake of calcium.
- For women with osteoporosis up to 10 years post-menopausal offer bisphosphonates or hormone therapy[4,5,6] (**Evidence A**).
- For men, pre-menopausal women, and women more than 10 years since menopause consider treatment with a bisphosphonate[7] (**Evidence A**).

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Side effects -The systemic side effects of long-term oral or parenteral glucocorticosteroid treatment include osteoporosis, arterial hypertension, diabetes, hypothalamic-pituitary-adrenal axis suppression, obesity, cataracts, glaucoma, skin thinning leading to cutaneous striae and easy bruising, and muscle weakness. Patients with asthma who are on long-term systemic glucocorticosteroids in any form should receive preventive treatment for osteoporosis (**Figure 3-2**)[97-99]. Although it is rare, withdrawal of oral glucocorticosteroids can elicit adrenal failure or unmask underlying disease, such as Churg-Strauss Syndrome[100]. Caution and close medical supervision are recommended when considering the use of systemic glucocorticosteroids in patients with asthma who also have tuberculosis, parasitic infections, osteoporosis, glaucoma, diabetes, severe depression, or peptic ulcers. Fatal herpes virus infections have been reported among patients who are exposed to these viruses while taking systemic glucocorticosteroids, even short bursts.

Oral anti-allergic compounds.

Role in therapy -Several oral anti-allergic compounds have been introduced in some countries for the treatment of mild to moderate allergic asthma. These include tranilast, repirinast, tazanolast, pemirolast, ozagrel, seratrodast, amlexanox, and ibudilast. In general, their anti-asthma effect appears to be limited[101], but studies on the relative efficacy of these compounds are needed before recommendations can be made about their role in the long-term treatment of asthma.

Side effects -Sedation is a potential side effect of some of these medications.

Other controller therapies.

Role in therapy -Various therapeutic regimens to reduce the dose of oral glucocorticosteroids required by patients with severe asthma have been proposed. These medications should be used only in selected patients under the supervision of an asthma specialist, as their potential steroid-sparing effects may not outweigh the risk of serious side effects. Two meta-analyses of the steroid-sparing effect of low-dose methotrexate showed a small overall benefit, but a relatively high frequency of adverse effects[102,103]. This small potential to reduce the impact of glucocorticosteroid side effects is probably insufficient to offset the adverse effects of methotrexate[104]. Cyclosporin[105] and gold[106,107] have also been shown to be effective in some patients. The macrolide, troleandomycin, has a small steroid-sparing effect when used with systemic methylprednisolone, but its effect may result from the macrolide decreasing metabolism of the glucocorticosteroid and therefore not improving safety. However, other effects of the long-term use of macrolides in asthma remain under study[108]. The use of intravenous immunoglobulin is not recommended[109-111]. Data on a human monoclonal antibody against tumor necrosis factor (TNF)-alpha suggest that the risk benefit equation does not favor the use of this class of treatments in severe asthma[216].

Side effects -Macrolide use is frequently associated with nausea, vomiting, and abdominal pain and occasionally liver toxicity. Methotrexate also causes gastrointestinal symptoms, and on rare occasions hepatic and diffuse pulmonary parenchymal disease, and hematological and teratogenic effects.

Allergen-specific immunotherapy.

Role in therapy -The role of specific immunotherapy in adult asthma is limited. Appropriate immunotherapy requires the identification and use of a single well-defined clinically relevant allergen. The later is administered in progressively higher doses in order to induce tolerance. A Cochrane review[112] that examined 75 randomized controlled trials of specific immunotherapy compared to placebo confirmed the efficacy of this therapy in asthma in reducing symptom scores and medication requirements, and improving allergen-specific and non-specific airway hyperresponsiveness. Similar modest effects were identified in a systematic review of sublingual immunotherapy (SLIT)[196]. Specific immunotherapy has long-term clinical effects and the potential of preventing development of asthma in children with allergic rhino conjunctivitis up to 7 years after treatment termination[208]. However, in view of the relatively modest effect of allergen-specific immunotherapy compared to other treatment options, these benefits must be weighed against the risk of adverse effects and the inconvenience of the prolonged course of injection therapy, including the minimum half-hour wait required after each injection. Specific immunotherapy should be considered only after strict environmental avoidance and pharmacologic intervention, including inhaled glucocorticosteroids, have failed to control a patient's asthma[113]. There are no studies that compare specific immunotherapy with pharmacologic therapy for asthma. The value of immunotherapy using multiple allergens does not have support.

Side effects -Local and systemic side effects may occur in conjunction with specific immunotherapy administration. Reactions localized to the injection site may range from a minimal immediate wheal and flare to a large, painful, delayed allergic response. Systemic effects may include anaphylactic reactions, which may be life threatening, as well as severe exacerbations of asthma. Deaths from specific immunotherapy have occurred in patients with severe asthma.

Reliever Medications

Reliever medications act quickly to relieve bronchoconstriction and its accompanying acute symptoms.

Rapid-acting inhaled β_2-agonists.

Role in therapy -Rapid-acting inhaled β_2-agonists are the medications of choice for relief of bronchospasm during acute exacerbations of asthma and for the pretreatment of exercise-induced bronchoconstriction. They include salbutamol, terbutaline, fenoterol, levalbuterol HFA[209], reproterol, and pirbuterol. Formoterol, a long-acting β_2-agonist, is approved for symptom relief because of its rapid onset of action, but it should only be used for this purpose in patients on regular controller therapy with inhaled glucocorticosteroids[230].

Rapid-acting inhaled β_2-agonists should be used only on an as-needed basis at the lowest dose and frequency required. Increased use, especially daily use, is a warning of deterioration of asthma control and indicates the need to reassess treatment. Similarly, failure to achieve a quick and sustained response to β_2-agonist treatment during an exacerbation mandates medical attention, and may indicate the need for short-term treatment with oral glucocorticosteroids.

Side effects -Use of oral β_2-agonists given in standard doses are associated with more adverse systemic effects

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such as tremor and tachycardia than occur with inhaled preparations.

Systemic glucocorticosteroids.

Role in therapy -Although systemic glucocorticosteroids are not usually thought of as reliever medications, they are important in the treatment of severe acute exacerbations because they prevent progression of the asthma exacerbation, reduce the need for referral to emergency departments and hospitalization, prevent early relapse after emergency treatment, and reduce the morbidity of the illness. The main effects of systemic glucocorticosteroids in acute asthma are only evident after 4 to 6 hours. Oral therapy is preferred and is as effective as intravenous hydrocortisone[114]. A typical short course of oral glucocorticosterods for an exacerbation is 40-50 mg[115] prednisolone given daily for 5 to 10 days depending on the severity of the exacerbation. When symptoms have subsided and lung function has approached the patient's personal best value, the oral glucocorticosteroids can be stopped or tapered, provided that treatment with inhaled glucocorticosteroids continues[116]. Intramuscular injection of glucocorticosteroids has no advantage over a short course of oral glucocorticosteroids in preventing relapse[114,116].

Side effects -Adverse effects of short-term high-dose systemic therapy are uncommon but include reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, rounding of the face, mood alteration, hypertension, peptic ulcer, and aseptic necrosis of the femur.

Anticholinergics.

Role in therapy -Anticholinergic bronchodilators used in asthma include ipratropium bromide and oxitropium bromide. Inhaled ipratropium bromide is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists. A meta-analysis of trials of inhaled ipratropium bromide used in association with an inhaled β_2-agonists in acute asthma showed that the anticholinergic produces a statistically significant, albeit modest, improvement in pulmonary function, and significantly reduces the risk of hospital admission[117]. The benefits of ipratropium bromide in the long-term management of asthma have not been established, although it is recognized as an alternative bronchodilator for patients who experience such adverse effects as tachycardia, arrhythmia, and tremor from rapid-acting β_2-agonists.

Side effects -Inhalation of ipratropium or oxitropium can cause a dryness of the mouth and a bitter taste. There is no evidence for any adverse effects on mucus secretion[118].

Theophylline.

Role in therapy -Short-acting theophylline may be considered for relief of asthma symptoms[119]. The role of theophylline in treating exacerbations remains controversial. Short-acting theophylline may provide no additive bronchodilator effect over adequate doses of rapid-acting β_2-agonists, but it may benefit respiratory drive.

Side effects -Theophylline has the potential for significant adverse effects, although these can generally be avoided by appropriate dosing and monitoring. Short-acting theophylline should not be administered to patients already on long-term treatment with sustained-release theophylline unless the serum concentration of theophylline is known to be low and/or can be monitored.

Short-acting oral β_2-agonists.

Short-acting oral β_2-agonists are appropriate for use in the few patients who are unable to use inhaled medication. However, their use is associated with a higher prevalence of adverse effects.

Complementary And Alternative Medicine

The roles of complementary and alternative medicine in adult asthma treatment are limited because these approaches have been insufficiently researched and their effectiveness is largely unproven. Generally, these therapies have not been validated by conventional standards. Although the psychotherapeutic role of the therapist forms part of the placebo effect of all treatments, this aspect is viewed as an integral part of the so-called holistic approach used by practitioners of complementary and alternative methods, and mitigates against performance of the large, multicenter, placebo-controlled randomized studies required to confirm efficacy. However, without these the relative efficacy of these alternative measures will remain unknown.

Complementary and alternative therapies include acupuncture, homeopathy, herbal medicine, Ayurvedic medicine, ionizers, osteopathy and chiropractic manipulation, and speleotherapy among others. Apart from those mentioned below, there have been few satisfactory studies from which conclusions about their efficacy can be drawn.

Dietary supplements, including selenium therapy[197] are not of proven benefit and the use of a low sodium diet as an adjunctive therapy to normal treatment has no additional therapeutic benefit in adults with asthma. In addition, it has no effect on bronchial reactivity to methacholine[217].

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Evidence from the most rigorous studies available to date indicates that spinal manipulation is not an effective treatment for asthma[121]. Systematic reviews indicate that homeopathic medicines have no effects beyond placebo[222]. A systematic review of yoga interventions for asthma found no convincing evidence of benefit; the quality of studies was generally poor[236].

Several studies of breathing and/or relaxation techniques for asthma and/or dysfunctional breathing, including the Buteyko method and the Papworth method[210], have shown improvements in symptoms, short-acting β_2-agonist use, quality of life and/or psychological measures, but not in physiological outcomes. A study of two physiologically-contrasting breathing techniques, in which contact with health professionals and instructions about rescue inhaler use were matched, showed similar improvements in reliever and inhaled glucocorticosteroid use in both groups[122]. This suggests that perceived improvement with breathing techniques may be largely due to factors such as relaxation, voluntary reduction in use of rescue medication, or engagement of the patient in their care. Breathing techniques may thus provide a useful supplement to conventional asthma management strategies, particularly in anxious patients or those habitually over-using rescue medication. The cost of some programs may be a potential limitation.

Side effects -Acupuncture-associated hepatitis B, bilateral pneumothorax, and burns have been described. Side effects of other alternative and complementary medicines are largely unknown. However, some popular herbal medicines could potentially be dangerous, as exemplified by the occurrence of hepatic veno-occlusive disease associated with the consumption of the commercially available herb comfrey. Comfrey products are sold as herbal teas and herbal root powders, and their toxicity is due to the presence of pyrroli idine alkaloids.

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ASTHMA TREATMENT: CHILDREN**

Route of Administration

Inhaled therapy is the cornerstone of asthma treatment for children of all ages. Almost all children can be taught to effectively use inhaled therapy. Different age groups require different inhalers for effective therapy, so the choice of inhaler must be individualized. Information about the lung dose for a particular drug formulation is seldom available for children, and marked differences exist between the various inhalers. This should be considered whenever one inhaler device is substituted with another. In addition, the choice of inhaler device should include consideration of the efficacy of drug delivery, cost, safety, ease of use, convenience, and documentation of its use in the patient's age group[123-125]. In general, a metered-dose inhaler (MDI) with spacer is preferable to nebulized therapy due to its greater convenience, more effective lung deposition, lower risk of side effects, and lower cost. Based on these considerations, a general strategy for choosing inhalers in children is given in **Figure 3-3**.

Figure 3-3: Choosing an Inhaler Device for Children with Asthma*

Age Group	Preferred Device	Alternate Device
Younger than 4 years	Pressurized metered-dose inhaler *plus* dedicated spacer with face mask	Nebulizer with face mask
4 – 6 years	Pressurized metered-dose inhaler *plus* dedicated spacer with mouthpiece	Nebulizer with mouthpiece
Older than 6 years	Dry powder inhaler, *or* breath-actuated pressurized metered-dose inhaler, *or* pressurized metered-dose inhaler with spacer and mouthpiece	Nebulizer with mouthpiece

**Based on efficacy of drug delivery, cost effectiveness, safety, ease of use, and convenience.*

Spacers retain large drug particles that would normally be deposited in the oropharynx, reducing oral and gastrointestinal absorption and thus systemic availability of the inhaled drug. This is mainly important when inhaled glucocorticosteroids with first-pass metabolism (beclomethasone dipropionate, flunisolide, triamcinolone, and budesonide) are given via pressurized MDI. Use of a spacer also reduces oropharyngeal side effects. During acute asthma attacks, an MDI should always be used with a spacer, as in this situation a child may be unable to correctly coordinate inhalation with actuation of the MDI.

Commercially produced spacers with well-characterized drug output characteristics are preferable, although spacer devices or face masks differ in their drug delivery and therefore may not be interchangable[237]. If these are not available or feasible, a homemade spacer (for example, one made from a 500 ml plastic cold drink bottle) may be used[126]. Nebulizers have rather imprecise dosing, are expensive, are time consuming to use and care for, and require maintenance. They are mainly reserved for children who cannot use other inhaler devices. In severe acute asthma exacerbations a nebulizer is often used, although an MDI with a spacer is equally effective[127].

**See also the "Asthma Medications: Adults" section at the beginning of this chapter for more information on the therapeutic role and side effects of various therapies. In this section, only information specific to children is provided.

Figure 3-4. Estimated Equipotent Daily Doses of Inhaled Glucocorticosteroids for Children Older than 5 Years

Drug	Low Daily Dose (μg)	Medium Daily Dose (μg)	High Daily Dose (μg)‡
Beclomethasone dipropionate- CFC	100 - 200	>200 - 400	>400
Budesonide*	100 - 200	>200 - 400	>400
Budesonide-Neb	250 - 500	>500 - 1000	>1000
Ciclesonide*	80 - 160	>160 - 320	>320
Flunisolide	500 - 750	>750 - 1250	>1250
Fluticasone propionate	100 - 200	>200 - 500	>500
Mometasone furoate*	100	≥200	≥400
Triamcinolone acetonide	400 - 800	>800 - 1200	>1200

† Comparisons based upon efficacy data.

‡ Patients considered for high daily doses except for short periods should be referred to a specialist for assessment to consider alternative combinations of controllers. Maximum recommended doses are arbitrary but with prolonged use are associated with increased risk of systemic side effects.

* Approved for once-daily dosing in mild patients.

Notes

- The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy. The clinician must monitor the patient's response in terms of clinical control and adjust the dose accordingly. Once control of asthma is achieved, the dose of medication should be carefully titrated to the **minimum** dose required to maintain control, thus reducing the potential for adverse effects.
- Designation of low, medium, and high doses is provided from manufacturers' recommendations where possible. Clear demonstration of dose-response relationships is seldom provided or available. The principle is therefore to establish the minimum effective controlling dose in each patient, as higher doses may not be more effective and are likely to be associated with greater potential for adverse effects.
- As CFC preparations are taken from the market, medication inserts for HFA preparations should be carefully reviewed by the clinician for the correct equivalent dosage.

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Controller Medications

Controller medications for children include inhaled and systemic glucocorticosteroids, leukotriene modifiers, long-acting inhaled β_2-agonists, theophylline, cromones, and long-acting oral β_2-agonists.

Inhaled glucocorticosteroids.

Role in Therapy -Inhaled glucocorticosteroids are the most effective controller therapy, and are therefore the recommended treatment for asthma for children of all ages. **Figure 3-4** lists approximately equipotent doses of different inhaled glucocorticosteroids administered via different inhalation devices for children older than 5 years.

Children older than 5 years. Dose-response studies and dose titration studies in children[128,129] demonstrate marked and rapid clinical improvements in symptoms and lung function at low doses of inhaled glucocorticosteroids (e.g., 100-200 μg budesonide daily)[130-134], and mild disease is well controlled by such doses in the majority of patients[132]. Early intervention with inhaled budesonide is associated with improved asthma control and less additional asthma medication use[132]. Some patients require higher doses (400 μg/day) to achieve optimal asthma control and effective protection against exercise-induced asthma. Only a minority of patients require treatment with high doses of inhaled glucocorticosteroids[133,134]. In children older than 5 years, maintenance treatment with inhaled glucocorticosteroids controls asthma symptoms, reduces the frequency of acute exacerbations and the number of hospital admissions, improves quality of life, lung function, and bronchial hyperresponsiveness, and reduces exercise-induced bronchoconstriction[10]. Symptom control and improvements in lung function occur rapidly (after 1 to 2 weeks), although longer treatment (over the course of months) and sometimes higher doses may be required to achieve maximum improvements in airway hyperresponsiveness[10]. When glucocorticosteroid treatment is discontinued, asthma control deteriorates within weeks to months[10].

Children 5 years and younger. Treatment with inhaled glucocorticosteroids in children 5 years and younger with asthma generally produces similar clinical effects as in older children, but dose-response relationships have been less well studied. The clinical response may differ depending on the inhaler and the child's ability to use the inhaler correctly. With use of a spacer device, a low-dose inhaled glucocorticosteroid results in near-maximum benefits in the majority of patients[136,137]. Use of inhaled glucocorticosteroids does not induce remission of asthma and it returns when treatment is stopped[138].

The clinical benefits of intermittent systemic or inhaled glucocorticosteroids for children with intermittent, viral-induced wheeze remain controversial. A one year study of intermittent treatment with inhaled glucocorticosteroids was equally effective as daily treatment, and reduced the total glucocorticosteroid dose threefold in preschool children with frequent wheezing and a high asthma predictive index[238]. Some studies in older children found small benefits while another study in young children found no effects on wheezing symptoms[139]. There is no evidence to support the use of maintenance low-dose inhaled glucocorticosteroids for preventing early transient wheezing[136,139,199].

