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GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION

UPDATED 2004

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Global Strategy for Asthma Management and Prevention
NIH Publication No 02-3659 Issued January, 1995 (updated 2002)
Management Segment (Chapter 7): Updated 2004 from the 2003 document.
The GINA reports are available on www.ginasthma.org.

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GINA Workshop Report (Updated 2004)
Global Strategy for Asthma Management and Prevention

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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 can be severe and sometimes fatal. The prevalence of asthma is increasing everywhere, 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 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 disease, and best education methods in order to develop asthma care services and programs responsive to the particular needs and circumstances within their countries.

Accordingly, in 1993, the National Heart, Lung, and Blood Institute collaborated with the World Health Organization to convene a workshop that led to the *Global Strategy for Asthma Management and Prevention*, a Workshop Report that 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, a program called 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. Three publications based on the Workshop Report were prepared to promote international collaboration and dissemination of information:

- *Asthma Management and Prevention: A Practical Guide for Public Health Officials and Health Care Professionals*
- *Pocket Guide for Asthma Management and Prevention*
- *What You and Your Family Can Do About Asthma*

These documents have been widely disseminated, and translated into several languages. GINA has conducted workshops with local doctors and national opinion leaders, held seminars at national and international meetings, and helped support a “train the trainer” program through the National Research Training Center in the UK.

In 2000, the GINA Executive Committee recommended updating the 1995 Workshop Report to incorporate new scientific information. The methods used to prepare the update are described in the Introduction. 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 educational grants from Altana, Andi-Ventis, AstraZeneca, Aventis, Bayer, Boehringer Ingelheim, Chiesi Group, GlaxoSmithKline, Merck, Sharp & Dohme, , Mitsubishi-Pharma Corporation, Nikken Chemicals Co., LTD., Novartis, Schering-Plough International, Sepracor and Viatris. The generous contributions of these companies assured that workshop members could meet together to discuss issues and reach consensus in a constructive and timely manner. The workshop members are, however, solely responsible for the statements and conclusions presented in this publication.

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

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Methodology and Summary of New Recommendations Global Strategy for Asthma Management and Prevention: 2004 Update

When the Global Initiative for Asthma (GINA) program was initiated in 1993, the first goal was to produce recommendations for asthma management 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. This report, and its companion documents, have been widely distributed and translated into many languages. The 1995 report was revised in 2002 under the leadership of the GINA Executive Committee and can be found on the GINA website (www.ginasthma.org). The 2002 report, a revision of the entire document, was based on research published through 2000.

In an effort to keep the 2002 GINA Workshop report as up to date as possible, a GINA Science Committee * was established 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. A 2003 update was posted in October 2003 and included the impact of publications from October 2000 through December 2002. This 2004 update includes the impact of publications from January 1 through December 2003.

Methods: The process included a Pub Med search 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. In addition, publications in peer review journals not captured by Pub Med could be submitted to individual members of the Committee providing an abstract and the full paper were submitted in (or translated into) English.

All members of the Committee received a summary of citations and all abstracts. Each abstract was assigned to two Committee members, although any member was offered the opportunity to provide an opinion on any abstract. Members evaluated the abstract or, up to her/his judgment, the full publication, by answering specific written questions from a short questionnaire, and to indicate if the scientific data presented impacted on recommendations in the GINA Workshop report. If so, the member was asked to specifically identify modifications that should be made. The entire GINA Science Committee met on a regular basis to discuss each individual publication that was indicated to have an impact on asthma management and prevention by at least 1 member of the Committee, and to reach a consensus on the changes in the report. Disagreements were decided by vote.

Summary of Recommendations in the 2004 Update: Between January 1 and December 31, 2003, 319 articles met the search criteria. Of these, 29 papers were identified to have an impact on the GINA Workshop Report that was posted on the website in October 2003 either by: 1) confirming, that is, adding or replacing an existing reference, or 2) modifying, that is, changing the text or introducing a concept that required a new recommendation to the report. The major modifications introduced in the management section in this 2004 update include:

Pg 100: Results from research on domestic dust mite allergens[663,664] led to a revision of the section on this topic.

Pg 101: Cigarette smoking has now been shown to reduce the anti-inflammatory action of glucocorticostoroids[621,665], another reason to vigorously encourage avoidance of any tobacco products by, and near, people with asthma.

Pg 109: Several short-term studies have demonstrated that leukotriene modifiers are less effective than long-acting inhaled β_2-agonists as add on therapy[196,632,633,676] (**Evidence A**). However, a single one year study demonstrated equivalent effects of long-acting inhaled B2-agonists and leukotriene modifiers as add-on therapy on asthma exacerbations[677].

Pg 114: ***Dietary supplements:*** Although vitamin supplements are commonly taken by patients with asthma, regular dietary supplementation with vitamin C or magnesium adds no clinical benefit to current standard asthma therapy[680].

** Members: E. Bateman, *Chair*; P. Barnes, J. Bousquet, W. Busse, J. Drazen, M. FitzGerald, P. Gibson, S. Hurd, J. Kips, K. Ohta, P. O'Byrne, S. Pedersen, S. Wenzel.

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Pg 114: Section on Buteyko was modified to state: Buteyko, a breathing technique consisting of a series of exercises in which subjects reduce the depth and the frequency of respiration, does not modify asthma, but may improve symptoms in some people, although the mechanism for this is not known[682]. A randomized controlled trial[239] concluded that patients with asthma who practiced the Buteyko breathing technique reduced their alveolar ventilation (this finding was especially prominent in patients who tended to hyperventilate) and their use of β_2-agonists. No objective change in measures of airway calibre or end-tidal PaCO2 values were found. The results suggest that benefits, if any, may be in patients who tend to hyperventilate and use excessive amounts of β_2-agonist.

Pg 139: One study suggests that $PaCO_2$ may worsen in some patients on 100 percent oxygen, especially those with more severe airflow obstruction[508]. Oxygen therapy should be titrated against pulse oximetry to maintain a satisfactory oxygen saturation (> 92%)[683].