Side effects -The majority of studies evaluating the systemic effects of inhaled glucocorticosteroids have been undertaken in children older than 5 years.

Growth. When assessing the effects of inhaled glucocorticosteroids on growth in children with asthma, it is important to consider potential confounding factors. For example, many children with asthma receiving inhaled glucocorticosteroids experience a reduction in growth rate toward the end of the first decade of life[140]. This reduced growth rate continues into the mid-teens and is associated with a delay in the onset of puberty. The pre-pubertal deceleration of growth velocity resembles growth retardation. However, the delay in pubertal growth is also associated with a delay in skeletal maturation, so that the child's bone age corresponds to his or her height[140,141] Ultimately, adult height is not decreased, although it is reached at a later than normal age. The use of 400 µg inhaled budesonide or equivalent per day to control asthma has less impact on growth than does low socioeconomic status[141]. A summary of the findings of studies on inhaled glucocorticosteroids and growth is provided in **Figure 3-5**.

Figure 3-5. Summary: Glucocorticosteroids and Growth in Children[140-142,239]

- Uncontrolled or severe asthma adversely affects growth and final adult height.
- No long-term controlled studies have reported any statistically or clinically significant adverse effects on growth of 100 to 200 µg per day of inhaled glucocorticosteroids.
- Growth retardation may be seen with all inhaled glucocorticosteroids when a high dose is administered.
- Growth retardation in both short-and medium-term studies is dose dependent.
- Important differences seem to exist between the growth-retarding effects of various inhaled glucocorticosteroids and inhalers.
- Different age groups seem to differ in their susceptibility to the growth-retarding effects of inhaled glucocorticosteroids; children aged 2 to 10 are more susceptible than adolescents.
- Glucocorticosteroid-induced changes in growth rate during the first year of treatment appear to be temporary. Children with asthma treated with inhaled glucocorticosteroids attain normal adult height (predicted from family members) but at a later age.

Bones. The potential clinically relevant adverse effects of inhaled glucocorticosteroids on bones in children are osteoporosis and fracture. Several cross-sectional and longitudinal epidemiologic studies have assessed the effects of long-term inhaled glucocorticosteroid treatment on these outcomes[132,143-149]. The conclusions are summarized in **Figure 3-6**.

Figure 3-6. Summary: Bones and Glucocorticosteroids in Children[10,143,144]

- No studies have reported any statistically significant increased of risk of fractures in children taking inhaled glucocorticosteroids.
- Oral or systemic glucocorticosteroid use increases the risk of fracture. The risk of fracture increases along with the number of treatments, with a 32% increase at four courses ever. Use of inhaled glucocorticosteroids reduces the need for systemic courses.
- Controlled longitudinal studies of 2 to 5 years' duration and several cross-sectional studies found no adverse effects of inhaled glucocorticosteroid treatment on bone mineral density.
- Inhaled glucocorticosteroid use has the potential for reducing bone mineral accretion in male children progressing through puberty, but this risk is likely to be outweighed by the ability to re¬duce the amount of oral corticosteroids used in these children[218] .

Hypothalamic-pituitary-adrenal (HPA) axis. Though differences exist between the various inhaled glucocorticosteroids and inhaler devices, treatment with inhaled glucocorticosteroid doses of less than 200 µg budesonide or equivalent daily is normally not associated with any significant suppression of the HPA axis in children. At higher doses, small changes in HPA axis function can be detected with sensitive methods[148]. The clinical relevance of these findings is not known, since there have not been reports of adrenal crisis in clinical trials of inhaled glucocorticosteroids in children. However, adrenal crisis has been reported in children treated with excessively high doses of inhaled glucocorticosteroids[150].

Cataracts. Inhaled glucocorticosteroids have not been associated with an increased occurrence of cataract development in children[30].

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Central nervous system effects. Although isolated case reports have suggested that hyperactive behavior, aggressiveness, insomnia, uninhibited behavior, and impaired concentration may be seen with inhaled glucocorticosteroid treatment, no increase in such effects has been found in a long-term controlled trial of inhaled budesonide[132].

Oral candidiasis, hoarseness, and bruising. Clinical thrush is seldom a problem in children treated with inhaled or systemic glucocorticosteroids. This side effect seems to be related to concomitant use of antibiotics, high daily doses, dose frequency, and inhaler device. Spacers reduce the incidence of oral candidiasis[151]. Mouth rinsing is beneficial[152]. The occurrence of hoarseness or other noticeable voice changes during budesonide treatment is similar to placebo[30]. Treatment with an average daily dose of 500 µg budesonide for 3 to 6 years is not associated with an increased tendency to bruise[30].

Dental side effects. Inhaled glucocorticosteroid treatment is not associated with increased incidence of caries. However, the increased level of dental erosion reported in children with asthma[153] may be due to a reduction in oral pH that may result from inhalation of β_2-agonists[154].

Other local side effects. The long-term use of inhaled glucocorticosteroids is not associated with an increased incidence of lower respiratory tract infections, including tuberculosis.

Leukotriene modifiers.

Children older than 5 years. Leukotriene modifiers provide clinical benefit in children older than 5 years at all levels of severity[155-159], but generally less than that of low-dose inhaled glucocorticosteroids[160]. Leukotriene modifiers provide partial protection against exercise-induced bronchoconstriction within hours after administration with no loss of bronchoprotective effect[200]. As add-on treatment in children whose asthma is insufficiently controlled by low doses of inhaled glucocorticosteroids, leukotriene modifiers provide moderate clinical improvements, including a significant reduction in exacerbations[162]. Combination therapy is less effective in controlling asthma in children with moderate persistent asthma than increasing to moderate doses of inhaled glucocorticosteroids[201]. Montelukast has not been demonstrated to be an effective inhaled glucocorticosteroid sparing alternative in children with moderate-to-severe persistent asthma[219].

Children 5 years and younger. In addition to the efficacy as described above[163,164], leukotriene modifiers reduce viral-induced asthma exacerbations in children ages 2-5 with a history of intermittent asthma[164].

Side effects -No safety concerns have been demonstrated from the use of leukotriene modifiers in children.

Long-acting inhaled β_2-agonists.

Role in therapy -Long-acting inhaled β_2-agonists are primarily used as add-on therapy in children older than 5 years whose asthma is insufficiently controlled by medium doses of inhaled glucocorticosteroids or as single-dose therapy before vigorous exercise. Monotherapy with long-acting inhaled β_2-agonists should be avoided[75,234].

Children older than 5 years. Long-acting inhaled β_2-agonists have mainly been studied in children older than 5 years as add-on therapy for patients whose asthma is not controlled on low to high doses of inhaled glucocorticosteroids. Significant improvements in peak flow and other lung function measurements have been found in most studies[55,165-169, 234]. However, the effects on other outcomes such as symptoms and need for reliever medication have been less consistent and have only been observed in about half of the trials conducted. Add-on treatment with long-acting inhaled β_2-agonists has not been shown to reduce the frequency of exacerbations[170]. Inhalation of a single dose of long-acting inhaled β_2-agonists effectively blocks exercise-induced bronchoconstriction for several hours[171]. With daily therapy the duration of the protection is somewhat reduced[171], but is still longer than that provided by short-acting β_2-agonists. Combination products containing an inhaled glucocorticosteroid and a long-acting inhaled β_2-agonists are preferred to long-acting inhaled β_2-agonists and inhaled glucocorticosteroids administered by separate inhalers. Fixed combination inhalers ensure that the long-acting β_2-agonists is always accompanied by a glucocorticosteroid.

Children 5 years and younger. The effect of long-acting inhaled β_2-agonists has not yet been adequately studied. Combination therapy with budesonide and formoterol used both as maintenance and rescue has been shown to reduce asthma exacerbations in children ages 4 years and older with moderate to severe asthma[202].

Side effects -Although long-acting inhaled β_2-agonists are well-tolerated in children, even after long-term use, because of inconsistency of reports on their effects on exacerbations of asthma, they are not the recommended option when more than one controller is required[170]. If used, long-acting β_2-agonists should only be used in combination with an appropriate dose of inhaled glucocorticosteroid as determined by a physician, preferably in a fixed combination inhaler.

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Theophylline.

Role in therapy -Theophylline has been shown to be effective as monotherapy and as add-on treatment to inhaled or oral glucocorticosteroids in children older than 5 years. It is significantly more effective than placebo at controlling day and night symptoms and improving lung function[172-174]. Maintenance treatment offers a marginal protective effect against exercise-induced broncho-constriction[175]. Add-on treatment with theophylline has been found to improve asthma control and reduce the maintenance glucocorticosteroid dose necessary in children with severe asthma treated with inhaled or oral glucocorticosteroids[176,177]. A few studies in children 5 years and younger also suggest some clinical benefit. However, the efficacy of theophylline is less than that of low-dose inhaled glucocorticosteroids.

Most clinical evidence regarding the use of theophylline in children has been obtained from studies in which plasma theophylline levels were maintained within the therapeutic range of 55-110 µmol/L (5-10 µg/ml). Further studies suggest that its controller functions may occur at lower plasma levels (corresponding to doses of around 10 mg/kg/day). Sustained-release products are preferable for maintenance therapy, since they enable twice-daily dosing. Sustained-release products with reliable absorption profiles and complete bioavailability with and without concomitant food intake are preferred.
Theophylline elimination may vary up to tenfold between individuals. Measurement of plasma theophylline levels is not necessary in otherwise healthy children when doses less than 10 mg/kg/day are used. However, when higher doses are used or when drugs that may increase theophylline levels are also used chronically, plasma theophylline levels should be measured two hours before administration of the next dose once steady state has been reached (after 3 days).

Side effects -The most common side effects of theophylline are anorexia, nausea, vomiting, and headache[178]. Mild central nervous stimulation, palpitations, tachycardia, arrhythmias, abdominal pain, diarrhea, and, rarely, gastric bleeding may also occur. These side effects are mainly seen at doses higher than 10 mg/kg/day. The risk of adverse effects is reduced if treatment is initiated with daily doses around 5 mg/kg/day and then gradually increased to 10 mg/kg/day. Severe overdosing with theophylline can be fatal.

Anti-IgE.

Role in therapy - Anti-IgE (omalizumab) has proven efficacy in children age 6 to 12 years with moderate-to-severe and severe persistent allergic (IgE-mediated) asthma. A 28 week, randomized, double-blind, placebo-controlled study[223, 224] included 334 children with moderate to severe allergic asthma who were well controlled on inhaled glucocorticosteroid doses equivalent to 200-500 µg/day of beclomethasone. There was no difference in clinical effects between placebo and anti-IgE during a 16-week stable inhaled glucocorticosteroid dose period. During a 12-week tapering period urgent, unscheduled physician visits were significantly reduced from by 30.3% in the anti-IgE compared with placebo (12.9%) group[223], and there were significant improvements in quality of life in the patients receiving anti-IgE, both during stable inhaled glucocorticosteroid dosing and during tapering[224]. The remaining outcomes were very similar in the two treatment groups.

A one-year study evaluated the efficacy and safety of anti-IgE in 627 children with IgE-mediated asthma inadequately controlled on doses of inhaled glucocorticosteroid equivalent to 200 µg/day fluticasone propionate or higher (mean dose 500 µg/day)[225]. Anti-IgE treatment was associated with a significantly lower exacerbation rate and the overall incidence of serious adverse events was significantly lower in the children receiving anti-IgE than placebo.

A substantial number of children with difficult asthma will have higher IgE levels than the upper limit of IgE recommended for therapy (1,300 IU)[226]. It is unknown if these patients will still benefit from omalizumab therapy. There are no tests that can currently be recommended in order to predict who will respond[227].

Anti-IgE therapy is expensive and requires regular injections and observation after each injection. A cost benefit analysis suggested that there would be a fiscal saving if this treatment is given to children with five or more hospital admissions and cumulatively twenty days or more in hospital[228].

Side effects: Drug-related adverse events in anti-IgE treated patients are mild to moderate in severity and include urticaria, rash, flushing, and pruritus[223]. The long-term (beyond one year) safety and efficacy has not yet been studied.

Cromones: sodium cromoglycate and nedocromil sodium.

Role in therapy -Sodium cromoglycate and nedocromil sodium have a limited role in the long-term treatment of asthma in children. One meta-analysis has concluded that long-term treatment with sodium cromoglycate is not significantly better than placebo for management of asthma in children[179]. Another has confirmed superiority of low dose

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inhaled glucocorticosteroids over sodium cromoglycate in persistent asthma, but as there were no placebo arms in these studies, the efficacy of sodium cromoglycate cannot be confirmed from the studies reviewed; no between treatment difference in safety was observed[180].

Nedocromil sodium has been shown to reduce exacerbations, but its effect on other asthma outcomes is not superior to placebo. A single dose of sodium cromoglycate or nedocromil sodium attenuates broncho-spasm induced by exercise or cold air[181]. Studies of the use of these medications in children 5 years and younger are sparse and results are conflicting.

Side effects -Cough, throat irritation, and broncho-constriction occur in a small proportion of patients treated with sodium cromoglycate. A bad taste, headache, and nausea are the most common side effects of nedocromil[182].

Long-acting oral β_2-agonists.

Treatment with long-acting oral β_2-agonist such as slow release formulations of salbutamol, terbutaline, and bambuterol reduces nocturnal symptoms of asthma[183,184]. Due to their potential side effects of cardiovascular stimulation, anxiety, and skeletal muscle tremor, their use is not encouraged. If used, dosing should be individuali ed, and the therapeutic response monitored to limit side effects[185]. Long-acting oralβ_2-agonist therapy offers little or no protection against exercise-induced bronchoconstriction.

Systemic glucocorticosteroids.

Because of the side effects of prolonged use, oral glucocorticosteroids in children with asthma should be restricted to the treatment of acute severe exacerbations, whether viral-induced or otherwise.

Reliever Medications

Rapid-acting inhaled ß$_2$-agonists and short-acting oral ß$_2$-agonists.

Role in therapy -Rapid-acting inhaled ß$_2$-agonists are the most effective bronchodilators available and therefore the preferred treatment for acute asthma in children of all ages. The inhaled route results in more rapid bronchodilation at a lower dose and with fewer side effects than oral or intravenous administration[186]. Furthermore, inhaled therapy offers significant protection against exercise-induced bronchoconstriction and other challenges for 0.5 to 2 hours (long-acting ß$_2$-agonists offer longer protection)[187]. This is not seen after systemic administration[188]. Oral therapy is rarely needed and reserved mainly for young children who cannot use inhaled therapy.

Side effects -Skeletal muscle tremor, headache, palpitations, and some agitation are the most common complaints associated with high doses of ß$_2$-agonists in children. These complaints are more common after systemic administration and disappear with continued treatment[189].

Anticholinergics.

Role in therapy -Inhaled anticholinergics are not recommended for long-term management of asthma in children[190].

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CHAPTER

4

ASTHMA MANAGEMENT AND PREVENTION

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CHAPTER 4: ASTHMA MANAGEMENT AND PREVENTION

INTRODUCTION

Asthma has a significant impact on individuals, their families, and society. Although there is no cure for asthma, appropriate management that includes a partnership between the physician and the patient/family most often results in the achievement of control.

The goals for successful management of asthma are to:

- Achieve and maintain control of symptoms
- Maintain normal activity levels, including exercise
- Maintain pulmonary function as close to normal as
- possible
- Prevent asthma exacerbations
- Avoid adverse effects from asthma medications
- Prevent asthma mortality.

These goals for therapy reflect an understanding of asthma as a chronic inflammatory disorder of the airways characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. Clinical studies have shown that asthma can be effectively controlled by intervening to suppress and reverse the inflammation as well as treating the bronchoconstriction and related symptoms. Furthermore, early intervention to stop exposure to the risk factors that sensitized the airway may help improve the control of asthma and reduce medication needs. Experience in occupational asthma indicates that long-standing exposure to sensitizing agents may lead to irreversible airflow limitation.

The management of asthma can be approached in different ways, depending on the availability of the various forms of asthma treatment and taking into account cultural preferences and differing health care systems. The recommendations in this chapter reflect the current scientific understanding of asthma. They are based as far as possible on controlled clinical studies, and the text references many of these studies. For those aspects of the clinical management of asthma that have not been the subject of specific clinical studies, recommendations are based on literature review, clinical experience, and expert opinion of project members.

The recommendations for asthma management are laid out in five interrelated components of therapy:

1. Develop Patient/Doctor Partnership
2. Identify and Reduce Exposure to Risk Factors
3. Assess, Treat, and Monitor Asthma
4. Manage Asthma Exacerbations
5. Special Considerations.

COMPONENT 1: DEVELOP PATIENT/DOCTOR PARTNERSHIP

KEY POINTS:

- The effective management of asthma requires the development of a partnership between the person with asthma and his or her health care professional(s) (and parents/caregivers, in the case of children with asthma).
- The aim of this partnership is guided self-management—that is, to give people with asthma the ability to control their own condition with guidance from health care professionals.
- The partnership is formed and strengthened as patients and their health care professionals discuss and agree on the goals of treatment, develop a personalized, written asthma action plan including self-monitoring, and periodically review the patient's treatment and level of asthma control.
- Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages.
- Personal written asthma action plans help individuals with asthma make changes to their treatment in response to changes in their level of asthma control, as indicated by symptoms and/or peak expiratory flow, in accordance with written predetermined guidelines.

INTRODUCTION

The effective management of asthma requires the development of a partnership between the person with asthma and his or her health care professional(s) (and parents/caregivers in the case of children with asthma). The aim of this partnership is to enable patients with asthma to gain the knowledge, confidence, and skills to assume a major role in the management of their asthma. The partnership is formed and strengthened as patients and their health care professionals discuss and agree on the goals of treatment, develop a personalized, written asthma action plan including self-monitoring, and periodically review the patient's treatment and level of asthma control (**Figure 4.1-1**).

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This approach is called guided self-management and has been shown to reduce asthma morbidity in both adults (**Evidence A**) and children (**Evidence A**). A number of specific systems of guided self-management have been developed[1-10] for use in a wide range of settings: primary care[1,4,6], hospitals[2,3,7,10], and emergency departments[8]. Internet-based home monitoring[340,372], and mobile phones[395] have been shown to be successful modes to improve asthma control. Self-management programs have been tested in diverse groups, including community health workers[371], pregnant women with asthma[11], children and adolescents[12,13], and in multi-racial populations[14].

Guided self-management may involve varying degrees of independence, ranging broadly from patient-directed self-management in which patients make changes without reference to their caregiver, but in accordance with a prior written action plan, to doctor-directed self-management in which patients rely follow a written action plan, but refer most major treatment changes to their physician at the time of planned or unplanned consultations. Cochrane systematic reviews[13,15-18] have examined the role of education and self-management strategies in the care of asthma patients.

Figure 4.1-1. Essential Features of the Doctor-Patient Partnership to Achieve Guided Self-Management in Asthma

- Education
- Joint setting of goals
- Self-monitoring. The person with asthma is taught to combine assessment of asthma control with educated interpretation of key symptoms
- Regular review of asthma control, treatment, and skills by a health care professional
- Written action plan. The person with asthma is taught which medications to use regularly and which to use as needed, and how to adjust treatment in response to worsening asthma control
- Self-monitoring is integrated with written guidelines for both the long-term treatment of asthma and the treatment of asthma exacerbations.

ASTHMA EDUCATION

Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages. Although the focus of education for small children will be on the parents and caregivers, children as young as 3 years of age can be taught simple asthma management skills. Adolescents may have some unique difficulties regarding adherence that may be helped through peer support group education in addition to education provided by the health care professional[12] but regional issues and the developmental stage of the children may affect the outcomes of such programs[373].

Figure 4.1-2 outlines the key features and components of an asthma education program. The information and skills training required by each person may vary, and their ability or willingness to take responsibility similarly differs. Thus all individuals require certain core information and skills, but most education must be personalized and given to the person in a number of steps. Social and psychological support may also be required to maintain positive behavioral change.

Figure 4.1-2. Education and the Patient Doctor Partnership

Goal: To provide the person with asthma, their family, and other caregivers with suitable information and training so that they can keep well and adjust treatment according to a medication plan developed with the health care professional.

Key Components:
- ❑ Focus on the development of the partnership
- ❑ Acceptance that this is a continuing process
- ❑ A sharing of information
- ❑ Full discussion of expectations
- ❑ Expression of fears and concerns

Key Components:
- ❑ Diagnosis
- ❑ Difference between "relievers" and "controllers"
- ❑ Potential side effects of medications
- ❑ Use of inhaler devices
- ❑ Prevention of symptoms and attacks
- ❑ Signs that suggest asthma is worsening and actions to take
- ❑ Monitoring control of asthma
- ❑ How and when to seek medical attention

The person then requires:
- ❑ A written asthma action plan
- ❑ Regular supervision, revision, reward, and reinforcement

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Good communication is essential as the basis for subsequent good compliance/adherence[19-22,414] (**Evidence B**). Key factors that facilitate good communication are[23]:

- A congenial demeanor (friendliness, humor, and attentiveness)
- Engaging in interactive dialogue
- Giving encouragement and praise

- Empathy, reassurance, and prompt handling of any concerns
- Giving of appropriate (personalized) information
- Eliciting shared goals
- Feedback and review

Teaching health care professionals to improve their communication skills can result in measurably better outcomes–including increased patient satisfaction, better health, and reduced use of health care–and these benefits may be achieved without any increase in consultation times[24]. Studies have also shown that patients can be trained to benefit more from consultations. Patients taught how to give information to doctors in a clearer manner, and how to seek information and check their understanding of what the doctor had told them gained significant improvements in compliance with treatment recommendations[25]. Lay educators can be recruited and trained to deliver a discrete area of respiratory care (for example, asthma self-management education) with comparable outcomes to those achieved by primary care based practice nurses[362] (**Evidence B**).

At the Initial Consultation

Early in the consultation the person with asthma needs information about the diagnosis and simple information about the types of treatment available, the rationale for the specific therapeutic interventions being recommended, and strategies for avoiding factors that cause asthma symptoms[374]. Different inhaler devices can be demonstrated, and the person with asthma encouraged to participate in the decision as to which is most suitable for them. Some of these devices and techniques for their use are illustrated on the GINA Website (http://www.ginasthma.org). Criteria for initial selection of inhaler device include device availability and cost, patient skills, and preferences of the health professional and patient[26-28] . Patients should be given adequate opportunity to express their expectations of both their asthma and its treatment. A frank appraisal should be made of how far their expectations may or may not be met, and agreement should be made about specific goals for therapy.

At the initial consultation, verbal information should be supplemented by the provision of written or pictorial[29, 30] information about asthma and its treatment. The GINA Website (http://www.ginasthma.org) contains patient educational materials, as well as links to several asthma websites. The patient and his or her family 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.

Personal Written Asthma Action Plans

Personal written asthma action plans help individuals with asthma make changes to their treatment in response to changes in their level of asthma control, as indicated by symptoms and/or peak expiratory flow, in accordance with written predetermined guidelines[23,31,32] .

The effects were greatest where the intervention involved each of the following elements: education, self-monitoring, regular review, and patient-directed management using a written asthma action plan (**Evidence A**). Within these studies, the effects were also greater when the action plans themselves both stepped up inhaled glucocorticosteroids and added oral glucocorticosteroids, and for peak flow-based plans, when they were based on personal best rather than percent predicted peak flow[32]. Patients experience a one-third to two-thirds reduction in hospitalizations, emergency room visits, unscheduled visits to the doctor for asthma, missed days of work, and nocturnal wakening. It has been estimated that the implementation of a self-management program in 20 patients prevents one hospitalization, and successful completion of such a program by eight patients prevents one emergency department visit[16-18,23] . Less intensive interventions that involve self-management education but not a written plan are less effective[15]. The efficacy is similar regardless of whether patients self-adjust their medications according to an individual written plan or adjustments of medication are made by a doctor[15] (**Evidence B**). Thus, patients who are unable to undertake guided self-management can still achieve benefit from a structured program of regular medical review. Although interactive computerized asthma education programs may improve patient asthma knowledge and symptoms, their effect on objective clinical outcomes is less consistent[353] .

Examples of written asthma action plans that have been recommended can be found on several Websites (UK National Asthma Campaign Plan, www.asthma.org.uk; International Asthma Management Plan “Zone System,” www.nhlbisupport.com/asthma/index.html; New Zealand “Credit Card” System, www.asthmanz.co.nz. An example of the contents for an asthma plan for patients to maintain control of asthma, and respond to worsening asthma, is shown in **Figure 4.1-3**.

Follow-Up and Review

Follow-up consultations should take place at regular intervals. At these visits, the patient’s questions are discussed, and any problems with asthma and its initial treatment are reviewed. Patients should be asked to demonstrate their inhaler device technique at every visit, with correction and re-checking if it is inadequate[33,375].

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Follow-up consultations should also include checking the person's adherence/compliance to the medication plan and recommendations for reducing exposure to risk factors. If the patient has been asked to keep a diary of symptoms (and where appropriate, home peak flow recordings) this should also be reviewed regularly. After a period of initial training, the frequency of home peak flow and symptom monitoring depends in part on the level of control of the person's asthma. Routine follow-up visits may be an effective time to review the written asthma action plan and its understanding[354] . Educational messages should be reviewed and repeated or added to if necessary. A single page prompt to clinicians has been shown to improve the provision of preventive care to children with asthma during office visits[341]. Telehealthcare follow-up is unlikely to benefit in mild asthma but may be of benefit in those with severe disease at risk of hospital admission[397].

Figure 4.1-3 Example of Contents of Written Asthma Action Plan to Maintain Asthma Control

Your Regular Treatment:

1. **Each day take** _____
2. **Before exercise, take** _____

WHEN TO INCREASE TREATMENT

Assess your level of Asthma Control

In the past week have you had:

Daytime asthma symptoms more than 2 times ?	**No**	**Yes**
Activity or exercise limited by asthma?	**No**	**Yes**
Waking at night because of asthma?	**No**	**Yes**
The need to use your [rescue medication] more than 2 times?	**No**	**Yes**
If you are monitoring peak flow, peak flow less than_____?	**No**	**Yes**

If you answered YES to three or more of these questions, your asthma is uncontrolled and you may need to step up your treatment.

HOW TO INCREASE TREATMENT

STEP-UP your treatment as follows and assess improvement every day:

_____ **[Write in next treatment step here]**

Maintain this treatment for _____ **days [specify number]**

WHEN TO CALL THE DOCTOR/CLINIC.

Call your doctor/clinic: _____ **[provide phone numbers]**

If you don't respond in _____ **days [specify number]**

_____ **[optional lines for additional instruction]**

EMERGENCY/SEVERE LOSS OF CONTROL

- ✓**If you have severe shortness of breath, and can only speak in short sentences,**
- ✓**If you are having a severe attack of asthma and are frightened,**
- ✓**If you need your reliever medication more than every 4 hours and are not improving.**

1. **Take 2 to 4 puffs** _____ **[reliever medication]**
2. **Take** ____**mg of** _____ **[oral glucocorticosteroid]**
3. **Seek medical help: Go to** _____**; Address**_____ **Phone:** _____
4. **Continue to use your** _____**[reliever medication] until you are able to get medical help.**

Figure 4.1-4. Factors Involved in Poor Adherence

Drug factors	Non-drug factors
Difficulties with inhaler devices	Misunderstanding or lack of instruction
Awkward regimes (e.g., four times daily or multiple drugs)	Fears about side effects
Side effects	Dissatisfaction with health care professionals
Cost of medication	Unexpressed/undiscussed fears or concerns
Dislike of medication	Inappropriate expectations
Distant pharmacies	Poor supervision, training, or follow-up
	Anger about condition or its treatment
	Underestimation of severity
	Cultural issues
	Stigmatization
	Forgetfulness or complacency
	Attitudes toward ill health
	Religious issues

Improving Adherence

Although interventions for enhancing medication adherence have been developed[363], studies of adults and children with asthma[34] have shown that around 50% of those on Long-term therapy fail to take medications as directed at least part of the time. Patient concern about side-effects of inhaled glucocorticosteroids whether real or perceived may influence adherence[342]. Non-adherence may be defined in a nonjudgmental way as the failure of treatment to be taken as agreed upon by the patient and the health care professional. Non-adherence may be identified by prescription monitoring, pill counting, or drug assay, but at a clinical level it is best detected by asking about therapy in a way that acknowledges the likelihood of incomplete adherence (e.g., "So that we may plan therapy, do you mind telling me how often you actually take the medicine?"). Short questionnaires can assist with identification of poor adherence[376]. Providing adherence information to clinicians does not improve use of inhaled glucocorticosteroid among patients with asthma unless clinicians are sufficiently interested in adherence to view the details of this medication use[398]. Specific drug and non-drug factors involved in non-adherence are listed in **Figure 4.1-4.**

Self-Management in Children

Children with asthma (with the help of their parents/ caregivers) also need to know how to manage their own condition. Simple educational interventions (designed to teach self-management skills) among children admitted to the hospital with asthma have been shown to significantly reduce the readmission rate and reduce morbidity[13] . A systematic review found that educational programs for the self-management of asthma in children and adolescents led to improvements in lung function and feelings of self-control, and reduced absences from school, the number of days with restricted activity, and the number of emergency department visits[13,343] . For children, symptom-based action plans are more effective than those based on peak flows[355]. School-based asthma education improves knowledge of

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asthma, self-efficacy, and self-management behaviors[377]. A comprehensive school-based program for adolescents and academic detailing for their physicians was associated with significantly improved asthma outcomes including reduced hospitalizations[399].

THE EDUCATION OF OTHERS

The education of the general public about asthma is helpful in that it enables members of the public to recognize asthma symptoms and their consequences and encourages those with asthma to seek medical attention and follow their asthma management program. Greater awareness of asthma is also likely to help dispel misconceptions that may exist about the condition and reduce feelings of stigmatization on the part of patients.

Specific advice about asthma and its management should be offered to school teachers and physical education instructors, and several organizations produce materials for this purpose. Schools may need advice on improving the environment and air quality for children with asthma[35] . It is also helpful for employers to have access to clear advice about asthma. Most occupations are as suitable for those with asthma as for those without, but there may be some circumstances where caution is needed.

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COMPONENT 2: IDENTIFY AND REDUCE EXPOSURE TO RISK FACTORS

KEY POINTS:

- Pharmacologic intervention to treat established asthma is highly effective in controlling symptoms and improving quality of life. However, measures to prevent the development of asthma, asthma symptoms, and asthma exacerbations by avoiding or reducing exposure to risk factors should be implemented wherever possible.
- At this time, few measures can be recommended for prevention of asthma because the development of the disease is complex and incompletely understood.
- Asthma exacerbations may be caused by a variety of risk factors, sometimes referred to as "triggers", including allergens, viral infections, pollutants, and drugs.
- Reducing a patient's exposure to some categories of risk factors improves the control of asthma and reduces medication needs.
- The early identification of occupational sensitizers and the removal of sensitized patients from any further exposure are important aspects of the management of occupational asthma.

INTRODUCTION

Although pharmacologic intervention to treat established asthma is highly effective in controlling symptoms and improving quality of life, measures to prevent the development of asthma, asthma symptoms, and asthma by avoiding or reducing exposure to risk factors should be implemented wherever possible[36]. At this time, few measures can be recommended for prevention of asthma because the development of the disease is complex and incompletely understood. This area is a focus of intensive research, but until such measures are developed prevention efforts must primarily focus on prevention of asthma symptoms and attacks.

ASTHMA PREVENTION

Measures to prevent asthma may be aimed at the prevention of allergic sensitization (i.e., the development of atopy, likely to be most relevant prenatally and perinatally), or the prevention of asthma development in sensitized people. Other than preventing tobacco exposure both *in utero* and after birth, there are no proven and widely accepted interventions that can prevent the development of asthma.

Allergic sensitzation can occur prenatally[37,38]. There is currently insufficient information on the critical doses and timing of allergen exposure to permit intervention in this process, and no strategies can be recommended to prevent allergic sensitization prenatally[415]. Prescription of an antigen-avoidance diet to a high-risk woman during pregnancy is unlikely to reduce substantially her risk of giving birth to an atopic child[39]. Moreover, such a diet may have an adverse effect on maternal and/or fetal nutrition.

The role of diet, particularly breast-feeding, in relation to the development of asthma has been extensively studied and, in general, infants fed formulas of intact cow's milk or soy protein compared with breast milk have a higher incidence of wheezing illnesses in early childhood[40]. Exclusive breast-feeding during the first months after birth is associated with lower asthma rates during childhood[41].

The "hygiene hypothesis" of asthma, though controversial, has led to the suggestion that strategies to prevent allergic sensitization should focus on redirecting the immune response of infants toward a Th1, nonallergic response or on modulating T regulator cells[42], but such strategies currently remain in the realm of hypothesis and require further investigation. The role of probiotics in the prevention of allergy and asthma is also unclear[43] . Exposure to cats has been shown to reduce risk of atopy in some studies[44].

Exposure to tobacco smoke both prenatally and postnatally is associated with measurable harmful effects, including effects on lung development[45] and a greater risk of developing wheezing illnesses in childhood[46]. Although there is little evidence that maternal smoking during pregnancy has an effect on allergic sensitization[47], passive smoking increases the risk of allergic sensitization in children[47,48]. Both prenatal and postnatal maternal smoking is problematic[49]. Pregnant women and parents of young children should be advised not to smoke (**Evidence B**).

Once allergic sensitization has occurred, there are theoretically still opportunities to prevent the actual

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development of asthma. Whether H_1-antagonists (antihistamines)[50,51] or allergen-specific immunotherapy[52,53] can prevent the development of asthma in children who have other atopic diseases remains an area of investigation, and these interventions cannot be recommended for wide adoption in clinical practice at this time.

PREVENTION OF ASTHMA SYMPTOMS AND EXACERBATIONS

Asthma exacerbations may be caused by a variety of factors, sometimes referred to as "triggers," including allergens, viral infections[400], pollutants, and drugs. Reducing a patient's exposure to some of these categories of risk factors (e.g., smoking cessation, reducing exposure to secondhand smoke, reducing or eliminating exposure to occupational agents known to cause symptoms, and avoiding foods/additives/drugs known to cause symptoms) improves the control of asthma and reduces medication needs. In the case of other factors (e.g., allergens, viral infections and pollutants), measures where possible should be taken to avoid these. Because many asthma patients react to multiple factors that are ubiquitous in the environment, avoiding these factors completely is usually impractical and very limiting to the patient. Thus, medications to maintain asthma control have an important role because patients are often less sensitive to these risk factors when their asthma is under good control. Patients with well-controlled asthma are less likely to experience exacerbations than those whose asthma is not well-controlled[364] .

Indoor Allergens

Among the wide variety of allergen sources in human dwellings are domestic mites, furred animals, cockroaches, and fungi. However, there is conflicting evidence about whether measures to create a low-allergen environment in patients' homes and reduce exposure to indoor allergens are effective at reducing asthma symptoms[54,55] . The majority of single interventions have failed to achieve a sufficient reduction in allergen load to lead to clinical improvement[55-57]. It is likely that no single intervention will achieve sufficient benefits to be cost effective.However, among inner-city children with atopic asthma, an individualized, home-based, comprehensive environmental intervention decreased exposure to indoor allergens and resulted in reduced asthma-associated morbidity[58]. More properly powered and well-designed studies of combined allergen-reduction strategies in large groups of patients are needed.

Figure 4.2-1: Effectiveness of Avoidance Measures for Some Indoor Allergens*

Measure	Evidence of effect on allergen levels	Evidence of clinical benefit
House dust mites		
Encase bedding in impermeable covers	**Some**	**None (adults) Some (children)**
Wash bedding in the hot cycle (55-60°C)	**Some**	**None**
Replace carpets with hard flooring	**Some**	**None**
Acaricides and/or tannic acid	**Weak**	**None**
Minimize objects that accumulate dust	**None**	**None**
Vacuum cleaners with integral HEPA filter and double-thickness bags	**Weak**	**None**
Remove, hot wash, or freeze soft toys	**None**	**None**
Pets		
Remove cat/dog from the home	**Weak**	**None**
Keep pet from main living areas/bedrooms	**Weak**	**None**
HEPA-filter air cleaners	**Some**	**None**
Wash pet	**Weak**	**None**
Replace carpets with hard flooring	**None**	**None**
Vacuum cleaners with integral HEPA filter and double-thickness bags	**None**	**None**

**Adapted from* Custovic A, Wijk RG. The effectiveness of measures to change the indoor environment in the treatment of allergic rhinitis and asthma: ARIA update (in collaboration with GA(2)LEN). *Allergy* 2005;60(9):1112-1115.