Pg 139: Although short-acting β_2-agonists are the recommended treatment in acute asthma, the long-acting bronchodilator, formoterol, which has rapid onset of action, was shown to be equivalent without increasing side effects, but is considerably more expensive[684].

Pg 141: One study[690] indicated that use of isotonic magnesium as an adjuvant to nebulized salbutamol results in an enhanced bronchodilator response in treatment of severe asthma. Before this therapy is routinely used further studies are needed.

Pg 141: The role of heliox, a mixture of helium and oxygen, for the treatment of moderate to severe asthma in emergency department patients is uncertain[691].

A paper on levabuterol and racemic albuterol led the committee to review the work already published on this topic. After this review, the committee added a paragraph (on *Pg 139*): Compared to racemic albuterol, a modest additional bronchodilator effect has been shown with levabuterol[685-687]. However, there is a substantially higher cost to this therapy which does not support its use in stable asthma[688]. In a large pediatric acute asthma study, levabuterol treatment reduced hospitalization rates compared to the racemic albuterol treatment group[689], but length of hospital stay was no different between groups.

The committee added eleven references that provided confirmation of previous recommendations.

Prior to its release, the proposed modifications to the GINA Workshop Report were submitted to the GINA Executive Committee for approval. The GINA Workshop Report – Updated 2004, updated Pocket Guide, and the complete list of references examined by the Committee are available on the GINA website (www.ginasthma.org).

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INTRODUCTION (FROM 2002 REPORT)

Asthma is a major, chronic airway disorder that is a serious public health problem in countries throughout the world. Asthma affects people of all ages, can be severe, 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 and its companion documents have been widely distributed and translated into many languages. A large network of individuals and organizations interested in asthma care has been created and has initiated several country-specific asthma management programs. Yet much work is still required to reduce morbidity and mortality from this chronic disease.

SUMMARY OF THE REPORT (Revised 2002)

The GINA program is conducted under the leadership of an Executive Committee. In January 2000, this Committee suggested that the Workshop Report be updated to incorporate the many advances detailed in scientific publications since 1995. The Committee recommended that the Workshop Report provide a comprehensive summary of the scientific findings on which management decisions are made. Thus, Chapters 1 through 4 of this updated Workshop Report include new findings on the genetics, risk factors, natural history, and pathogenesis of asthma. Chapter 5 provides an update on diagnosis and assessment; Chapter 6 provides recommendations for patient education and the scientific background of these recommendations. Chapter 7 provides details of a six-part asthma management program for both adults and children. Research recommendations are summarized in Chapter 8.

Highlights of some of the features in this updated Workshop Report include:

- Chapter 1, Definition, updates information that leads to the definition of asthma as a chronic inflammatory disorder of the airways.

- Chapter 2, Burden of Asthma, combines Chapter 2, Epidemiology, and Chapter 8, Socioeconomics, from the 1995 Workshop Report. The new chapter details the available data on asthma prevalence throughout the world.

- Chapter 3, Risk Factors, includes information about the risk factors for asthma. Asthma risk factors are divided into two categories, host factors and environmental factors.

- Chapter 4, Mechanisms of Asthma, updates information about the cellular and molecular events that lead to inflammation and airway remodeling. A section on pathophysiology provides an overview of the role of inflammation in causing the airflow limitation and symptoms characteristic of asthma.

- Chapter 5, Diagnosis and Classification, recommends a system for classifying asthma severity that includes four steps (Intermittent, Mild Persistent, Moderate Persistent, and Severe Persistent Asthma) based on the presence of clinical features before optimal treatment is achieved and/or on the amount of daily medication required for control of asthma.

- Chapter 6, Education and Delivery of Care, provides the scientific background for asthma education efforts and recommends tools that may be helpful in the education of patients and health professionals.

- Chapter 7, A Six-Part Asthma Management Program, provides a comprehensive asthma management plan using the same six parts as the 1995 Workshop Report. Among the important changes in the updated Report are:

  - Chapter 7.3, Avoid Exposure to Risk Factors, combines Chapter 6 (Prevention) and Chapter 7.3 (Avoid or Control Asthma Triggers: Non-Pharmacological Secondary Prevention) of the 1995 Workshop Report. The updated chapter includes segments on primary, secondary, and tertiary prevention of asthma.

  - Chapter 7.4, Establish Medication Plans for Long-Term Asthma Management, includes separate sections detailing asthma management in adults and children. Both sections emphasize the importance of inhaled glucocorticosteroids for asthma management at all steps of severity except intermittent asthma.

  - Chapter 8, Research Recommendations, details some of the important research questions related to asthma that require investigation.

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FUTURE CHALLENGES

In spite of the efforts to improve asthma care that have taken place 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 and evaluate asthma care programs to meet local needs. The GINA Executive Committee recognizes that this is a difficult task and, to aid in this work, has formed a Dissemination Committee. The Dissemination Committee will work to enhance communication with asthma specialists, primary-care health professionals, other health care workers, and patient support organizations. The Committee will also examine barriers to implementation of the recommendations in this Report, especially the challenges that arise in primary-care settings and in developing countries.

The GINA program has developed a network of individuals who care for asthma patients in many different health care settings, including many developing countries. Many of these individuals were invited to review this Report. While the reviewers acknowledged that early diagnosis of asthma and implementation of appropriate therapy significantly reduce the socioeconomic burdens of asthma and enhance patients' quality of life, many of them also emphasized that medications continue to be the major component of the cost of asthma treatment. They urged that the pricing of asthma medications continue to be examined, as this has important implications for the overall costs of asthma management.

It is recognized that a large segment of the world's population lives in areas with inadequate medical facilities and meager financial resources. In this regard, one reviewer emphasized the importance of using alternative methods to measure and monitor the severity of asthma in the absence of funds to purchase peak flow meters, and this recommendation was incorporated into the Report. It is also recognized that "fixed" international guidelines and "rigid" scientific protocols will not work in many locations, and for this reason GINA encourages that recommendations found in this Report be adapted to fit local practices and the availability of health care resources. As the GINA Dissemination Committee undertakes its 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.