Domestic mites. Domestic mite allergy is a universal health problem[59]. Since mites live and thrive in many sites throughout the house, they are difficult to reduce and impossible to eradicate (**Figure 4.2-1**). No single measure is likely to reduce exposure to mite allergens, and single chemical and physical methods aimed at reducing mite allergens are not effective in reducing asthma symptoms in adults[55,60-62] (**Evidence A**). One study showed some efficacy of mattress encasing at reducing airway hyperresponsiveness in children[63] (**Evidence B**). An integrated approach including barrier methods, dust removal, and reduction of microhabitats favorable to mites has been suggested, although its efficacy at reducing symptoms has only been confirmed in deprived populations with a specific environmental exposure[58] (**Evidence B**) and a recommendation for its widespread use cannot be made.

Furred animals. Complete avoidance of pet allergens is impossible, as the allergens are ubiquitous and can be found in many environments outside the home[64], including schools[65], public transportation, and cat-free buildings[66]. Although removal of such animals from the home is encouraged, even after permanent removal of the animal

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it can be many months before allergen levels decrease[67] and the clinical effectiveness of this and other interventions remains unproven (**Figure 4.2-1**).

Cockroaches. Avoidance measures for cockroaches include eliminating suitable environments (restricting havens by caulking and sealing cracks in the plasterwork and flooring, controlling dampness, and reducing the availability of food), restricting access (sealing entry sources such as around paperwork and doors), chemical control, and traps. However, these measures are only partially effective in removing residual allergens[68] (**Evidence C**).

Fungi. Fungal exposure has been associated with exacerbations from asthma and the number of fungal spores can best be reduced by removing or cleaning mold-laden objects[69]. In tropical and subtropical climates, fungi may grow on the walls of the house due to water seepage and humidity. To avoid this, the walls could be tiled or cleaned as necessary. Air conditioners and dehumidifiers may be used to reduce humidity to levels 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[70].

Outdoor Allergens

Outdoor allergens such as pollens and molds are impossible to avoid completely. Exposure may be reduced by closing windows and doors, remaining indoors when pollen and mold counts are highest, and using air conditioning if possible. Some countries use radio, television, and the Internet to provide information on outdoor allergen levels. The impact of these measures is difficult to assess.

Indoor Air Pollutants

The most important measure in controlling indoor air pollutants is to avoid passive and active smoking. Secondhand smoke increases the frequency and severity of symptoms in children with asthma. Parents/caregivers of children with asthma should be advised not to smoke and not to allow smoking in rooms their children use. In addition to increasing asthma symptoms and causing long-term impairments in lung function, active cigarette smoking reduces the efficacy of inhaled and systemic glucocorticosteroids[71,72] (**Evidence B**). Asthma patients who smoke, and are not treated with inhaled glucocorticosteroids, have a greater decline in lung function than asthmatic patients who do not smoke[378]. Smoking cessation needs to be vigorously encouraged for all patients with asthma who smoke.

Other major indoor air pollutants include nitric oxide, nitrogen oxides, carbon monoxide, carbon dioxide, sulfur dioxide, formaldehyde, and biologicals (endotoxin)[73]. 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 does significantly reduce symptoms of asthma, days off school, healthcare utilization, and visits to a pharmacist[365].

Outdoor Air Pollutants

Several studies have suggested that outdoor pollutants aggravate asthma symptoms[74, 356], possibly having an additive effect with allergen exposure[75] . Outbreaks of asthma exacerbations have been shown to occur in relationship to increased levels of air pollution, and this may be related to a general increase in pollutant levels or to an increase in specific allergens to which individuals are sensitized[76-78]. Most epidemiological studies show a significant association between air pollutants–such as ozone, nitrogen oxides, acidic aerosols, and particulate matter–and symptoms or exacerbations of asthma. On occasion, certain weather and atmospheric conditions, e.g., thunderstorms[78] favor the development of asthma exacerbations by a variety of mechanisms, including dust and pollution, increases in respirable allergens, and changes in temperature/humidity.

Avoidance of unfavorable environmental conditions is usually unnecessary for patients whose asthma is controlled. For patients with asthma that is difficult to control, practical steps to take during unfavorable environmental conditions include avoiding strenuous physical activity in cold weather, low humidity, or high air pollution; avoiding smoking and smoke-filled rooms; and staying indoors in a climate-controlled environment.

Occupational Exposures

Occupational exposures account for a substantial proportion of adult asthma incidence[357] . The early identification of occupational sensitizers and the removal of sensitized patients from any further exposure are important aspects of the management of occupational asthma (**Evidence B**). Once a patient has become sensitized to an occupational allergen, the level of exposure necessary to induce symptoms may be extremely low, and resulting exacerbations become increasingly severe. Attempts to reduce occupational exposure have been successful especially in industrial settings, and some potent sensitizers, such as soy castor bean, have been replaced by less allergenic substances[80] (**Evidence B**). Prevention of latex sensitization has been made possible by the

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production of hypoallergenic gloves, which are powder free and have a lower allergen content[81,82] (**Evidence C**). Although more expensive than untreated gloves, they are cost effective.

Food and Food Additives

Food allergy as an exacerbating factor for asthma is uncommon and occurs primarily in young children. Food avoidance should not be recommended until an allergy has been clearly demonstrated (usually by oral challenges)[83]. When food allergy is demonstrated, food allergen avoidance can reduce asthma exacerbations[84] (**Evidence D**). 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 but the likelihood of a reaction is dependent on the nature of the food, the level of residual sulfite, the sensitivity of the patient, the form of residual sulfite and the mechanism of the sulfite-induced reaction[85] . The role of other dietary substances—including the yellow dye tartrazine, benzoate, and monosodium glutamate—in exacerbating asthma is probably minimal; confirmation of their relevance requires double-blind challenge before making specific dietary restrictions.

Drugs

Some medications can exacerbate asthma. Aspirin and other nonsteroidal anti-inflammatory drugs can cause severe exacerbations and should be avoided in patients with a history of reacting to these agents[86]. There is some evidence that exposure to acetaminophen increases the risk of asthma and wheezing in children[401] and adults but further studies are needed[379].

Beta-blocker drugs administered orally or intraocularly may exacerbate bronchospasm (**Evidence A**) and close medical supervision is essential when these are used by patients with asthma[87]. Beta blockers have a proven benefit in the management of patients with acute coronary syndromes and for secondary prevention of coronary events. Data suggest that patients with asthma who receive newer more cardio-selective beta blockers within 24 hours of hospital admission for an acute coronary event have lower in-hospital mortality rates[366, 367].

Influenza Vaccination

Patients with moderate to severe asthma should be advised to receive an influenza vaccination every year[88] or at least when vaccination of the general population is advised. However, routine influenza vaccination of children[89] and adults[90] with asthma does not appear to protect them from asthma exacerbations or improve asthma control. Inactivated influenza vaccines are associated with few side effects and are safe to administer to asthmatic adults and children over the age of 3 years, including those with difficult-to-treat asthma[91]. There are data to suggest that intranasal vaccination in children under age 3 may be associated with an increased incidence of asthma exacerbations[92].

Obesity

Increases in body mass index (BMI) have been associated with increased prevalence of asthma[93]. Weight reduction in obese patients with asthma, including by bariatric surgery, has been has been demonstrated to improve lung function, symptoms, morbidity, and health status[94] (**Evidence B**).

Emotional Stress

Emotional stress may lead to asthma exacerbations in children[402] and adults. Extreme emotional expressions (laughing, crying, anger, or fear) can lead to hyperventilation and hypocapnia that can cause airway narrowing[95,96]. Panic attacks, that are rare but not exceptional in some patients with asthma, have a similar effect[97,98]. However, it is important to note that asthma is not primarily a psychosomatic disorder.

Other Factors That May Exacerbate Asthma

Rhinitis, sinusitis, and polyposis are frequently associated with asthma and need to be treated. In children, antibiotic treatment of bacterial sinusitis has been shown to reduce the severity of asthma[99]. However, sinusitis and asthma may simply coexist. Apart from sinusitis, there is little evidence that bacterial infections exacerbate asthma. Gastroesophageal reflux can exacerbate asthma, especially in children, and asthma sometimes improves when the reflux is corrected[100,101]. Many women complain that their asthma is worse at the time of menstruation, and premenstrual exacerbations have been documented[102]. Similarly, asthma may improve, worsen, or remain unchanged during pregnancy[103]. A randomized clinical trial of a self-regulation, telephone counseling intervention emphasizing sex and gender role factors in the management of asthma indicated that a program with a focus on asthma management problems particular to women can significantly assist female asthma patients[358].

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COMPONENT 3: ASSESS, TREAT, AND MONITOR ASTHMA

KEY POINTS:

- The goal of asthma treatment, to achieve and maintain clinical control, can be reached in a majority of patients with a pharmacologic intervention strategy developed in partnership between the patient/family and the doctor.
- Treatment should be adjusted in a continuous cycle driven by the patients' asthma control status. If asthma is not controlled on the current treatment regimen, treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down.
- In treatment-naïve patients with persistent asthma, treatment should be started at *Step 2*, or, if very symptomatic (uncontrolled), at *Step 3*. For *Steps 2* through *5*, a variety of controller medications are available.
- At each treatment step, reliever medication should be provided for quick relief of symptoms as needed.
- Ongoing monitoring is essential to maintain control and to establish the lowest step and dose of treatment to minimize cost and maximize safety.

INTRODUCTION

The goal of asthma treatment, to achieve and maintain clinical control, can be reached in a majority of patients[104,344] with a pharmacologic intervention strategy developed in partnership between the patient/family and the doctor. Each patient is assigned to one of five "treatment steps" depending on their current level of control and treatment is adjusted in a continuous cycle driven by changes in their asthma control status. This cycle involves:

- Assessing Asthma Control
- Treating to Achieve Control
- Monitoring to Maintain Control

In this Component, this cycle is described for long-term treatment of asthma. Treatment for exacerbations is detailed in Component 4.

ASSESSING ASTHMA CONTROL

Each patient should be assessed to establish his or her current treatment regimen, adherence to the current regimen, and level of asthma control. A simplified scheme for recognizing controlled, partly controlled, and uncontrolled asthma in a given week is provided in **Figure 4.3-1**. This is a working scheme based on current opinion and has not been validated. Several composite control measures (e.g., Asthma Control Test[105], Asthma Control Questionnaire[106-108], Asthma Therapy Assessment Questionnaire[109], Asthma Control Scoring System[110]) have been developed and are being validated for various applications, including use by health care providers to assess the state of control of their patients' asthma and by patients for self-assessments as part of a written personal asthma action plan. Uncontrolled asthma may progress to the point of an exacerbation, and immediate steps, described in Component 4, should be taken to regain control.

TREATING TO ACHIEVE CONTROL

The patient's current level of asthma control and current treatment determine the selection of pharmacologic treatment. For example, if asthma is not controlled on the current treatment regimen, treatment should be stepped up until control is achieved. If control has been maintained for at least three months, treatment can be stepped down with the aim of establishing the lowest step and dose of treatment that maintains control (see Monitoring to Maintain Control below). If asthma is partly controlled, an increase in treatment should be considered, subject to whether more effective options are available (e.g., increased dose or an additional treatment), safety and cost of possible treatment options, and the patient's satisfaction with the level of control achieved. The scheme presented in **Figure 4.3-2** is based upon these principles, but the range and sequence of medications used in each clinical setting will vary depending on local availability (for cost or other reasons), acceptability, and preference.

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Figure 4.3-1. LEVELS OF ASTHMA CONTROL

A. Assessment of current clinical control (preferably over 4 weeks)

Characteristic	Controlled (All of the following)	Partly Controlled (Any measure present)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma*†
Limitation of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/ rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV_1)‡	Normal	<80% predicted or personal best (if known)	

B. Assessment of Future Risk (risk of exacerbations, instability, rapid decline in lung function, side-effects)

Features that are associated with increased risk of adverse events in the future include:

Poor clinical control, frequent exacerbations in past year*, ever admission to critical care for asthma, low FEV_1, exposure to cigarette smoke, high dose medications

* Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate
† By definition, an exacerbation in any week makes that an uncontrolled asthma week
‡ Without administration of bronchodilator.
Lung function is not a reliable test for children 5 years and younger.

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Treatment Steps for Achieving Control

Most of the medications available for asthma patients, when compared with medications used for other chronic diseases, have extremely favorable therapeutic ratios. Each step represents treatment options that, although not of identical efficacy, are alternatives for controlling asthma. *Steps 1* to *5* provide options of increasing efficacy, except for *Step 5* where issues of availability and safety influence the selection of treatment. *Step 2* is the initial treatment for most treatment-naïve patients with persistent asthma symptoms. If symptoms at the initial consultation suggest that asthma is severely uncontrolled (**Figure 4.3-1**), treatment should be commenced at *Step 3*.

At each treatment step, a reliever medication (**rapid-onset bronchodilator**, either short-acting or long-acting) should be provided for quick relief of symptoms. However, regular use of reliever medication is one of the elements defining uncontrolled asthma, and indicates that controller treatment should be increased. Thus, reducing or eliminating the need for reliever treatment is both an important goal and measure of success of treatment. For *Steps 2* through *5*, a variety of controller medications are available.

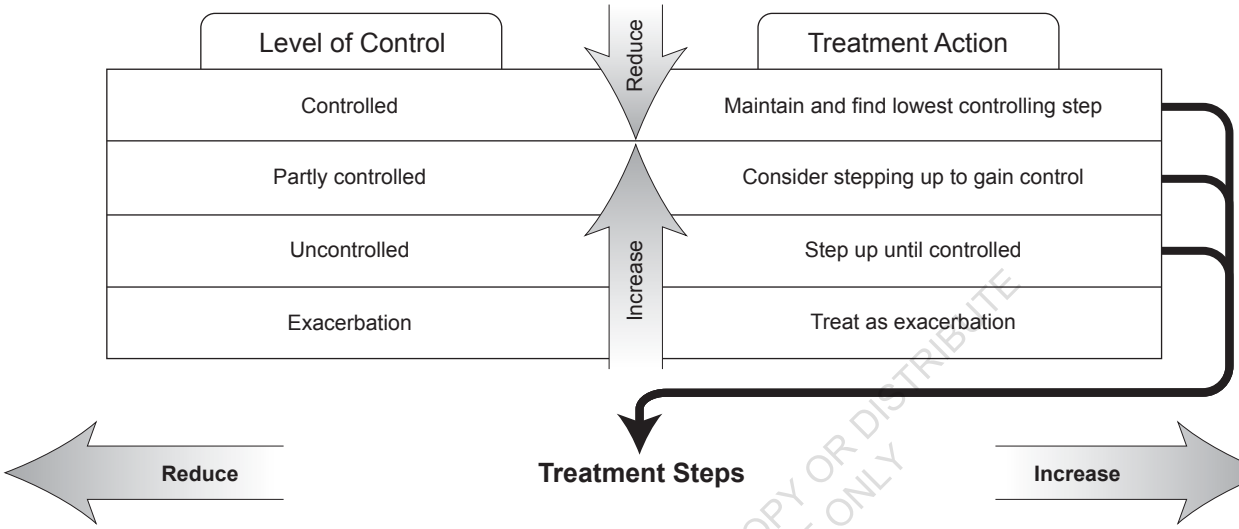
Step 1: as-needed reliever medication. *Step 1* treatment with an as-needed reliever medication is reserved for untreated patients with occasional daytime symptoms (cough, wheeze, dyspnea occurring twice or less per week, or less frequently if nocturnal) of short duration (lasting only a few hours) comparable with controlled asthma (**Figure 4.3-1**). Between episodes, the patient is asymptomatic with normal lung function and there is no nocturnal awakening. When symptoms are more frequent, and/or worsen periodically, patients require regular controller treatment (see *Steps 2* or higher) in addition to as-needed reliever medication[111-113] (**Evidence B**).

For the majority of patients in *Step 1*, **a rapid-acting inhaled β_2-agonist** is the recommended reliever treatment[114] (**Evidence A**). An inhaled anticholinergic, short-acting oral β_2-agonist, or short-acting theophylline may be considered as alternatives, although they have a slower onset of action and higher risk of side effects (**Evidence A**).

Figure 4.3-2.

Management Approach Based On Control

For Children Older Than 5 Years, Adolescents and Adults



Reduce **Treatment Steps** **Increase**

Step 1	Step 2	Step 3	Step 4	Step 5
Asthma education. Environmental control. (If step-up treatment is being considered for poor symptom control, first check inhaler technique, check adherence, and confirm symptoms are due to asthma.)				
As needed rapid-acting β_2-agonist	As needed rapid-acting β_2-agonist			
Controller options***	Select one	Select one	To Step 3 treatment, select one or more	To Step 4 treatment, add either
	Low-dose inhaled ICS*	Low-dose ICS plus long-acting β_2-agonist	Medium-or high-dose ICS plus long-acting β_2-agonist	Oral glucocorticosteroid (lowest dose)
	Leukotriene modifier**	Medium-or high-dose ICS Low-dose ICS plus leukotriene modifier	Leukotriene modifier Sustained release theophylline	Anti-IgE treatment
		Low-dose ICS plus sustained release theophylline		

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* ICS = inhaled glucocorticosteroids
**= Receptor antagonist or synthesis inhibitors
*** = Recommended treatment (shaded boxes) based on group mean data. Individual patient needs, preferences, and circumstances (including costs) should be considered.

Alternative reliever treatments include inhaled anticholinergics, short-acting oral β_2-agonists, some long-acting β_2-agonists, and short-acting theophylline. Regular dosing with short and long-acting β_2-agonists is not advised unless accompanied by regular use of an inhaled glucocorticorsteriod.

For management of asthma in children 5 years and younger, refer to the *Global Strategy for the Diagnosis and Management of Asthma in Children 5 Years and Younger,* available at http://www.ginasthma.org.

Exercise-induced bronchoconstriction. Physical activity is an important cause of asthma symptoms for most asthma patients, and for some it is the only cause. However, exercise-induced bronchoconstriction often indicates that the patient's asthma is not well controlled, and stepping up controller therapy generally results in the reduction of exercise-related symptoms. For those patients who still experience exercise-induced bronchoconstriction despite otherwise well-controlled asthma, and for those in whom exercise-induced bronchoconstriction is the only manifestation of asthma, a rapid-acting inhaled β_2-agonist (short-or long-acting), taken prior to exercise or to relieve symptoms that develop after exercise, is recommended[115]. A leukotriene modifier[116,345] or cromone[117] are alternatives (**Evidence A**). Training and sufficient warm-up also reduce the incidence and severity of exercise-induced bronchoconstriction[118,119] (**Evidence B**). 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[359] and the World Anti-Doping Agency website (www.wada-ama.org).

Step 2: Reliever medication plus a single controller. Treatment *Steps 2* through *5*, combine an as-needed reliever treatment with regular controller treatment. At *Step 2*,a **low-dose inhaled glucocorticosteroid** is recommended as the initial controller treatment for asthma patients of all ages[111,120] (**Evidence A**). Equivalent doses of inhaled glucocorticosteroids, some of which may be given as a single daily dose, are provided in **Figure 3-1** for adults and in **Figure 3-4** for children older than 5 years.

Alternative controller medications include **leukotriene modifiers**[121-123] (**Evidence A**), appropriate particularly for patients who are unable or unwilling to use inhaled glucocorticosteroids, or who experience intolerable side effects such as persistent hoarseness from inhaled glucocorticosteroid treatment and those with concomitant allergic rhinitis[124,125] (**Evidence C**).

Other options are available but not recommended for routine use as initial or first-line controllers in *Step 2*. **Sustained-release theophylline** has only weak anti-inflammatory and controller efficacy[126-130] (**Evidence B**) and is commonly associated with side effects that range from trivial to intolerable[131,132] . **Cromones (nedocromil sodium and sodium cromoglycate)** have comparatively low efficacy, though a favorable safety profile[133-136] (**Evidence A**).

Step 3: Reliever medication plus one or two controllers. At *Step 3*, the recommended option for children[403] and adolescents and adults is to combine a **low-dose of inhaled glucocorticosteroid with an inhaled long-acting ß$_2$-agonist**, either in a combination inhaler device or as separate components[137-144] (**Evidence A**). Because of the additive effect of this combination, the low-dose of glucocorticosteroid is usually sufficient, and need only be increased if control is not achieved within 3 or 4 months with this regimen (**Evidence A**). The long-acting β_2-agonist formoterol, which has a rapid onset of action whether given alone[145,146,148] or in combination inhaler with budesonide[149], has been shown to be as effective as short-acting β_2-agonist in acute asthma exacerbation. However its use as monotherapy as a reliever medication is strongly discouraged since it must always be used in association with an inhaled glucocorticosteroid.

For all children but particularly those 5 years and younger, combination therapy has been less well studied and the addition of a long-acting β_2-agonist may not be as effective as increasing the dose of inhaled glucocorticosteroids in reducing exacerbations[151-153] . However, the interpretation of some studies is problematic as not all children received concurrent inhaled glucocorticosteroids[152,153] .

If a combination inhaler containing formoterol and budesonide is selected, it may be used for both rescue and maintenance. This approach has been shown to result in reductions in exacerbations and improvements in asthma control in adults and adolescents at relatively low doses of treatment[154-157] (**Evidence A**). Whether this approach can be employed with other combinations of controller and reliever requires further study.

Another option for both adults and children, but the one recommended for children[158], is to increase to a **medium-dose of inhaled glucocorticosteroids**[104,159-161] (**Evidence A**). For patients of all ages on medium-or high-dose of inhaled glucocorticosteroid delivered by a pressurized metered-dose inhaler, use of a spacer device is recommended to improve delivery to the airways, reduce oropharyngeal side effects, and reduce systemic absorption[162-164] (**Evidence A**).

Another option at *Step 3* is to combine a low-dose inhaled glucocorticosteroid with leukotriene modifiers[165-173] (**Evidence A**). Alternatively, the use of sustained-release theophylline given at low-dose may be considered[129] (**Evidence B**). These options have not been fully studied in children 5 years and younger.

Step 4: Reliever medication plus two or more controllers. The selection of treatment at *Step 4* depends on prior selections at *Steps 2* and *3*. However, the order in which additional medications should be added is based, as far as possible, upon evidence of their relative efficacy in clinical trials. Where possible, patients who are not

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controlled on *Step 3* treatments should be **referred to a health professional with expertise in the management of asthma** for investigation of alternative diagnoses and/or causes of difficult-to-treat asthma.

The preferred treatment at *Step 4* is to combine a **medium-or high-dose of inhaled glucocorticosteroid with a long-acting inhaled β2-agonist**. However, in most patients, the increase from a medium-to a high-dose of inhaled glucocorticosteroid provides relatively little additional benefit[104,159-161,174] (**Evidence A**), and the high-dose is recommended only on a trial basis for 3 to 6 months when control cannot be achieved with medium-dose inhaled glucocorticosteroid combined with a long-acting β_2-agonist and/or a third controller (e.g. leukotriene modifiers or sustained-release theophylline)[130,175,346] (**Evidence B**). Prolonged use of high-dose inhaled glucocorticosteroids is also associated with increased potential for adverse effects. At medium-and high-doses, twice-daily dosing is necessary for most but not all inhaled glucocorticosteroids[176] (**Evidence A**). With budesonide, efficacy may be improved with more frequent dosing (four times daily)[177] (**Evidence B**). (Refer to **Figure 3-1** for adults and **Figure 3-4** for children older than 5 years for recommendations on dosing and frequency for different inhaled glucocorticosteroids.)

Leukotriene modifiers as add-on treatment to medium-to high-dose inhaled glucocorticosteroids have been shown to provide benefit (**Evidence A**), but usually less than that achieved with the addition of a long-acting β_2-agonist[165-168,175,178] (**Evidence A**). The addition of a low-dose of **sustained-release theophylline**[130] to medium-or high-dose inhaled glucocorticosteroid and long-acting β_2-agonist may also provide benefit (**Evidence B**)[129] .

Step 5: Reliever medication plus additional controller options. Addition of **oral glucocorticosteroids** to other controller medications may be effective[179] (**Evidence D**) but is associated with severe side effects[180] (**Evidence A**) and should only be considered if the patient's asthma remains severely uncontrolled on *Step 4* medications with daily limitation of activities and frequent exacerbations. Patients should be counseled about potential side effects and all other alternative treatments must be considered.

Addition of **anti-IgE treatment** to other controller medications has been shown to improve control of allergic asthma when control has not been achieved on combinations of other controllers including high-doses of inhaled or oral glucocorticosteroids[181-186] (**Evidence B**).

MONITORING TO MAINTAIN CONTROL

When asthma control has been achieved, ongoing monitoring is essential to maintain control and to establish the lowest step and dose of treatment necessary, which minimizes the cost and maximizes the safety of treatment. On the other hand, asthma is a variable disease, and treatment has to be adjusted periodically in response to loss of control as indicated by worsening symptoms or the development of an exacerbation.

Asthma control should be monitored by the health care professional and preferably also by the patient at regular intervals, using either a simplified scheme as presented in **Figure 4.3-1** or a validated composite measure of control. The frequency of health care visits and assessments depends upon the patient's initial clinical severity, and the patient's training and confidence in playing a role in the on-going control of his or her asthma. Typically, patients are seen one to three months after the initial visit, and every three months thereafter. After an exacerbation, follow-up should be offered within two weeks to one month (**Evidence D**). General practitioners should be encouraged to assess asthma control at every visit, not just when the patient presents because of their asthma[380].

Duration and Adjustments to Treatment

For most classes of controller medications, improvement begins within days of initiating treatment, but the full benefit may only be evident after 3 or 4 months[360]. In severe and chronically undertreated disease, this can take even longer[188].

The reduced need for medication once control is achieved is not fully understood, but may reflect the reversal of some of the consequences of long-term inflammation of the airways. Higher doses of anti-inflammatory medication may be required to achieve this benefit than to maintain it. Alternatively, the reduced need for medication might simply represent spontaneous improvement as part of the cyclical natural history of asthma. Rarely, asthma may go into remission particularly in children aged 5 years and younger and during puberty. Whatever the explanation, in all patients the minimum controlling dose of treatment must be sought through a process of regular follow-up and staged dose reductions.

At other times treatment may need to be increased either in response to loss of control or threat of loss of control (return of symptoms) or an acute exacerbation, which is defined as a more acute and severe loss of control that

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requires urgent treatment. (An approach to exacerbations is provided in Component 4.4.)

Stepping Down Treatment When Asthma Is Controlled

There is little experimental data on the optimal timing, sequence, and magnitude of treatment reductions in asthma, and the approach will differ from patient to patient depending on the combination of medications and the doses that were needed to achieve control. These changes should ideally be made by agreement between patient and health care professional, with full discussion of potential consequences including reappearance of symptoms and increased risk of exacerbations. Although further research on stepping down asthma treatment is needed, some recommendations can be made based on the current evidence:

- When **inhaled glucocorticosteroids alone** in medium-to high-doses are being used, a 50% reduction in dose should be attempted at 3 month intervals[189-191] (**Evidence B**).
- Where control is achieved at a low-dose of inhaled glucocorticosteroids alone, in most patients treatment may be switched to once-daily dosing[192,193] (**Evidence A**).
- When asthma is controlled with a **combination of inhaled glucocorticosteroid and long-acting ß$_2$-agonist**, the preferred approach to is to begin by reducing the dose of inhaled glucocorticosteroid by approximately 50% while continuing the long-acting β_2-agonist (**Evidence B**). If control is maintained, further reductions in the glucocorticosteroid should be attempted until a low-dose is reached, when the long-acting β_2-agonist may be stopped (**Evidence D**). An alternative is to switch the combination treatment to once-daily dosing[187,194]. A second alternative is to discontinue the long-acting β_2-agonist at an earlier stage and substitute the combination treatment with inhaled glucocorticosteroid monotherapy at the same dose contained in the combination inhaler. However, this is more likely to lead to loss of asthma control[368] (**Evidence B**).
- When asthma is controlled with **inhaled glucocorticosteroids in combination with controllers other than long-acting β_2-agonists**, the dose of inhaled glucocorticosteroid should be reduced by 50% until a low-dose of inhaled glucocorticosteroid is reached, then the combination treatment stopped as described above (**Evidence D**).
- **Controller treatment may be stopped** if the patient's asthma remains controlled on the lowest dose of controller and no recurrence of symptoms occurs for one year (**Evidence D**).

Stepping Up Treatment In Response To Loss Of Control

Treatment has to be adjusted periodically in response to worsening control, which may be recognized by the minor recurrence or worsening of symptoms[195]. Treatment options are as follows:

- **Rapid-onset, short-acting or long-acting ß$_2$-agonist bronchodilators.** Repeated dosing with bronchodilators in this class provides temporary relief until the cause of the worsening symptoms passes. The need for repeated doses over more than one or two days signals the need for review and possible increase of controller therapy.
- In the context of asthma self-management studies, action plans in which the dose of inhaled glucocorticosteroids was at least doubled were associated with improved asthma outcomes and reduced health care utilisation[32]. In placebo-controlled trials, temporarily doubling the dose of inhaled glucocorticosteroids was not effective[404] (**Evidence A**), but an average interval of 5-7 days between the onset of worsening symptoms and increase of the inhaled glucocorticosteroid dose[194, 196] may have been a factor. There is emerging evidence that higher doses of inhaled glucocorticosteroid might be effective for preventing progression to severe exacerbation[195,404]. Patients who quadrupled their dose of inhaled glucocorticosteroid after their peak flow fell were significantly less likely to require oral glucocorticosteroids[381]. In adult patients with an acute deterioration, high-dose inhaled glucocorticosteroids have been demonstrated to be equivalent to a short course of oral glucocorticosteroids[195] (**Evidence A**). In these studies, the higher dose was maintained for seven to fourteen days. More research is needed in both adults and children to standardize the approach.
- **Combination of inhaled glucocorticosteroids and rapid and long-acting ß$_2$-agonist bronchodilator (e.g. formoterol) for combined relief and control.** The use of the combination of a rapid and long-acting β_2-agonist (formoterol) and an inhaled glucocorticosteroid (budesonide) in a single inhaler both as a controller and reliever is effective in maintaining a high level of asthma control and reduces exacerbations requiring systemic glucocorticosteroids and hospitalization[111,156,157,197]

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(**Evidence A**). The benefit in preventing exacerbations appears to be the consequence of early intervention at a very early stage of a threatened exacerbation since studies involving doubling or quadrupling doses of combination treatment once deterioration is established (for 2 or more days) show some benefit but results are inconsistent[195]. Because there are no studies using this approach with other combinations of controller and relievers, other than budesonide/formoterol, the alternative approaches described in this section should be used for patients on other controller therapies.

For children (6 to 17 years) who have uncontrolled asthma despite the use of low-dose inhaled glucocorticosteroids, step-up therapy with long-acting β_2-agonist bronchodilator was significantly more likely to provide the best response than either step-up therapy with inhaled glucocorticosteroids or leukotriene receptor antagonist. However, many children had a best response to inhaled glucocorticosteroids or leukotriene receptor antagonist step-up therapy, highlighting the need to regularly monitor and appropriately adjust each child's asthma therapy[382].

Combination therapy with budesonide and formoterol used both as maintenance and rescue has been shown to reduce asthma exacerbations in children ages 4 years and older with moderate to severe asthma[347].

The usual treatment for an acute exacerbation is a high-dose of β_2-agonist and a burst of systemic glucocorticosteroids administered orally or intravenously. (Refer to Component 4 for more information.)

Following treatment for an exacerbation of asthma, maintenance treatment can generally be resumed at previous levels unless the exacerbation was associated with a gradual loss of control suggesting chronic undertreatment. In this case, provided inhaler technique has been checked, a step-wise increase in treatment (either in dose or number of controllers) is indicated.

Difficult-to-Treat Asthma

Although the majority of asthma patients can obtain the targeted level of control (**Figure 4.3-1**), some patients will not do so even with the best therapy[104]. Patients who do not reach an acceptable level of control at *Step 4* (**reliever medication plus two or more controllers**) can be considered to have difficult-to-treat asthma[198]. These patients may have an element of poor glucocorticosteroid responsiveness, and require higher doses of inhaled glucocorticosteroids than are routinely used in patients whose asthma is easy to control. However, there is currently no evidence to support continuing these high-doses of inhaled glucocorticosteroids beyond 6 months in the hope of achieving better control. Instead, dose optimization should be pursued by stepping down to a dose that maintains the maximal level of control achieved on the higher dose.

Because very few patients are completely resistant to glucocorticosteroids, these medications remain a mainstay of therapy for difficult-to-treat asthma, while additional diagnostic and generalized therapeutic options can and should also be considered:

- Confirm the **diagnosis** of asthma. In particular, the presence of COPD must be excluded. Vocal cord dysfunction must be considered.
- Investigate and confirm **adherence** with treatment. Incorrect or inadequate use of medications and inhalers[405] remains the most common reason for failure to achieve good control. In patients with difficult-to-treat asthma, improved adherence and improved health outcomes can be achieved with a comprehensive concordance intervention[416].
- Consider **smoking, current or past**, and encourage complete cessation. A history of past tobacco smoking is associated with a reduced likelihood of complete asthma control, and this is only partly attributable to the presence of fixed airflow obstruction. In addition, current smoking reduces the effectiveness of inhaled and oral glucocorticosteroids[71,72,378]. Counseling and smoking cessation programs should be offered to all asthma patients who smoke.
- Investigate the presence of **comorbidities** that may aggravate asthma. Chronic sinusitis, gastroesophageal reflux, and obesity/obstructive sleep apnea have been reported in higher percentages in patients with difficult-to-treat asthma. Psychological and psychiatric disorders should also be considered. If found, these comorbidities should be addressed and treated as appropriate, although the ability to improve asthma control by doing so remains unconfirmed[200,348].

When these reasons for lack of treatment response have been considered and addressed, a compromise level of control may need to be accepted and discussed with the patient to avoid futile over-treatment (with its attendant cost and potential for adverse effects). The objective is then to minimize exacerbations and need for emergency medical interventions while achieving as high a level of

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clinical control with as little disruption of activities and as few daily symptoms as possible. For these difficult-to-treat patients, frequent use of rescue medication is accepted, as is a degree of chronic lung function impairment. Although lower levels of control are generally associated with an increased risk of exacerbations, not all patients with chronically impaired lung function, reduced activity levels, and daily symptoms have frequent exacerbations. In such patients, the lowest level of treatment that retains the benefits achieved at the higher doses of treatment should be employed. Reductions should be made cautiously and slowly at intervals not more frequent than 3 to 6 months, as carryover of the effects of the higher dose may last for several months and make it difficult to assess the impact of the dose reduction (**Evidence D**). Referral to a physician with an interest in and/or special focus on asthma may be helpful and patients may benefit from phenotyping into categories such as allergic, aspirin-sensitive, and/or eosinophilic asthma[201]. Patients categorized as allergic might benefit from anti-IgE therapy[183], and leukotriene modifiers can be helpful for patients determined to be aspirin sensitive (who are often eosinophilic as well)[172] .

Thermoplasty

GRADE evidence technology was used to evaluate research on thermoplasty:

Question: "In adult patient whose asthma is uncontrolled despite recommended therapeutic regimens, does thermoplasty, compared to placebo improve patient outcomes?" The consensus recommendation:

- For adult patients whose asthma remains uncontrolled despite application of this therapeutic paradigm, and referral to an asthma specialty center, bronchial thermoplasty is now a possible option in some countries[406-408]. In this bronchoscopic treatment, airways are treated on three occasions with a localized radiofrequency pulse. The treatment, which itself is associated with asthma exacerbations in the months post bronchoscopy, results in a subsequent decrease in exacerbations. There are no significant effects on lung function or asthma symptoms. Extended follow-up on a small number of patients has provided some additional support for long-term safety of bronchial thermoplasty[417]. However, longer-term follow-up of larger number of control and active patients is needed to assess effectiveness and caution should be used in selecting patients for this procedure.