In an effort to evaluate new scientific findings and their im-pact on management recommendations made in the Workshop Report, the GINA Executive Committee has formed a GINA Scientific Committee. This Committee will examine new clinical trial publications in peer-reviewed journals. As new findings are identified that affect recommendations made in the GINA publications, they will be described on the GINA website (http://www.ginasthma.com).

Developments in asthma prevention are promising and research in this important area is a priority. There are many other important areas for investigation, one of which is continued epidemiologic studies. One of our colleagues, Dr. Ann Woolcock, who devoted much of her career to the study of asthma through epidemiologic studies in large populations, died on February 17, 2001. Her contributions to asthma research, and the GINA program, will be greatly missed.

METHODS USED TO DEVELOP THE 2002 REPORT

After the GINA Executive Committee recommended preparation of an updated Workshop Report in January 2000, the Committee members worked in concert with NHLBI and WHO staff to identify individuals from the scientific community to participate as Consultant Contributors in producing the update. The Executive Committee members and these additional members of the scientific community formed an Expert Panel to write the update of the Report.

One member of the Executive Committee, along with one or more members of the scientific community, prepared an updated draft of each chapter. The first draft of the updated document was discussed during a workshop cosponsored by the NHLBI and the WHO in Toronto, Canada in May 2000 at the time of the American Thoracic Society meeting. Additional drafts of the chapters were prepared and reviewed by members of the Executive Committee in October 2000, January 2001, and May 2001.

In July 2001, the document was sent for review to all authors, as well as individuals and medical societies interested in the management of asthma. The reviewers' comments were incorporated, as appropriate, into the final document by the Chair of the GINA Executive Committee and the Chair of the GINA Scientific Committee in cooperation with members of the Expert Panel.

Throughout the process, the GINA Executive Committee agreed that clinical recommendations would require

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scientific evidence and that each chapter would contain updated scientific references as appropriate. Members chose to assign levels of evidence to statements using the system developed by the NHLBI (**Table A**). Levels of evidence are assigned to management recommendations where appropriate in Chapter 6, Education and Delivery of Care, and Chapter 7, A Six-Part Asthma Management Program, and are indicated in boldface type enclosed in parentheses after the relevant statement–e.g., (**Evidence A**). However, the Committee also recognized that evidence may not be available for all recommendations and, in this case, should be clearly labeled as "expert opinion" (**Evidence D**). The methodological issues concerning the use of evidence from meta-analyses were carefully considered (e.g., a meta-analysis of a number of smaller studies was considered to be evidence level B)[1].

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 undertaken 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 nonrandomized 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

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KEY POINTS:

- Asthma–irrespective of the severity–is a chronic inflammatory disorder of the airways.
- Airway inflammation is associated with airway hyperresponsiveness, airflow limitation, and respiratory symptoms.
- Airway inflammation produces four forms of airflow limitation: acute bronchoconstriction, swelling of the airway wall, chronic mucus plug formation, and airway wall remodeling.
- Atopy, the production of abnormal amounts of IgE antibodies in response to common environmental allergens, is the strongest identifiable predisposing factor for developing asthma.
- Considering asthma an inflammatory disorder has implications for the diagnosis, prevention, and management of the disorder.

In the untreated state, bronchial asthma is recognized by recurrent episodes of airflow limitation that are usually reversible either spontaneously or with appropriate treatment[1]. Depending on severity, the airflow limitation is accompanied by symptoms of breathlessness, wheezing, chest tightness, and cough. Production of sputum is also a feature in some patients with asthma, particularly following acute exacerbations and in its chronic persistent form. It is important to differentiate the underlying condition from the recurrent exacerbations. Asthma is a chronic disorder of the airways resulting in variable symptoms and airflow limitation over time. Exacerbations of asthma (attacks or worsening of asthma symptoms and lung function) are acute; they can be rapid in onset or occur gradually. However, under both circumstances exacerbations can be severe and even result in death in the absence of effective treatment. More often, presenting symptoms are less severe, and occasionally they may be totally absent.

DEFINITION OF ASTHMA

Many attempts have been made to define asthma in terms of its impact on lung function–that is, airflow limitation, its reversibility, and airway hyperresponsiveness[1]. However, these attempts have been frustrated by a lack of understanding of the mechanisms involved in asthma.

Appreciation of the key role of the underlying inflammatory response in asthma leads to a more complete definition of asthma[2].

Based on the functional consequences of airway inflammation, an operational description of asthma is that:

> *Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in 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 that is often reversible either spontaneously or with treatment.*

The remainder of this chapter provides the framework for this working definition of asthma based on the underlying pathology of airway inflammation and its relation to disordered lung function[3]. This view of asthma has profound implications in terms of diagnosis, prevention, and management. A greater understanding of asthma management has been achieved by accepting the persistence of the chronic inflammatory response, with variations in the magnitude of the inflammation reflecting the clinical activity of asthma.

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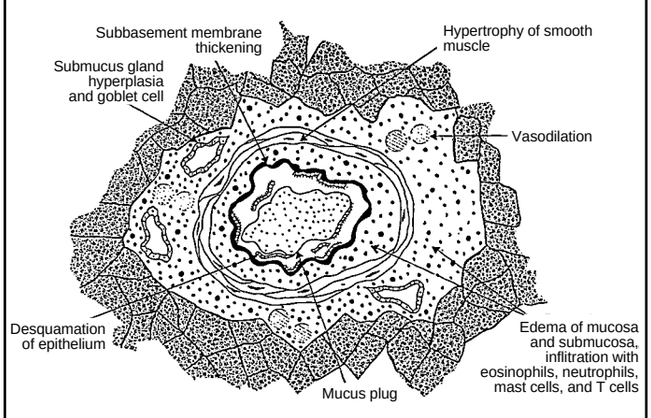
AIRWAY PATHOLOGY IN ASTHMA

Until recently most information on the pathology of asthma has been obtained from postmortem tissue. Macroscopically in patients who have died of asthma the lung is overinflated,