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COMPONENT 4: MANAGE ASTHMA EXACERBATIONS

KEY POINTS:

- Exacerbations of asthma (asthma attacks or acute asthma) are episodes of progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms.
- Exacerbations are characterized by decreases in expiratory airflow that can be quantified and monitored by measurement of lung function (PEF or FEV_1).
- The primary therapies for exacerbations include the repetitive administration of rapid-acting inhaled bronchodilators, the early introduction of systemic glucocorticosteroids, and oxygen supplementation.
- The aims of treatment are to relieve airflow obstruction and hypoxemia as quickly as possible, and to plan the prevention of future relapses.
- Severe exacerbations are potentially life threatening, and their treatment requires close supervision. Most patients with severe asthma exacerbations should be treated in an acute care facility. Patients at high risk of asthma-related death also require closer attention.
- Milder exacerbations, defined by a reduction in peak flow of less than 20%, nocturnal awakening, and increased use of short acting β_2-agonists can usually be treated in a community setting.

INTRODUCTION

Exacerbations of asthma (asthma attacks or acute asthma) are episodes of progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms. Exacerbations usually have a progressive onset but a subset of patients (mostly adults) present more acutely[361]. Respiratory distress is common. Exacerbations are characterized by decreases in expiratory airflow that can be quantified by measurement of lung function (PEF or FEV_1)[202] . These measurements are more reliable indicators of the severity of airflow limitation than is the degree of symptoms. The degree of symptoms may, however, be a more sensitive measure of the onset of an exacerbation because the increase in symptoms usually precedes the deterioration in peak flow rate[203] . Still, a minority of patients perceive symptoms poorly, and may have a significant decline in lung function without a significant change in symptoms. This situation especially affects patients with a history of near-fatal asthma and also appears to be more likely in males. A clinically useful tool to assess the likelihood of asthma-related hospitalizations or emergency department visits in adults with severe or difficult to treat asthma have been described[349,418].

Strategies for treating exacerbations, though generalizable, are best adapted and implemented at a local level[204,205]. Severe exacerbations are potentially life threatening, and their treatment requires close supervision. Patients with severe exacerbations should be encouraged to see their physician promptly or, depending on the organization of local health services, to proceed to the nearest clinic or hospital that provides emergency access for patients with acute asthma. Close objective monitoring (PEF) of the response to therapy is essential.

The primary therapies for exacerbations include—in the order in which they are introduced, depending on severity— repetitive administration of rapid-acting inhaled bronchodilators, early introduction of systemic glucocorticosteroids, and oxygen supplementation[202]. The aims of treatment are to relieve airflow obstruction and hypoxemia as quickly as possible, and to plan the prevention of future relapses.

Patients at high risk of asthma-related death require closer attention and should be encouraged to seek urgent care early in the course of their exacerbations. These patients include those:

- With a history of near-fatal asthma requiring intubation and mechanical ventilation[206]
- Who have had a hospitalization or emergency care visit for asthma in the past year
- Who are currently using or have recently stopped using oral glucocorticosteroids
- Who are not currently using inhaled glucocorticosteroids[207]
- Who are overdependent on rapid-acting inhaled β2-agonists, especially those who use more than one canister of salbutamol (or equivalent) monthly[208]
- With a history of psychiatric disease or psychosocial[350] problems, including the use of sedatives[209]
- With a history of poor adherence with asthma medications and/or a written asthma action plan.

Response to treatment may take time and patients should be closely monitored using clinical as well as objective measurements. The increased treatment should continue

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until measurements of lung function (PEF or FEV_1) return to their previous best (ideally) or plateau, at which time a decision to admit or discharge can be made based upon these values. Patients who can be safely discharged will have responded within the first two hours, at which time decisions regarding patient disposition can be made.

ASSESSMENT OF SEVERITY

The severity of the exacerbation (**Figure 4.4-1**) determines the treatment administered. Indices of severity, particularly PEF (in patients older than 5 years), pulse rate, respiratory rate, and pulse oximetry[210], should be monitored during treatment.

MANAGEMENT—COMMUNITY SETTINGS

Most patients with severe asthma exacerbations should be treated in an acute care facility (such as a hospital emergency department) where monitoring, including

Figure 4.4-1. Severity of Asthma Exacerbations*

	Mild	Moderate	Severe	Respiratory arrest imminent
Breathless	Walking Can lie down	Talking Infant—softer shorter cry; difficulty feeding Prefers sitting	At rest Infant stops feeding Hunched forward	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Respiratory rate	Increased	Increased	Often > 30/min	
	Normal rates of breathing in awake children: *Age* — *Normal rate* < 2 months — < 60/min 2-12 months — < 50/min 1-5 years — < 40/min 6-8 years — < 30/min			
Accessory muscles and suprasternal retractions	Usually not	Usually	Usually	Paradoxical thoraco-abdominal movement
Wheeze	Moderate, often only end expiratory	Loud	Usually loud	Absence of wheeze
Pulse/min.	< 100	100-120	>120	Bradycardia
	Guide to limits of normal pulse rate in children: Infants — 2-12 months–Normal Rate — < 160/min Preschool — 1-2 years — < 120/min School age — 2-8 years — < 110/min			
Pulsus paradoxus	Absent < 10 mm Hg	May be present 10-25 mm Hg	Often present > 25 mm Hg (adult) 20-40 mm Hg (child)	Absence suggests respiratory muscle fatigue
PEF after initial bronchodilator % predicted or % personal best	Over 80%	Approx. 60-80%	< 60% predicted or personal best (< 100 L/min adults) or response lasts < 2 hrs	
PaO_2 (on air)† and/or $PaCO_2$†	Normal Test not usually necessary < 45 mm Hg	> 60 mm Hg < 45 mm Hg	< 60 mm Hg Possible cyanosis > 45 mm Hg; Possible respiratory failure (see text)	
SaO_2% (on air)†	> 95%	91-95%	< 90%	
	Hypercapnea (hypoventilation) develops more readily in young children than in adults and adolescents.			

*Note: The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.
†Note: Kilopascals are also used internationally; conversion would be appropriate in this regard.

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objective measurement of airflow obstruction, oxygen saturation, and cardiac function, is possible. Milder exacerbations, defined by a reduction in peak flow of less than 20%, nocturnal awakening, and increased use of short acting β_2-agonists can usually be treated in a community setting. If the patient responds to the increase in inhaled bronchodilator treatment after the first few doses, referral to an acute care facility is not required, but further management under the direction of a primary care physician may include the use of systemic glucocorticosteroids. Patient education and review of maintenance therapy should also be undertaken.

Treatment

Bronchodilators. For mild to moderate exacerbations, repeated administration of rapid-acting inhaled β-agonists (2 to 4 puffs every 20 minutes for the first hour) is usually the best and most cost-effective method of achieving rapid reversal of airflow limitation. After the first hour, the dose of β-agonist required will depend on the severity of the exacerbation. Mild exacerbations respond to 2 to 4 puffs every 3 to 4 hours; moderate exacerbations will require 6 to 10 puffs every 1 or 2 hours. Treatment should also be titrated depending upon the individual patient's response, and if there is a lack of response or other concern about how the patient is responding, the patient should be referred to an acute care facility.

Many patients will be able to monitor their PEF after the initiation of increased bronchodilator therapy. Bronchodilator therapy delivered via a metered-dose inhaler (MDI), ideally with a spacer, produces at least an equivalent improvement in lung function as the same dose [164,211] delivered via nebulizer. At the clinic level, this route of delivery is the most cost effective[212], provided patients are able to use an MDI. No additional medication is necessary if the rapid-acting inhaled β-agonist produces a complete response (PEF returns to greater than 80% of predicted or personal best) and the response lasts for 3 to 4 hours.

Glucocorticosteroids. Oral glucocorticosteroids (0.5 to 1 mg of prednisolone/kg or equivalent during a 24-hour period) should be used to treat exacerbations, especially if they develop after instituting the other short-term treatment options recommended for loss of control (see "Stepping up treatment in response to loss of control" in Component 3). If patients fail to respond to bronchodilator therapy, as indicated by persistent airflow obstruction, prompt transfer to an acute care setting is recommended, especially if they are in a high risk group.

MANAGEMENT—ACUTE CARE SETTINGS

Severe exacerbations of asthma are life-threatening medical emergencies, treatment of which is often most safely undertaken in an emergency department. **Figure 4.4-2** illustrates the approach to acute care-based management of exacerbations.

Assessment

A brief history and physical examination pertinent to the exacerbation should be conducted concurrently with the prompt initiation of therapy. The history should include: severity and duration of symptoms, including exercise limitation and sleep disturbance; all current medications, including dose (and device) prescribed, dose usually taken, dose taken in response to the deterioration, and the patient's response (or lack thereof) to this therapy; time of onset and cause of the present exacerbation; and risk factors for asthma-related death.

The physical examination should assess exacerbation severity by evaluating the patient's ability to complete a sentence, pulse rate, respiratory rate, use of accessory muscles, and other signs detailed in **Figure 4.4-2**. Any complicating factors should be identified (e.g., pneumonia, atelectasis, pneumothorax, or pneumomediastinum). Functional assessments such as PEF or FEV_1 and arterial oxygen saturation measurements are strongly recommended as physical examination alone may not fully indicate the severity of the exacerbation, particularly the degree of hypoxemia[213,214] . Without unduly delaying treatment, a baseline PEF or FEV_1 measurement should be made before treatment is initiated, although spirometry may not be possible in children with acute asthma. Subsequent measurements should be made at intervals until a clear response to treatment has occurred.

Oxygen saturation should be closely monitored, preferably by pulse oximetry. This is especially useful in children because objective measurements of lung function may be difficult. Oxygen saturation in children should normally be greater than 95%, and oxygen saturation less than 92% is a good predictor of the need for hospitalization[210] (**Evidence C**).

In adults a chest X-ray is not routinely required, but should be carried out if a complicating cardiopulmonary process is suspected, in patients requiring hospitalization, and in those not responding to treatment where a pneumothorax may be difficult to diagnose clinically[215] . Similarly, in children routine chest X-rays are not recommended unless there are physical signs suggestive of parenchymal disease[216] .

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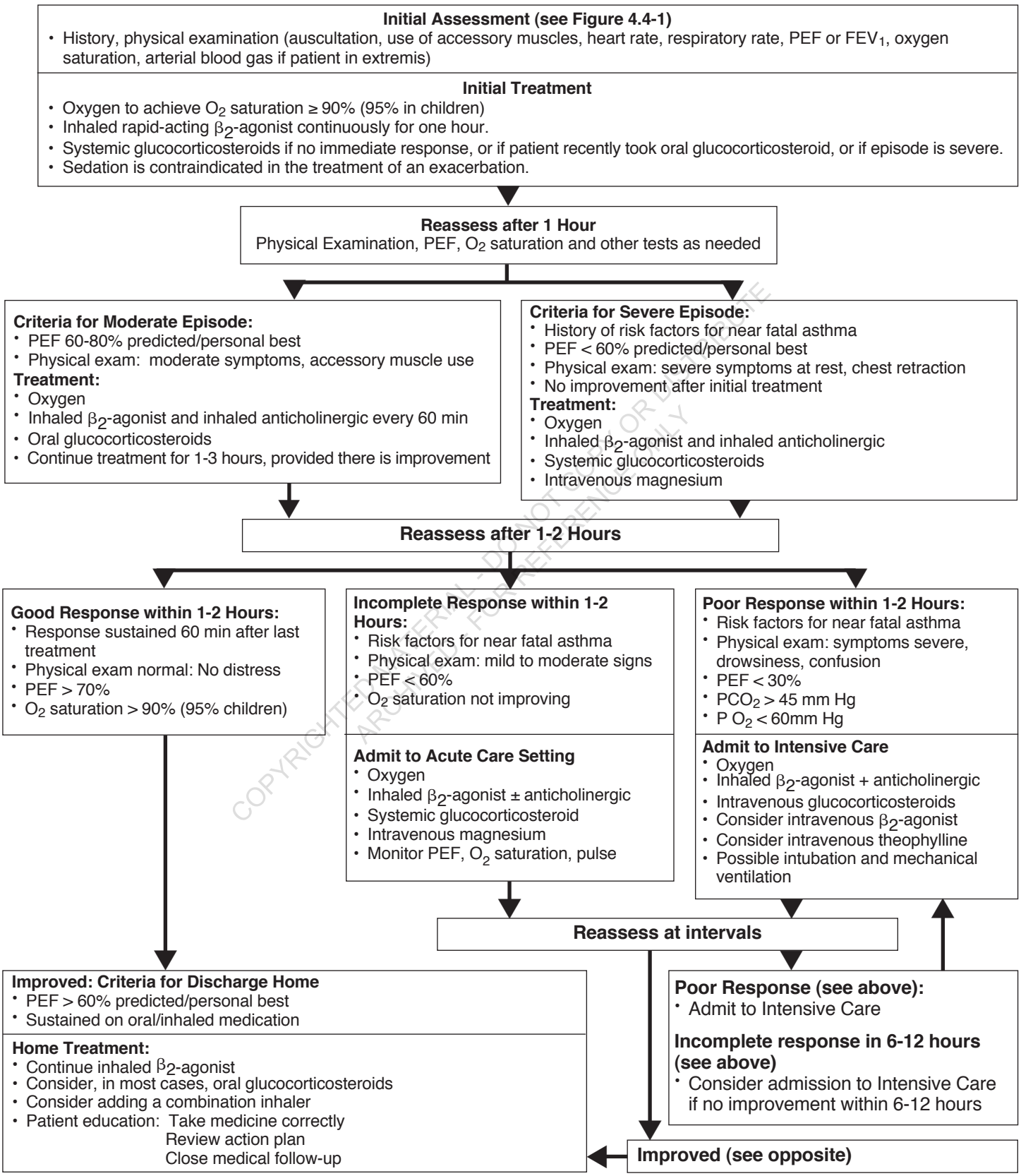
Figure 4.4-2: Management of Asthma Exacerbations in Acute Care Setting



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Although arterial blood gas measurements are not routinely required[216], they should be completed in patients with a PEF of 30 to 50% predicted, those who do not respond to initial treatment, or when there is concern regarding deterioration. The patient should continue on supplemental oxygen while the measurement is made. A PaO_2 < 60 mm Hg (8 kPa) and a normal or increased PaCO2 (especially > 45 mm Hg, 6 kPa) indicates the presence of respiratory failure.

Treatment

The following treatments are usually administered concurrently to achieve the most rapid resolution of the exacerbation[217]:

Oxygen. To achieve arterial oxygen saturation of 90% (95% in children), oxygen should be administered by nasal cannulae, by mask, or rarely by head box in some infants. For severe asthma exacerbations, controlled oxygen therapy using pulse oximetry to maintain oxygen saturation at 90 – 93% is associated with better physiological outcomes, compared to high flow 100% oxygen therapy[218, 419]. Oxygen therapy should be titrated against pulse oximetry to maintain a satisfactory oxygen saturation[219]. However, oxygen should not be withheld if oximetry is not available.

Rapid-acting inhaled ß$_2$–agonists. Rapid-acting inhaled β_2-agonists should be administered at regular intervals[220-222] (**Evidence A**). The most cost effective and efficient delivery is by metered dose inhaler and a spacer device[164, 211]. Although most rapid-acting β_2-agonists have a short duration of effect, the long-acting bronchodilator formoterol, which has both a rapid onset of action and a long duration of effect, has been shown to be equally effective without increasing side effects, though it is considerably more expensive[148]. The importance of this feature of formoterol is that it provides support and reassurance regarding the use of a combination of formoterol and budesonide early in asthma exacerbations.

A modestly greater bronchodilator effect has been shown with levabuterol compared to racemic albuterol in both adults and children with an asthma exacerbation[223-226]. In a large study of acute asthma in children[227], and in adults not previously treated with glucocorticosteroids[226], levabuterol treatment resulted in lower hospitalization rates compared to racemic albuterol treatment, but in children the length of hospital stay was no different[227].

Studies of intermittent versus continuous nebulized short-acting β_2-agonists in acute asthma provide conflicting results. In a systematic review of six studies[228], there were no significant differences in bronchodilator effect or hospital admissions between the two treatments. In patients who require hospitalization, one study[229] found that intermittent on-demand therapy led to a significantly shorter hospital stay, fewer nebulizations, and fewer palpitations when compared with intermittent therapy given every 4 hours. A reasonable approach to inhaled therapy in exacerbations, therefore, would be the initial use of continuous therapy, followed by intermittent on-demand therapy for hospitalized patients. There is no evidence to support the routine use of intravenous β_2-agonists in patients with severe asthma exacerbations[230] .

Epinephrine. A subcutaneous or intramuscular injection of epinephrine (adrenaline) may be indicated for acute treatment of anaphylaxis and angioedema, but is not routinely indicated during asthma exacerbations.

Additional bronchodilators.

Ipratropium bromide. A combination of nebulized β_2-agonist with an anticholinergic (ipratropium bromide) may produce better bronchodilation than either drug alone[231] (**Evidence B**) and should be administered before methylxanthines are considered. Combination β_2-agonist/anticholinergic therapy is associated with lower hospitalization rates[212,232,233] (**Evidence A**) and greater improvement in PEF and FEV_1[233] (**Evidence B**). Similar data have been reported in the pediatric literature[212] (**Evidence A**). However, once children with asthma are hospitalized following intensive emergency department treatment, the addition of nebulized ipratropium bromide to nebulized β_2-agonist and systemic glucocorticosteroids appears to confer no extra benefit[234] .

Theophylline. In view of the effectiveness and relative safety of rapid-acting β_2-agonists, theophylline has a minimal role in the management of acute asthma[235] . Its use is associated with severe and potentially fatal side effects, particularly in those on long-term therapy with sustained-release theophylline, and their bronchodilator effect is less than that of β_2-agonists. The benefit as add-on treatment in adults with severe asthma exacerbations has not been demonstrated. However, in one study of children with near-fatal asthma, intravenous theophylline provided additional benefit to patients also receiving an aggressive regimen of inhaled and intravenous β_2-agonists, inhaled ipatropium bromide, and intravenous systemic glucocorticosteroids[236].

Systemic glucocorticosteroids. Systemic glucocorticosteroids speed resolution of exacerbations and should be utilized in the all but the mildest exacerbations[237,238] (**Evidence A**), especially if:

- The initial rapid-acting inhaled β_2-agonist therapy fails to achieve lasting improvement

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- The exacerbation develops even though the patient was already taking oral glucocorticosteroids
- Previous exacerbations required oral glucocorticosteroids.