Figure 1-1. Pathological Features of Asthma



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with both large and small airways being filled with plugs comprised of a mixture of mucus, serum proteins, inflammatory cells, and cell debris. Microscopically there is usually extensive infiltration of the airway lumen and wall with eosinophils and lymphocytes accompanied by vasodilatation, evidence of microvascular leakage, and epithelial disruption (**Figure 1-1**)[4]. Trophic changes identified in postmortem studies include smooth muscle hypertrophy, new vessel formation, increased numbers of epithelial goblet cells, and the deposition of interstitial collagens beneath the epithelium (basement membrane thickening), changes which may arise as the result of injury and may lead to remodeling. Thus, there is evidence of both acute and chronic inflammation that is irregularly distributed throughout the airways, including the smallest airways (less than 2 mm in diameter), and the parenchyma[5]. This wide distribution of inflammation carries implications for delivery of inhaled medications to the appropriate areas of the lung.

Most pathologic studies of living subjects with asthma have employed endobronchial biopsies of patients with mild disease. Generally, these tissue findings reflect those seen in autopsy. However, studies of patients with more severe asthma, in both acute and chronic settings, suggest that in addition to eosinophils and lymphocytes, neutrophils are also present and may play a contributing role in this more severe disease[6]. These reports support earlier studies that suggest neutrophils dominate the lungs of people with asthma who die suddenly of the disease[7].

The relationship between the pathological changes and clinical indices has been difficult to obtain. Because there are no well-validated noninvasive measurements of airway inflammation in asthma, clinicians have had to rely on surrogate indices such as sputum eosinophils and exhaled nitric oxide. Clinicians have long recognized an association of sputum and blood eosinophilia with asthma[8], although in parts of the world where parasitic disease is endemic, these tests are of limited value. The application of fiberoptic bronchoscopy to obtain lavage and tissue directly from the airways has provided the most convincing evidence linking disordered lung function to a specific type of mucosal inflammation[9]. In all forms of asthma, there is evidence to implicate mast cells and eosinophils as the key effector cells of the inflammatory response–through their capacity to secrete a wide range of preformed and newly generated mediators that act on the airways both directly and indirectly through neural mechanisms[10].

The application of immunological and molecular biological techniques to asthma has placed T lymphocytes as pivotal cells in orchestrating the inflammatory response through the release of multifunctional cytokines[11]. Whether the pattern of T-cell activation found in asthma is unique to this disease alone is not established but is unlikely. Other types of airway disease, including chronic bronchitis and bronchiectasis, also have lymphocyte involvement[12]. The generation of cytokines by "structural" (constituent) cells of the airways, including fibroblasts and endothelial and epithelial cells, is increasingly considered to be important in the maintenance of the inflammatory response[13]. Although the presence and quantification of inflammatory cells in sputum and their mediators in various body fluids have been used to reflect the activity of underlying airway inflammation, currently there is no direct measurement of this process that can be used routinely[14].

In addition to potent mediators that contract airway smooth muscle, increase microvascular leakage, activate different neurons, and stimulate mucus-secreting cells, a number of factors are released that have the capacity to produce structural changes in the airways or attract inflammatory cells to cause injury to bronchial tissue. Of particular importance is a targeted attack of these processes on the ciliated epithelium, which, in places, becomes stripped to a single layer of basal cells[15]. Moreover, epithelial cells and myofibroblasts, which lie beneath the epithelium, may proliferate, and, in doing so, deposit interstitial collagens in the *lamina reticularis* of the subbasement membrane area. This response and injury-repair process explains the apparent basement membrane thickening that is characteristic of asthma[16].

There is accumulating evidence that other trophic changes, including hypertrophy and hyperplasia of airway smooth muscle, increase in goblet cell number, enlargement of submucous glands, and remodeling of the airway connective tissue, are important components of the disease. Although many of the mediators responsible for these changes to the airway architecture have yet to be defined, cytokines, chemokines, and growth factors seem to be particularly important. These factors are produced by a wide variety of cells, including mast cells, lymphocytes, eosinophils, basophils, epithelial cells, dendritic cells, and smooth muscle cells.

Chemokines are important in the recruitment of inflammatory cells to the airway. Lymphocytes, particularly those that are polarized toward producing cytokines encoded in the IL-4 gene cluster on chromosome 5q (Th2 cells), have important functions in directing and maintaining the airway inflammatory process. The release of mediators and the regulation of the inflammatory process in asthma is complex, redundant, and self-perpetuating. **Figure 1-2** illustrates some of the relationships between mechanisms of inflammation and

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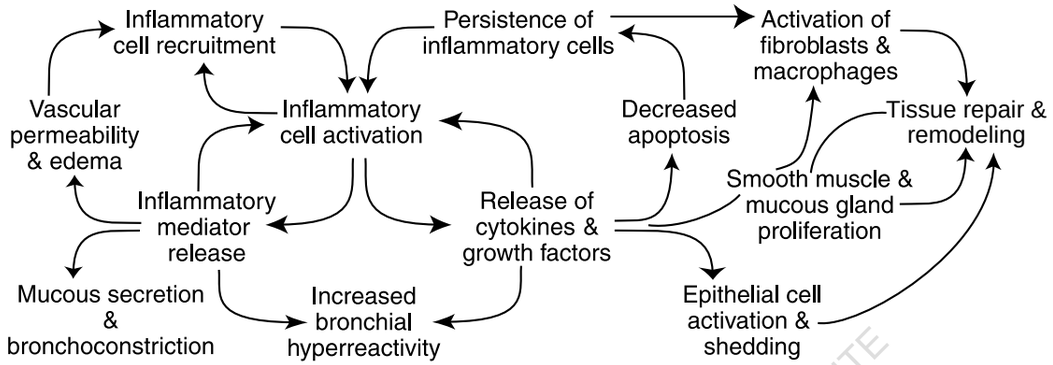
Figure 1-2. Mechanisms of Acute and Chronic Inflammation in Asthma and Remodeling Processes[3]



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remodeling processes in asthma. However, it is not clearly understood what factors regulate the transitions between acute inflammation, persistent disease, and remodeling, or the perpetuation of any of these states. Understanding these factors will be important to developing more effective treatments in the future[3].

Asthma in children and adults is frequently found in association with atopy, which is defined as the production of abnormal amounts of immunoglobulin E (IgE) directed to epitopes expressed on common environmental allergens such as dust mites, animal proteins, pollens, and fungi[17]. As a consequence the mast cell is sensitized and, when appropriately activated, initiates the inflammatory response. Atopy occurs in 30 to 50 percent of the population in developed countries[18] and frequently occurs in the absence of disease. However, when expressed in the lower airways, atopy is one of the strongest risk factors for asthma. When expressed in other organs, it gives rise to such diseases as rhinitis, conjunctivitis, eczema (atopic dermatitis), and food allergy.

For most patients with asthma, the disease begins prior to 6 years of age. However, there is evidence that processes involved in sensitization may begin *in utero*. The initiation of the potential for allergic sensitization and eventual translation into inflammation with wheezing appear to be influenced by many factors in early life, including exposure to tobacco smoke, viral respiratory infections (particularly respiratory syncytial virus), diet, antibiotic use, and domestic (house dust) mite sensitization at 1 to 2 years of age. The regulation of these processes and resulting balance, or imbalance, in cytokine production is not well established, but understanding them is likely important to the eventual understanding of airway inflammation and the possibility of an injury/repair process in asthma[19,20].

RELATIONSHIP OF AIRWAY PATHOLOGY TO DISORDERED LUNG FUNCTION

Airway hyperresponsiveness and acute airflow limitation are the two predominant manifestations of disordered lung function.

Airway Hyperresponsiveness

An important component of asthma underlying the instability of the airways is the presence of an exaggerated bronchoconstrictor response to a wide variety of exogenous and endogenous stimuli. Several mechanisms have been proposed to explain this airway hyperresponsiveness, but evidence suggests that airway inflammation is a key factor. The state of hyperresponsiveness in which the airways narrow too easily and too much in response to many different provoking stimuli is sometimes referred to as nonspecific, but in reality the stimuli often used to reveal it act by highly specific mechanisms. They may be classified as causing airflow limitation directly by stimulating airway smooth muscle (e.g., methacholine and histamine); indirectly by releasing pharmacologically active substances from mediator-secreting cells, such as mast cells (exercise hyper- and hypo-osmolar stimuli) or nonmyelinated sensory neurons (sulfur dioxide and bradykinin); or by a combination of both mechanisms (**Figure 1-3 and Figure 1-4**)[21].

In the laboratory, airway hyperresponsiveness can be quantified by constructing stimulus-response curves and describing the position and shape of these either in terms of the provocative dose or concentration of agonist producing a specified fall in lung function, usually in forced

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Figure 1-3. Heterogeneity of Airway Hyperresponsiveness in Asthma

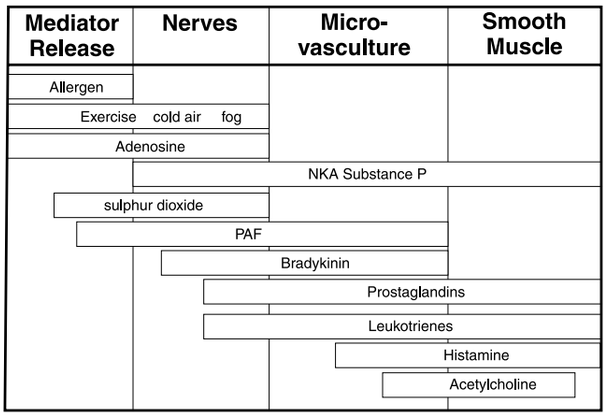

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Figure 1-4. Concept of Direct and Indirect Airway Hyperresponsiveness

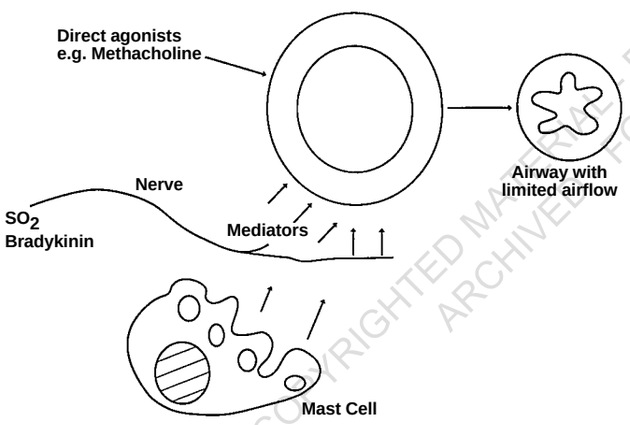

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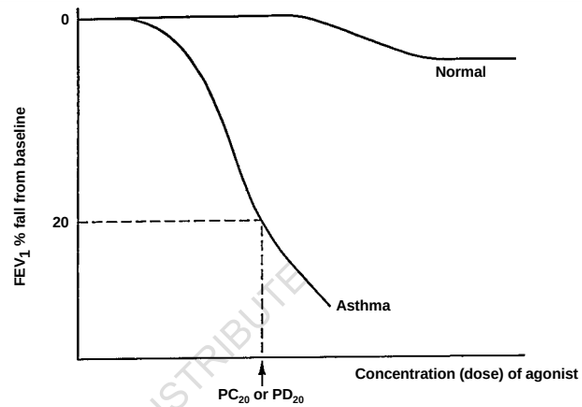
Figure 1-5. Dose-Response Relationship Between Constrictor Agonist and Decrease in an Index of Airway Caliber in Normal Subjects and People With Asthma



The position of the curve describes the level of airway reactivity (PEF and FEV_1). This is frequently defined as the concentration (or does) that reduces the index of airway caliber by 20 percent of starting baseline.