Oral glucocorticosteroids are usually as effective as those administered intravenously and are preferred because this route of delivery is less invasive and less expensive[239,240] . If vomiting has occurred shortly after administration of oral glucocorticosteroids, then an equivalent dose should be re-administered intravenously. In patients discharged from the emergency department, intramuscular administration may be helpful[241], especially if there are concerns about compliance with oral therapy. Oral glucocorticosteroids require at least 4 hours to produce clinical improvement. Daily doses of systemic glucocorticosteroids equivalent to 60-80 mg methylprednisolone as a single dose, or 300-400 mg hydrocortisone in divided doses, are adequate for hospitalized patients, and 40 mg methylprednisolone or 200 mg hydrocortisone is probably adequate in most cases[238,242] (**Evidence B**). An oral glucocorticosteroid dose of 1 mg/kg daily is adequate for treatment of exacerbations in children with mild persistent asthma[243]. A 7-day course in adults has been found to be as effective as a 14-day course[244], and a 3-to 5-day course in children is usually considered appropriate (**Evidence B**). Two days of oral dexamethasone can also be used to treat asthma exacerbations, but there are concerns about metabolic side-effects if dexamethasone is continued beyond two days[420]. Evidence suggests that there is no benefit to tapering the dose of oral glucocorticosteroids, either in the short-term[245] or over several weeks, as long as the patient is on maintenance inhaled glucocorticosteroids[246] (**Evidence B**).

Inhaled glucocorticosteroids. Inhaled glucocorticosteroids are effective as part of therapy for asthma exacerbations. In one study, the combination of high-dose inhaled glucocorticosteroids and salbutamol in acute asthma provided greater bronchodilation than salbutamol alone[247] (**Evidence B**), and conferred greater benefit than the addition of systemic glucocorticosteroids across all parameters, including hospitalizations, especially for patients with more severe attacks[248] .

Inhaled glucocorticosteroids can be as effective as oral glucocorticosteroids at preventing relapses[249,250]. Patients discharged from the emergency department on prednisone and inhaled budesonide have a lower rate of relapse than those on prednisone alone[237] (**Evidence B**). A high-dose of inhaled glucocorticosteroid (2.4 mg budesonide daily in four divided doses) achieves a relapse rate similar to 40 mg oral prednisone daily[251] (**Evidence A**). Cost is a significant factor in the use of such high-doses of inhaled glucocorticosteroids, and further studies are required to document their potential benefits, especially cost effectiveness, in acute asthma[252] .

Magnesium*. Intravenous magnesium sulphate (usually given as a single 2 g infusion over 20 minutes) is not recommended for routine use in asthma exacerbations, but can help reduce hospital admission rates in certain patients, including adults with FEV_1 25-30% predicted at presentation, adults and children who fail to respond to initial treatment, and children whose FEV_1 fails to improve above 60% predicted after 1 hour of care[253,254,409] (**Evidence A**). Nebulized salbutamol administered in isotonic magnesium sulfate provides greater benefit than if it is delivered in normal saline[255,256] (**Evidence A**). Intravenous magnesium sulphate has not been studied in young children.

Helium oxygen therapy. A systematic survey of studies that have evaluated the effect of a combination of helium and oxygen, compared to helium alone, suggests there is no routine role for this intervention. It might be considered for patients who do not respond to standard therapy[257].

Leukotriene modifiers. There are little data to suggest a role for leukotriene modifiers in acute asthma[258]. Small investigations have demonstrated improvement in PEF[410], but clinical relevance requires more study.

Sedatives. Sedation should be strictly avoided during exacerbations of asthma because of the respiratory depressant effect of anxiolytic and hypnotic drugs. An association between the use of these drugs and avoidable asthma deaths[209,259] has been demonstrated.

Criteria for Discharge from the Emergency Department vs. Hospitalization

Criteria for determining whether a patient should be discharged from the emergency department or admitted to the hospital have been succinctly reviewed and stratified based on consensus[260] . Patients with a pre-treatment FEV_1 or PEF < 25% percent predicted or personal best, or those with a post-treatment FEV_1 or PEF < 40% percent predicted or personal best, usually require hospitalization. Patients with post-treatment lung function of 40-60% predicted may be discharged, provided that adequate follow-up is available in the community and compliance is assured. Patients with post-treatment lung function 60% predicted can be discharged.

Management of acute asthma in the intensive care unit is beyond the scope of this document and readers are referred to recent comprehensive reviews[261] .

*Visit GINA website, www.ginasthma.org for GRADE review of question "In adults with acute exacerbations of asthma, does intravenous magnesium sulphate compared to placebo improve patient important outcomes?"

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For patients discharged from the emergency department:

- At a minimum, a 7-day course of oral glucocorticosteroids for adults and a shorter course (3-5 days) for children should be prescribed, along with continuation of bronchodilator therapy.
- The bronchodilator can be used on an as-needed basis, based on both symptomatic and objective improvement, until the patient returns to his or her pre-exacerbation use of rapid-acting inhaled β_2-agonists.
- Ipratropium bromide is unlikely to provide additional benefit beyond the acute phase and may be quickly discontinued.
- Patients should initiate or continue inhaled glucocorticosteroids.
- The patient's inhaler technique and use of peak flow meter to monitor therapy at home should be reviewed. Patients discharged from the emergency department with a peak flow meter and action plan have a better response than patients discharged without these resources[8].
- The factors that precipitated the exacerbation should be identified and strategies for their future avoidance implemented.
- The patient's response to the exacerbation should be evaluated. The action plan should be reviewed and written guidance provided[411].
- Use of controller therapy during the exacerbation should be reviewed: whether this therapy was increased promptly, by how much, and, if appropriate, why oral glucocorticosteroids were not added. Consider providing a short course of oral glucocorticosteroids to be on hand for subsequent exacerbations.
- The patient or family should be instructed to contact the primary health care professional or asthma specialist within 24 hours of discharge. A follow-up appointment with the patient's usual primary care professional or asthma specialist should be made within a few days of discharge to assure that treatment is continued until baseline control parameters, including personal best lung function, are reached. Prospective data indicate that patients discharged from the emergency department for follow-up with specialist care do better than patients returned to routine care[262].

An exacerbation severe enough to require hospitalization may reflect a failure of the patient's asthma management or lack of a written asthma action plan. Hospitalized patients may be particularly receptive to information and advice about their illness. Health care providers should take the opportunity to review patient understanding of the causes of asthma exacerbations, avoidance of factors that may cause exacerbations (including, where relevant smoking cessation), the purposes and correct uses of treatment, and the actions to be taken to respond to worsening symptoms or peak flow values[263] (**Evidence A**).

Referral to an asthma specialist should be considered for hospitalized patients. Following discharge from continuous supervision, the patient should be reviewed by the family health care professional or asthma specialist regularly over the subsequent weeks until personal best lung function is reached. Use of incentives improves primary care follow up but has shown no effect on long term outcomes[264]. Patients who come to the emergency department with an acute exacerbation should be especially targeted for an asthma education program, if one is available.

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COMPONENT 5: SPECIAL CONSIDERATIONS

Special considerations are required in managing asthma in relation to pregnancy; obesity; surgery; rhinitis, sinusitis, and nasal polyps; occupational asthma; respiratory infections; gastroesophageal reflux; aspirin-induced asthma; and anaphylaxis.

Pregnancy

During pregnancy the severity of asthma often changes, and patients may require close follow-up and adjustment of medications. In approximately one-third of women asthma becomes worse; in one-third asthma becomes less severe; and in the remaining one-third it remains unchanged during pregnancy[265-267].

Although there is a general concern about the use of any medication in pregnancy, poorly controlled asthma can have an adverse effect on the fetus, resulting in increased perinatal mortality, increased prematurity, and low birth weight[266,267]. The overall perinatal prognosis for children born to women with asthma that is well-managed during pregnancy is comparable to that for children born to women without asthma[268]. For this reason, using medications to obtain optimal control of asthma is justified even when their safety in pregnancy has not been unequivocally proven. For most medications used to treat asthma there is little evidence to suggest an increased risk to the fetus. Appropriately monitored use of theophylline, inhaled glucocorticosteroids[351], β_2-agonists, and leukotriene modifiers (specifically montelukast) is not associated with an increased incidence of fetal abnormalities[369] . Inhaled glucocorticosteroids have been shown to prevent exacerbations of asthma during pregnancy[269,270] (**Evidence B**). As in other situations, the focus of asthma treatment must remain on control of symptoms and maintenance of normal lung function[271]. Acute exacerbations should be treated aggressively in order to avoid fetal hypoxia. Treatment should include nebulized rapid-acting β_2-agonists and oxygen and systemic glucocorticosteroids should be instituted when necessary.

While all patients should have adequate opportunity to discuss the safety of their medications, pregnant patients with asthma should be advised that the greater risk to their baby lies with poorly controlled asthma, and the safety of most modern asthma treatments should be stressed. Even with a good patient/health care professional relationship, independent printed material, such as a statement from the US National Asthma Education and Prevention Program on the treatment of asthma during pregnancy[272], will provide important additional reassurance[265,273].

Obesity

Asthma is more difficult to control in the obese patient [383-386]. This may be due to a different type of airway inflammation (less eosinophilic), obesity-related co-morbidities such as obstructive sleep apnea and gastroesophageal reflux, mechanical factors or other as yet undefined factors. There is not sufficient evidence to suggest that the management of asthma in the obese should be different than in patients with normal weight. However, there seems to be a reduced response to inhaled glucocorticosteroids in the obese patient, and although this seems to be less evident with leukotriene antagonists, inhaled glucocorticosteroids are considered the mainstay of asthma treatment in this population[385, 386].

Although asthma is not more often over-diagnosed in obese compared to non-obese patients, it is particularly important to confirm the diagnosis by objective measures of variable airway obstruction or bronchial hyper-responsiveness, as respiratory symptoms associated to obesity may mimic asthma[388]. Weight loss in the obese patient improves asthma control, lung function and reduces medication needs and should be included in the treatment plan[94,389,390]

Surgery

Airway hyperresponsiveness, airflow limitation, and mucus hypersecretion predispose patients with asthma to intraoperative and postoperative respiratory complications. The likelihood of these complications depends on the severity of asthma at the time of surgery, the type of surgery (thoracic and upper abdominal surgeries pose the greatest risks), and type of anesthesia (general anesthesia with endotracheal intubation carries the greatest risk). These variables need to be assessed prior to surgery and pulmonary function should be measured. If possible, this evaluation should be undertaken several days before surgery to allow time for additional treatment. In particular, if the patient's FEV_1 is less than 80% of personal best, a brief course of oral glucocorticosteroids should be considered to reduce airflow limitation[274,275] (**Evidence C**). Furthermore, patients who have received systemic glucocorticosteroids within the past 6 months should have systemic coverage during the surgical period (100 mg hydrocortisone every 8 hours intravenously). This should be rapidly reduced 24 hours following surgery, as prolonged systemic glucocorticosteroid therapy may inhibit wound healing[276] (**Evidence C**).

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Rhinitis, Sinusitis, and Nasal Polyps

Upper airway diseases can influence lower airway function in some patients with asthma. Although the mechanisms behind this relationship have not been established, inflammation likely plays a similarly critical role in the pathogenesis of rhinitis, sinusitis, and nasal polyps as in asthma.

Rhinitis. The majority of patients with asthma have a history or evidence of rhinitis and up to 30% of patients with persistent rhinitis have or develop asthma[277,278]. Rhinitis frequently precedes asthma, and is both a risk factor for the development of asthma[279] and is associated with increased severity and health resource use in asthma[280]. Rhinitis and asthma share several risk factors: common indoor and outdoor allergens such as house dust mites, animal dander, and, less commonly, pollen affecting both the nose and bronchi[281,282], occupational sensitizers[283], and non-specific factors like aspirin. For these reasons, the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative recommends that the presence of asthma must be considered in all patients with rhinitis, and that in planning treatment, both should be considered together[284].

Both asthma and rhinitis are considered to be inflammatory disorders of the airway, but there are some differences between the two conditions in mechanisms, clinical features, and treatment approach. Although the inflammation of the nasal and bronchial mucosa may be similar, nasal obstruction is largely due to hyperemia in rhinitis, while airway smooth muscle contraction plays a dominant role in asthma[285].

Treatment of rhinitis may improve asthma symptoms[286,287] (**Evidence A**). Anti-inflammatory agents including glucocorticosteroids and cromones as well as leukotriene modifiers and anticholinergics can be effective in both conditions. However, some medications are selectively effective against rhinitis (e.g., H_1-antagonists) and others against asthma (e.g., β_2-agonists)[288] (**Evidence A**). Use of intra-nasal glucocorticosteroids for concurrent rhinitis has been found to have a limited benefit in improving asthma and reducing asthma morbidity in some but not all studies[289-291]. Leukotriene modifiers[125,292], allergen-specific immunotherapy[284,293], and anti-IgE therapy[294,295] are effective in both conditions (**Evidence A**).

Additional information on this topic from the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative can be found at http://www.whiar.org[284].

Sinusitis. Sinusitis is a complication of upper respiratory infections, allergic rhinitis, nasal polyps, and other forms of nasal obstruction. Both acute and chronic sinusitis can worsen asthma. Clinical features of sinusitis lack diagnostic precision[296], and CT Scan confirmation is recommended when available. In children with suspected rhinosinusitis, antibiotic therapy for 10 days is recommended (**Evidence B**). Treatment should also include medications to reduce nasal congestion, such as topical nasal decongestants or topical nasal or even systemic glucocorticosteroids. These agents remain secondary to primary asthma therapies[279,288].

Nasal polyps. Nasal polyps associated with asthma and rhinitis, and sometimes with aspirin hypersensitivity[298], are seen primarily in patients over 40 years old. Between 36% and 96% of aspirin-intolerant patients have polyps, and 29% to 70% of patients with nasal polyps may have asthma[298,299]. Children with nasal polyps should be assessed for cystic fibrosis and immotile cilia syndrome. Nasal polyps are quite responsive to topical glucocorticosteroids[288]. A limited number of patients with glucocorticosteroid-refractory polyps may benefit from surgery.

Occupational Asthma

Once a diagnosis of occupational asthma is established, complete avoidance of the relevant exposure is ideally an important component of management[300-302,412]. Occupational asthma may persist even several years after removal from exposure to the causative agent, especially when the patient has had symptoms for a long time before cessation of exposure[303,304]. Continued exposure may lead to increasingly severe and potentially fatal asthma exacerbations[305], a Gastroesophageal Reflux lower probability of subsequent remission, and, ultimately, permanently impaired lung function[306] . Pharmacologic therapy for occupational asthma is identical to therapy for other forms of asthma, but it is not a substitute for adequate avoidance. Consultation with a specialist in asthma management or occupational medicine is advisable.

The British Occupational Health Research Foundation Guidelines for the prevention, identification, and management of occupational asthma are available at http://www.bohrf.org.uk/downloads/asthevre.pdf. (See also reference 421.)

Respiratory Infections

Respiratory infections have an important relationship to asthma as they provoke wheezing and increased symptoms in many patients[307] and are commonly found in children with asthma exacerbation[391]. Epidemiological studies have found that infectious microorganisms associated with increased asthma symptoms are often

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respiratory viruses[308], but seldom bacteria[309]. Respiratory syncytial virus is the most common cause of wheezing in infancy[45], while rhinoviruses (which cause the common cold), are the principal triggers of wheezing and worsening of asthma in older children and adults[310]. Other respiratory viruses, such as parainfluenza, influenza, adenovirus, and coronavirus, are also associated with increased wheezing and asthma symptoms[311]. Adults with asthma may be at increased risk of serious pneumococcal disease[370].

A number of mechanisms have been identified that explain why respiratory infections trigger wheezing and increased airway responsiveness, including damage to airway epithelium, stimulation of virus-specific IgE antibody, enhanced mediator release, and the appearance of a late asthmatic response to inhaled antigen[312]. Thus, there is evidence that viral infections are an "adjuvant" to the inflammatory response and promote the development of airway injury by enhancing airway inflammation[313].

Treatment of an infectious exacerbation follows the same principles as treatment of other asthma exacerbations—that is, rapid-acting inhaled β_2-agonists and early introduction of oral glucocorticosteroids or increases in inhaled glucocorticosteroids by at least four-fold are recommended. Because increased asthma symptoms can often persist for weeks after the infection is cleared, anti-inflammatory treatment should be continued for this full period to ensure adequate control.

The role of chronic infection with Chlamydia pneumoniae and Mycoplasma pneumoniae in the pathogenesis or worsening of asthma is currently uncertain[314]. The benefit from macrolide antibiotics remains unclear[315-317]. A relatively small but well conducted study showed no evidence of benefit from the addition of clarithromycin to adults with mild to moderately severe asthma on low dose inhaled glucocorticosteroids[413]. However, further research in this area is required.

Gastroesophageal Reflux.

There is considerable evidence that gastroesophageal reflux is more common in patients with asthma than in the general population[392]. This has led to research to determine whether treatment of gastroesophageal reflux can improve asthma symptoms or control. Gastroesophageal reflux is undoubtedly a cause of dry cough and some of the confusion in the literature is probably due to patients with dry cough symptoms being attributed to asthma. This relationship may in part relate to the use of medications to manage asthma, such as β_2-agonists and theophylline that cause relaxation of the lower esophageal sphincter.

A review[320] of the effective treatments of gastroesophageal reflux with a variety of measures including proton pump inhibitors, H_2 antagonists, and surgery failed to show benefit. A study on adult patients with symptomatic asthma without symptoms of gastroesophageal reflux found that treatment with high dose proton pump inhibitors did not improve symptoms or exacerbations of asthma[393]. In patients with moderate to severe asthma treated with anti-inflammatory asthma medications and symptomatic gastroesophageal reflux, treatment with proton pump inhibitors demonstrated a small and probably clinically non-significant improvement in lung function and quality of life[392]. Few data are available on studies of treatment for children with asthma symptoms and symptoms of gastroesophageal reflux[394].

In summary, despite a high prevalence of asymptomatic gastroesophageal reflux among patients with poorly controlled asthma, treatment with proton-pump inhibitors does not improve asthma control in adults[392-394] or children[422]. Asymptomatic gastroesophageal reflux is not a likely cause of poorly controlled asthma. Surgery for gastroesophageal reflux is reserved for the severely symptomatic patient with well-documented esophagitis and failure of medical management. In patients with asthma, it should be demonstrated that the reflux causes asthma symptoms before surgery is advised[321,322].