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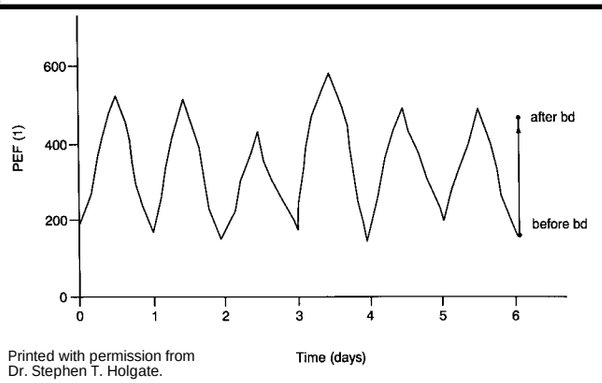
Figure 1-6. Characteristic PEF Chart of a Patient With Uncontrolled Asthma Showing Within- and Between-Day Variation and the Response of a Reduced Morning PEF to a Bronchodilator (bd)



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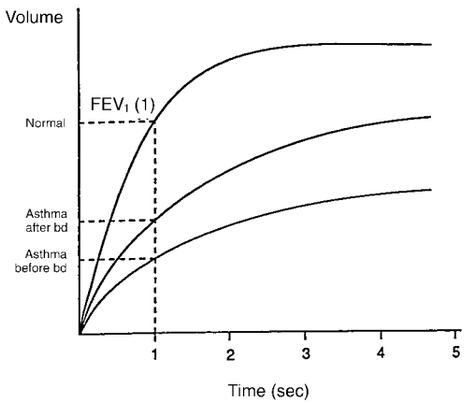
expiratory volume in 1 second (FEV_1), or by the presence of a plateau and the concentration of agonists at which this occurs (**Figure 1-5**)[22]. Measurement of airway hyperresponsiveness has been standardized for histamine and methacholine administered via aerosol inhalation by tidal breathing[23] or administered in predetermined amounts via a dosimeter[24]. Although several different tests of lung function have been used to measure changes in airway caliber following provocation, the FEV_1 has been most widely adopted, with the position of the stimulus-response curve identifying the provocative concentration (or dose) of agonist. The provocative concentration reduces FEV_1 by 20 percent from baseline (PC_{20} or PD_{20}) and serves as an index of responsiveness (**Figure 1-5**). Note that the cutoff point between normal and increased responsiveness is dependent on the method used and the population studied and should be adjusted accordingly[25].

The clinical consequences of airway hyperresponsiveness are reflected in an increased variation in airway caliber both within and between days (**Figure 1-6**)[26]. Nocturnal and/or early morning symptoms with a diurnal variation in peak expiratory flow (PEF) (which correlates well with FEV_1) of 20 percent or more are highly characteristic of

Figure 1-7. Typical Spirometric Tracings From a Normal Subject, a Subject With Asthma, and a Subject With Asthma After Using a Bronchodilator (bd)



Note: Each FEV_1 curve represents the highest of three repeat measurements.

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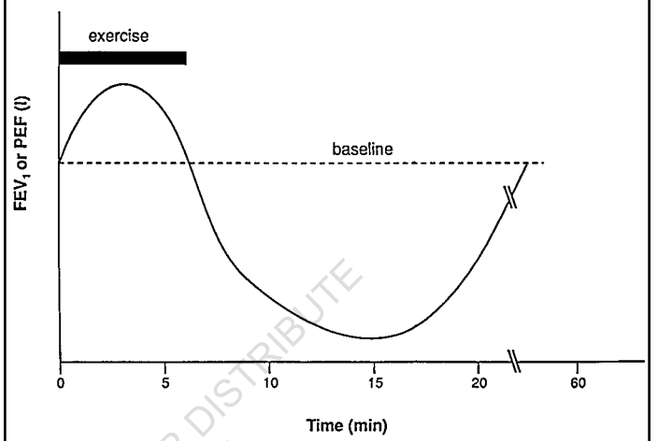
Figure 1-8. The Effect of an Exercise Test on Airway Caliber: Exercise-Induced Asthma Following a Brief Period of Bronchodilation



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asthma. Increased basal airway tone is a further consequence of airway hyperresponsiveness and forms the basis of the bronchodilator test for asthma; an increase of 15 percent or more in FEV_1 or PEF 10 to 20 minutes after inhalation of a short-acting β_2-agonist is accepted as diagnostic (**Figure 1-7**)[27]. In subjects with greatly reduced baseline airway caliber, it is important to consider the absolute change in volume rather than solely relying on the percentage change to determine reversibility[28].

Bronchodilation is of diagnostic help in demonstrating reversible airflow obstruction only if the baseline measure of pulmonary function is less than or equal to 80 percent of the predicted (or best) normal value. In subjects with baseline airway caliber falling within the normal range, provocation testing is helpful to identify bronchial hyperresponsiveness, which is compatible with, but not diagnostic of, asthma[25]. For example, exercise testing using a standard 6-minute protocol has found particular use in the diagnosis of asthma especially in children, with a 15 percent fall in FEV_1 or 20 percent fall in PEF from baseline 5 to 15 minutes post-exercise being diagnostic (**Figure 1-8**)[29,30]. In children, inhalation of mannitol or adenosine 5'-monophosphate (AMP) has been advocated as producing a bronchoprovocation that is more diagnostic for asthma than that produced by histamine or methacholine[31,32].

The relationship between airway hyperresponsiveness, asthma severity, and inflammatory processes remains complex. Although glucocorticosteroids commonly improve asthma symptoms and decrease the evidence of inflammation in the airways, their effect on airway responsiveness, although significant, does not always fully restore this manifestation to normal levels. Whether the persistence of airway hyperresponsiveness suggests that airway remodeling may contribute to hyperresponsive airways is not established. However, many children regain normal airway responsiveness as they enter adulthood[33].

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Airflow Limitation

The recurrent episodes of airflow limitation in asthma have four forms. Each relates to the airway inflammatory response (**Figure 1-9**).

Acute bronchoconstriction. The mechanism of acute airflow limitation varies according to the stimulus. Allergen-induced acute bronchoconstriction results from the IgE-dependent release from airway mast cells of mediators, including histamine, prostaglandins, and leukotrienes, that contract the smooth muscle[34]. This reaction, sometimes referred to as the early asthmatic response, forms the basis of bronchoconstriction upon exposure to aeroallergens. Asthma provoked by nonsteroidal anti-inflammatory drugs (NSAIDs) is also considered to be the consequence of mediator release (especially leukotrienes), although the precise mechanisms responsible for this have yet to be elucidated[35-37].

Acute airflow limitation may also occur because airways in asthma are hyperresponsive to a wide variety of stimuli.

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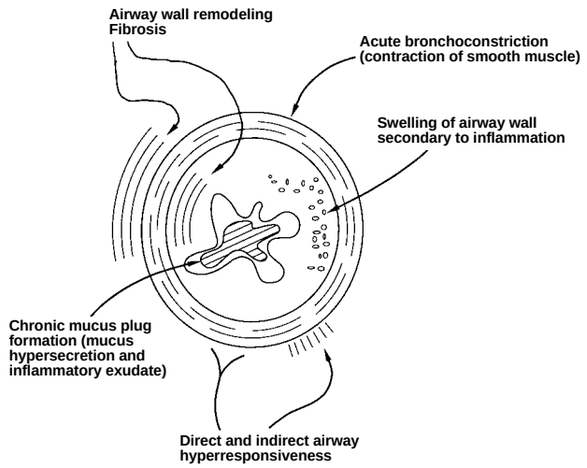
Figure 1-9. Factors That Contribute to Airflow Limitation in Asthma



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Many stimuli can cause acute bronchoconstriction, such as inhalation of allergens, exercise, cold air, fumes, chemicals, and strong emotional expressions like crying and laughing. Their mechanisms for causing bronchoconstriction use differing combinations of direct contraction of smooth muscle, mediator release from cytokine "primed" inflammatory cells, and stimulation of local and central neural reflexes (**Figure 1-4**).

Withdrawal of beta-adrenergic tone through the inadvertent use of antagonists may also produce acute severe bronchoconstriction secondary to the unopposed action of released constrictor mediators (especially acetylcholine)[38]. The acute bronchoconstriction form of airflow limitation is rapidly reversed with an inhaled bronchodilator agent, such as short-acting β_2-agonist[27].

Swelling of the airway wall. Airflow limitation also results from edematous swelling of the airway wall with or without smooth muscle contraction, or bronchoconstriction. Bronchodilators may relieve some of this component of airflow limitation, but it is more effectively reversed with anti-inflammatory drugs, especially glucocorticosteroids. This component of asthma is similar to the reduction in airway caliber that characteristically occurs 6 to 24 hours following allergen challenge of the airways and is referred to as the late asthmatic response[34]. The increase in microvascular permeability and leakage leads to the mucosal thickening and swelling of the airway outside the smooth muscle. This causes swelling of the airway wall and loss of elastic recoil pressure, both of which contribute to airway hyperresponsiveness[39,40].

Chronic mucus plug formation. This more intractable airflow limitation has proven difficult to study, as it usually takes weeks or longer to resolve following the introduction of anti-inflammatory treatment. Increased mucus secretion and an exudate of serum proteins and cell debris combine to produce inspissated plugs that in severe asthma characteristically occlude the more peripheral airways and are difficult to dislodge.

Airway wall remodeling. Airflow limitation sometimes fails to reverse with glucocorticosteroid treatment. The cellular and molecular basis of this lack of response may be associated with structural changes to the airway matrix accompanying longstanding and severe airway inflammation, or may relate to other, less well-defined effects that represent a diminished response to mediators, including glucocorticosteroids.

From a clinical standpoint, airway inflammation is the most likely factor to account for varying severity of asthma and is therefore the element most responsive to controller medications such as inhaled glucocorticosteroids. However, even in the absence of symptoms and overt airflow limitation, asthma continues to exist in the form of mild airway inflammation and airway hyperresponsiveness[10]. Death resulting from asthma is most usually characterized by extensive infiltration of the airways with eosinophils, mast cells, and mononuclear cells with extensive involvement of large as well as small airways[4]. Between these extremes lies the common exacerbation of asthma in which mucosal swelling, excess secretions, and increased airway hyperresponsiveness are features of the inflammatory response.

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CHAPTER 2

BURDEN OF ASTHMA

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KEY POINTS:

- Asthma is one of the most common chronic diseases worldwide, imposing a substantial social burden on both children and adults.
- Asthma occurs in all countries regardless of the level of development but varies greatly between populations, even within countries. There is evidence that over the last 20 years its prevalence has considerably increased, especially among children.
- Strategies to improve asthma control can lead to socioeconomic gains in terms of improved school attendance, fewer absences from work, and, by implication, a smaller burden on families.
- Data on asthma incidence, severity, hospitalization, and mortality are needed for all countries to assist in more effective health planning.
- Developed economies might expect 1 to 2 percent of total health care expenditures to be spent on asthma. Developing economies are likely to face an increased demand for health care expenditures related to asthma.
- Poorly controlled asthma is expensive to manage. Investment in preventive medication is likely to yield cost savings in emergency care for acute exacerbations.

Asthma is a problem worldwide, and the disease's social burden and costs to public and private health care systems are substantial. There is good evidence that asthma prevalence has been increasing in many countries, but as yet there are insufficient data to determine the likely causes of this increase and of the described variations in and between populations. The existing data on asthma prevalence are derived mainly from developed countries. There are almost no data on the severity of the disease in different populations, nor on the impact of asthma management guidelines. Further studies of the socioeconomic burden of asthma and the cost effectiveness of treatment are needed in both developed and developing countries.

DEFINITIONS RELATED TO ASTHMA EPIDEMIOLOGY

In this section, the terms used in asthma epidemiology in this report are defined, methods of classifying populations and countries for epidemiological studies are explained, and the difficulties in defining asthma for epidemiological studies are discussed.