Aspirin-Induced Asthma (AIA)

Up to 28% of adults with asthma, but rarely children with asthma, suffer from asthma exacerbations in response to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). This syndrome is more common in severe asthma[323] .

The clinical picture and course of aspirin-induced asthma (AIA) are characteristic[324]. The majority of patients first experience symptoms, which may include vasomotor rhinitis and profuse rhinorrhea, during the third to fourth decade of life. Chronic nasal congestion evolves, and physical examination often reveals nasal polyps. Asthma and hypersensitivity to aspirin often develop subsequently. The hypersensitivity to aspirin presents a unique picture: within minutes to one or two hours following ingestion of aspirin, an acute, often severe, asthma attack develops, and is usually accompanied by rhinorrhea, nasal obstruction, conjunctival irritation, and scarlet flush of the head and neck. This may be provoked by a single aspirin or other cyclooxygnease-1 (COX-1) inhibitor and include violent bronchospasm, shock, loss of consciousness, and even respiratory arrest[325,326].

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Persistent marked eosinophilic inflammation, epithelial disruption, cytokine production, and upregulation of adhesion molecules are found in the airways of patients with AIA[327,328]. Airway expression of interleukin-5 (IL-5), which is involved in recruitment and survival of eosinophils, is also increased[328]. AIA is further characterized by increased activation of cysteinyl leukotriene pathways, which may be partly explained by a genetic polymorphism of the LTC4 synthase gene found in about 70% percent of patients[329]. However, the exact mechanism by which aspirin triggers bronchoconstriction remains unknown[330].

The ability of a cyclooxygenase inhibitor to trigger reactions depends on the drug's cyclooxygenase inhibitory potency, as well as on the individual sensitivity of the patient[329].

A characteristic history of reaction is considered adequate for initiating avoidance strategies. However, the diagnosis can only be confirmed by aspirin challenge, as there are no suitable in vitro tests for diagnosis. The aspirin challenge test is not recommended for routine practice as it is associated with a high risk of potentially fatal consequences and must only be conducted in a facility with cardiopulmonary resuscitation capabilities[331]. Further safeguards are that patients should only be challenged when their asthma is in remission and their FEV_1 is greater than 70% of predicted or personal best. Bronchial (inhalational) and nasal challenges with lysine aspirin are safer than oral challenges and may be performed in specialized centers[332,333]. Once aspirin or NSAID hypersensitivity develops, it is present for life. Patients with AIA should avoid aspirin, products containing it, other analgesics that inhibit COX-1, and often also hydrocortisone hemisuccinate[334] . Avoidance does not prevent progression of the inflammatory disease of the respiratory tract. Where an NSAID is indicated, a cyclooxygenase-2 (COX-2) inhibitor may be considered[352] with appropriate physician supervision and observation for at least one hour after administration[335] (**Evidence B**). Glucocorticosteroids continue to be the mainstay of asthma therapy, but leukotriene modifiers may also be useful for additional control of the underlying disease[332,336] (**Evidence B**). For NSAID-sensitive patients with asthma who require NSAIDs for other medical conditions, desensitization may be conducted in the hospital under the care of a specialist[337]. Aspirin desensitization has also been used as a treatment for AIA, but long-term improvements appear to be more common with sinus symptoms than with lower airway disease. After aspirin desensitization, daily ingestion of 600-1200 mg of aspirin may reduce inflammatory mucosal disease symptoms, especially in the nose, in most patients with AIA[332] . Generally, asthma patients, especially those with adult onset asthma and associated upper airway disease (nasal polyposis), should be counseled to avoid NSAIDs, taking acetominophen/paracetemol instead.

Anaphylaxis and Asthma

Anaphylaxis is a potentially life-threatening condition that can both mimic and complicate severe asthma. Effective treatment of anaphylaxis demands early recognition of the event. The possibility of anaphylaxis should be considered in any setting where medication or biological substances are given, especially by injection. Examples of documented causes of anaphylaxis include the administration of allergenic extracts in immunotherapy, food intolerance (nuts, fish, shellfish, eggs, milk), avian-based vaccines, insect stings and bites, latex hypersensitivity, drugs (β-lactam antibiotics, aspirin and NSAIDs, and angiotensin converting enzyme (ACE) inhibitors), and exercise.

Symptoms of anaphylaxis include flushing, pruritis, urticaria, and angioedema; upper and lower airway involvement such as stridor, dyspnea, wheezing, or apnea; dizziness or syncope with or without hypotension; and gastrointestinal symptoms such as nausea, vomiting, cramping, and diarrhea. Exercise-induced anaphylaxis, often associated with medication or food allergy, is a unique physical allergy and should be differentiated from exercise-induced bronchoconstriction[338].

Airway anaphylaxis could account for the sudden onset of asthma attacks in severe asthma and the relative resistance of these attacks to increased doses of β_2-agonists[180]. If there is a possibility that anaphylaxis is involved in an asthma attack, epinephrine should be the bronchodilator of choice. Prompt treatment for anaphylaxis is crucial and includes oxygen, intramuscular epinephrine, injectable antihistamine, intravenous hydrocortisone, oropharyngeal airway, and intravenous fluid. Preventing a recurrence of anaphylaxis depends on identifying the cause and instructing the patient on avoidance measures and self-administered emergency treatment with pre-loaded epinephrine syringes[339].

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CHAPTER

5

IMPLEMENTATION OF ASTHMA GUIDELINES IN HEALTH SYSTEMS

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CHAPTER 5: IMPLEMENTATION OF ASTHMA GUIDELINES IN HEALTH SYSTEMS

KEY POINTS:

- In order to effect changes in medical practice and consequent improvements in patient outcomes, evidence-based guidelines must be implemented and disseminated at the national and local levels.
- Implementation of asthma guidelines should involve a wide variety of professional groups and other stakeholders, and take into account local cultural and economic conditions.
- An important part of the implementation process is to establish a system to evaluate the effectiveness and quality of care.
- Those involved in the adaptation and implementation of asthma guidelines require an understanding of the cost and cost effectiveness of various management recommendations in asthma care.
- GINA has developed a number of resources and programs to aid in guideline implementation and dissemination.

INTRODUCTION

It has been demonstrated in a variety of settings that patient care consistent with recommendations in evidence-based asthma guidelines leads to improved outcomes. Guidelines are designed to ensure that all members of a patient's health care team are aware of the goals of treatment and of the different ways of achieving these goals. They help set standards of clinical care, may serve as a basis for audit and payment, and act as a starting point for the education of health professionals and patients.

However, in order to effect changes in medical practice and consequent improvements in patient outcomes, evidence-based guidelines must be implemented and disseminated at national and local levels. Dissemination involves educating clinicians to improve their awareness, knowledge, and understanding of guideline recommendations. It is one part of implementation, which involves the translation of evidence-based asthma guidelines into real-life practice with improvement of health outcomes for the patient. Implementation remains a difficult problem worldwide. Barriers to implementation range from poor infrastructure that hampers delivery of medicines to remote parts of a country, to cultural factors that make patients reluctant to use recommended medications (e.g., inhaled preparations), suboptimal use of medications[21], and lack of physician use of guidelines.

An important barrier to the successful translation of asthma guidelines into clinical practice is access to available and affordable medication especially for patients in less developed economies where the cost of treatment is high in comparison to income and assets.

GUIDELINE IMPLEMENTATION STRATEGIES

Implementation of asthma guidelines should begin with the setting of goals and development of strategies for asthma care through collaboration among diverse professional groups including both primary and secondary health care professionals, public health officials, patients, asthma advocacy groups, and the general public. Goals and implementation strategies will vary from country to country-and within countries-for reasons of economics, culture, and environment. However, common issues are shown in **Figure 5-1**.

The next step is adaptation of guidelines on asthma management for local use by teams of local primary and secondary care health professionals. Many low-and middle income countries do not consider asthma a high-priority health concern because other, more common respiratory diseases such as tuberculosis and pneumonia are of greater public health importance[1]. Therefore, practical asthma guidelines for implementation in low-income countries should have a simple algorithm for separating non-infectious from infectious respiratory illnesses; simple objective measurements for diagnosis and management such as peak flow variability[2]; available, affordable, and low-risk medications recommended for asthma control; a simple regime for recognizing severe asthma; and simple diagnosis and management approaches relevant to the facilities and limited resources available.

Next, adapted guidelines must be widely disseminated in multiple venues and using multiple formats. This can be accomplished, for example, by publication in professional

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Figure 5-1. Checklist of Issues for National or Local Asthma Implementation

- What is the size of the problem and burden of asthma in this country or district?
- What arrangements will be made for shared care among different health care providers (doctors and nurses, hospital and primary care)?
- How will medical care be linked with community health facilities and educational initiatives?
- What are the major preventable factors in this country or district that could help prevent asthma from developing or could prevent asthma exacerbations from occurring in those who already have asthma?
- What preconceived assumptions about asthma and its treatment and what cultural factors will need special attention?
- What treatments are currently used?
- How affordable and accessible are medications and services to the patient?
- What other treatments are available, cheap enough for purchase, and stable in local climatic conditions?
- Can inhaler devices and medicines be standardized to reduce cost/storage/availability problems?
- Who will provide emergency care?
- Which groups of the population are at special risk (e.g., inner-city, poor, teenage, minority)?
- Whom can we enlist to help in education (community health workers/health-promotion facilitators/trained educators currently working on other programs/self-help support groups)?
- Who will take responsibility for the education of health care professionals?
- Who will take responsibility for the education of people with asthma and their family members/caregivers?
- How can asthma education and treatment be integrated into other programs (e.g., child health)?

journals, accompanied by multidisciplinary symposia, workshops, and conferences involving national and local experts with involvement of the professional and mass media to raise awareness of the key messages[3]. The most effective interventions to improve professional practice are multifaceted and interactive[4,5]. However, little is known of the cost effectiveness of these interventions[6]. Integrated care pathways are being explored as a mean to improve asthma care in specific settings, such as patients coming to emergency departments[22].

In some countries, implementation of asthma guidelines has been done at a national level with government health department collaboration. A model for an implementation program that has improved patient outcomes is provided by the national asthma program in Finland, a long-term, comprehensive, multifaceted public health initiative with well-defined targets for asthma guideline implementation[7,8]. Public health strategies involving a broad coalition of stakeholders in asthma care, including medical societies, health care professionals, patient support groups, government, and the private sector, have been implemented in Australia (Australian National Asthma Council, http://www.nationalasthma.org.au), and the United States (National Asthma Education and Prevention Program, http://www.nhlbi.nih.gov).

An important part of the implementation process is to establish a system to evaluate the effectiveness and quality of care. Evaluation involves surveillance of traditional epidemiological parameters, such as morbidity and mortality, as well as the specific audit 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. There are a variety of assessment tools which provide a consistent and objective assessment of asthma morbidity or control (e.g., Asthma Control Test[9], Asthma Control Questionnaire[10-12] , Asthma Therapy Assessment Questionnaire[13]). Results of these assessments should be recorded at each visit, providing a record of the long-term clinical response of the patient to treatment. Direct feedback provides several benefits-a means for the patient/caregiver to become familiar with, and sensitized to, satisfactory versus poor control of asthma; a reference point from which to evaluate deteriorating asthma; and an indicator of changes in asthma control in response to changes in treatment. Use of administrative datasets (e.g., dispensing records) or urgent health care utilization can help to identify at-risk patients or to audit the quality of health care[23] . The strategy of culturally appropriate direct feedback of clinical outcomes to physicians about specific health care results of their patients may be important for general practitioners who treat many diseases in addition to asthma and thus could not be expected to know guidelines in detail and handle patients accordingly.

ECONOMIC VALUE OF INTERVENTIONS AND GUIDELINE IMPLEMENTATION IN ASTHMA

Cost is recognized as an important barrier to the delivery of optimal evidence-based health care in almost every country, although its impact on patients' access to treatments varies widely both between and within countries. At the country or local level, health authorities make resource availability and allocation decisions affecting populations of asthma patients by considering the balance and tradeoffs between costs and clinical outcomes (benefits and harms), often in relation to competing public health and medical needs. Treatment costs must also be

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explicitly considered at each consultation between health care provider and patient to assure that cost does not present a barrier to achieving asthma control. Thus, those involved in the adaptation and implementation of asthma guidelines require an understanding of the cost and cost effectiveness of various management recommendations in asthma care. To this end, a short discussion of cost-effectiveness evaluation for asthma care follows.

Utilization and Cost of Health Care Resources

Between 35 and 50% of medical expenditures for asthma are consequences of exacerbations[14], an asthma outcome most view as representing treatment failure. Hospitalization, emergency department and unscheduled clinic visits, and use of rescue medication comprise the majority of exacerbation-related treatment costs. In clinical trials of asthma treatments, exacerbations are customarily characterized by use of health care resources, alone or in combination with symptom and lung function data, especially when the primary study outcome is reduction in the exacerbation frequency or time to an exacerbation event. Routine collection of health care resource consumption data can be undertaken in the field through patient or caregiver self-report. In some circumstances, automated data from clinical or billing records can substitute for self-report and are more reliable and valid[13,15].

Composite definitions of asthma control[16,17] may include one or more health care utilization items. These items typically describe the presence of an exacerbation or an exacerbation-related treatment in precise and valid terms. Many of the published composite measures of asthma control have included hospitalization and emergency treatment data, such as unscheduled or urgent care visits or use of nebulized β2-agonists and/or oral glucocorticosteroids[17] . Although health care utilization elements are essential to any pragmatic definition of asthma control, as yet unanswered in the literature is which of the number of possible health care options (single items or combinations of items) can contribute to an acceptable definition of control, and the values of each that might be viewed as acceptable control.

For studies to evaluate the cost impact of guideline implementation or of specific asthma interventions, data on costs of implementation (e.g., costs related to dissemination and publication of guidelines, costs of health professional education), preventive pharmacotherapy, diagnostic and follow-up spirometry, use of devices (spacers, peak flow meters), and routine office visits are required to supplement data on exacerbation-related treatments. Together, these data provide a comprehensive profile of health care resource consumption. These data can be acquired in a similar fashion using self-report or from automated databases.

Once data on use of health care resources are collected, costs can be determined by assigning local currency price weights to health care resources consumed. Unit price weights are normally collected from government reports, price audits of local payers, billing records, claims databases, and patient surveys.

Assessment of patient and caregiver travel and waiting time for medical visits, as well as absences from and productivity while at school or work, comprise additional and important outcome measures in asthma. These indirect costs of asthma are substantial, estimated to be roughly 50% of the overall disease burden[14] . However, there are no standardized, validated, and culturally adapted instruments for assessing these measures in a variety of populations.

Determining the Economic Value of Interventions in Asthma

Economic evaluations require the selection of three main outcome parameters-estimates of treatment-related health benefits, treatment-related risks, and treatment-related costs. These parameters can be determined directly from clinical studies or through the application of modeling studies. Local evidence requirements for economic evaluations determine the choices of health benefit measures. When the decision to be considered is at the macro-level, for example the inclusion of a new treatment in a government-sponsored health care program or the benefits package of a health insurer, economic evaluations require the use of a common metric such as life years gained, improvement in generic quality of life, or quality-adjusted life years (QALY) gained[18] . These outcomes support comparison of cost-effectiveness ratios across different disease states and patient populations. However, in asthma, QALYs are difficult to measure, particularly in children where validated preference measures are not available. Some have advocated the use of clinical measures such as symptom-free days or asthma control as the denominator in economic evaluations[19] . A unified definition of asthma control would substantially improve the acceptance of non-QALY economic evaluations among those interested in their design and application.

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GINA DISSEMINATION AND IMPLEMENTATION RESOURCES

Educational materials based on this *Global Strategy for Asthma Management and Prevention* are available in several forms, including a pocket guide for health care professionals and one for patients and families. These are available on the GINA Website (http://www.ginasthma.org). Each year, the GINA Science Committee examines peer-reviewed literature on asthma management and updates various GINA documents. A report of a GINA Working Group[20] provides a blueprint for implementation strategies.

Other activities to assist with implementation of asthma management recommendations through the GINA program include:

Gina Website -www.ginasthma.org. The Internet is creating a conduit for the access, sharing, and exchange of information and permits the global distribution of medical information. Although it is still not widely available, especially in low-income countries, the global trend is for increasing use of the Internet for medical education by asthma patients and their health care providers. Thus, to facilitate communication with health professionals, health policy experts, patients, and their families internationally, GINA has maintained a Website since 1995 to provide access to the GINA documents and educational materials for patients and the public as well as updates of activities and information about collaborating groups and contacts throughout the world.

World Asthma Day. Initiated in 1998, and held on the first Tuesday in May, World Asthma Day is organized by GINA in collaboration with health care groups and asthma educators throughout the world. World Asthma Day activities focus on dissemination of information about asthma among the general population, health care professionals, and government officials. For patients with asthma and their relatives, these activities foster an appreciation of the importance of asthma on a local, regional, national, and international level. Activities include sporting events; meetings of people with asthma and their families with health professionals; meetings with local health officials to discuss progress in asthma care; and reports in print media, radio, and television. Information about World Asthma Day can be found on the GINA Website.

Regional Initiatives. To examine the formation of networks to facilitate the process of guideline implementation, two pilot initiatives have been implemented in the Mesoamerica and Mediterranean regions. GINA leaders have been identified in each country in each region who will supervise collaboration between GINA and local groups and bring the GINA guidelines into forms that can be readily used by health care professionals and patients in each region.

GINA Assembly. To maximize interaction with global asthma-care practitioners, a GINA Assembly was initiated in January 2005. The Assembly provides a forum for dialogue among these health care professionals and facilitates sharing of information about scientific advances and implementation of health education, management, and prevention programs for asthma.

Global Alliance Against Chronic Respiratory Diseases (GARD). GINA is a partner organization of the Global Alliance Against Chronic Respiratory Diseases (GARD), a World Health Organization initiative (http://www.who.int/respiratory/gard/en/). The goal of GARD is to facilitate collaboration among existing governmental and nongovernmental programs interested in chronic respiratory diseases to assure more efficient utilization of resources and avoid duplication of efforts. The participating organizations will develop a comprehensive global approach to the prevention and control of chronic respiratory diseases, with a special emphasis on developing countries. Strategies for affordable drug procurement through an Asthma Drug Facility (www.GlobalADF.org) are among the goals of GARD and are being pursued actively by one of the partner groups, the International Union Against Tuberculosis and Lung Diseases (IUATLD).

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