Defining Terms

- Prevalence. The percentage of the population with a disease, disorder, or abnormality. Cumulative prevalence is the total number, expressed as a percentage of the population, who have developed the disorder at a given time. Point prevalence is the percentage with the disorder at a given time.
- Incidence. The number of individuals who develop an abnormality within a given time (usually a year) expressed as a percentage of the population.
- Morbidity. The impact of a disease (hospitalization, etc.) and the degree to which the disease impairs a person's quality of life.
- Airway responsiveness. The response of the airways to provoking stimuli, usually expressed as the provoking dose (concentration causing a 20 percent fall in FEV_1) or the slope of a dose-response curve.
- Airway hyperresponsiveness. A condition in which the airways narrow too easily or too much in response to a provoking stimulus, as documented with measurements of lung function under controlled conditions. In persistent asthma, the airways are hyperresponsive to many different provoking stimuli.
- Atopy. The production of abnormal amounts of IgE antibodies in response to common environmental allergens.

Defining Populations

Definitions of affluent, partly affluent, and non-affluent populations are based on economic grounds.

- Affluent populations. These populations have adequate housing, running water, and food. Most people in affluent populations have access to a universal health care system and medications (or are wealthy enough to purchase adequate medical care).
- Partly affluent populations. These populations have overcrowded housing, access to adequate water for washing, and enough food, but only partial access to health care and social services. Medications are available but rarely affordable.

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- Nonaffluent populations. These populations lack adequate housing and access to running water and may have irregular supply of food. Access to health care is inadequate.

- Migrants. People who have migrated or settled in another country.

Defining Countries

- Developed country. The majority of the population is affluent.

- Developing country. Most of the population is partly affluent and trying to gain affluent status.

Defining Asthma for Epidemiological Studies

Despite hundreds of reports on the prevalence and mortality of asthma in widely differing populations, the lack of precise definitions of asthma makes reliable comparison of reported prevalence from different parts of the world problematic. However, the recent application of standardized methods to measure the prevalence of asthma and wheezing illness in children[1] and adults[2] has aided in making such regional and international comparisons. Some data from phase 2 of the International Study of Asthma and Allergies in Childhood (ISAAC) permit between-population comparison of airway hyperresponsiveness, lung function, peak flow variability, and atopy in children[3,4]. The European Community Respiratory Health Study (ECRHS)[5] enabled between-population comparisons of airway hyperresponsiveness, atopy, and symptoms of asthma in adults, but so far these three aspects of asthma have not been correlated. Thus, because no epidemiological definition of asthma is emerging from current data, important components of epidemiological studies for asthma continue to include questionnaires, tests of airway hyperresponsiveness, and documentation of putative etiologic factors including atopic status.

Questionnaires. Most studies have used data obtained from questionnaires that, depending on the definitions used, may under- or overestimate the prevalence of asthma. Standardized questionnaires are now available for children[1] and adults[2], but questionnaires suffer from potential variable intercultural responses to the descriptive terms used. The video questionnaire used in the ISAAC study[6] has helped alleviate this problem and highlighted the potential for overdiagnosis of asthma based on questions about wheezing.

Questionnaire definitions of asthma can be based on symptoms such as "wheeze ever" (the least useful data because responses are influenced by the ability to recall the events), "wheeze in the past 12 months," or others such as chest tightness and cough. Defining asthma in terms of symptoms alone has formed the basis of many epidemiological studies, but this is fraught with difficulty in the absence of objective measurement of airflow limitation and its variability[7]. Diagnosis-based definitions include doctor/hospital diagnosis of asthma, which may be especially valuable because of medical certification. However, children in some communities have asthma that has never been diagnosed[8]. Questions about medication use and emergency visits can be used to supplement diagnosis-based questions.

Measurements of airway hyperresponsiveness. The definition of "current asthma" as symptoms of asthma within the past year associated with airway hyperresponsiveness, as defined by inhalation of histamine or methacholine, hypertonic saline challenge, or exercise challenge, is proving useful because it defines a group of subjects with clinically important asthma. These patients are more likely to have persistent asthma and they need more treatment than subjects with symptoms alone or with airway hyperresponsiveness alone[7].

In affluent countries methacholine or histamine challenge remains the method of choice. Exercise challenge, using strict environmental conditions, and hypertonic saline challenge are also used in some populations. However, these challenges do not measure the same abnormality as histamine and methacholine challenges. Alternatively, the serial measurement of peak expiratory flow rate may be carried out over a period of 1 or 2 weeks to demonstrate variability, but this requires a level of cooperation that may be difficult to accomplish in normal subjects[9-12].

It appears that airway hyperresponsiveness and symptoms of asthma (wheeze, chest tightness, and cough) measure different abnormalities in the airways, and the presence of both defines "clinically important" asthma–that is, asthma that places patients at risk from persistent disease. Using this definition, data are being obtained that allow populations to be compared, and information about causes, outcomes, and treatment regimens will become more meaningful.

Evaluation of etiologic factors. Because atopy is often associated with asthma, it is important to perform skin tests using a standardized panel of allergens relevant for

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the geographical area. The measurement of specific IgE in blood is an alternative, although it is more expensive. The measurement of total serum IgE is not a good method for determining the presence of atopy because it is affected by responses to parasites and other yet-to-be-defined antigens, and thus does not accurately reflect specific IgE.

The characterization of the environment of populations appears to be critical in order to interpret the results of other measurements. The environment can be assessed by measuring the amount of allergen (especially mite and cat allergen) present in the home, passive smoking, and outdoor air pollution.

PREVALENCE OF ASTHMA

Children

The prevalence of asthma symptoms in children varies from 0 to 30 percent in different populations. **Figure 2-1** shows illustrative (not comprehensive) data on the prevalence of current asthma, diagnosed asthma, recent wheeze (symptoms in the last 12 months), airway hyperresponsiveness, and atopy in children. There are many data available for Australia and England, but fewer data for other countries other than those derived from questions on wheeze in the ISAAC study[13].

There are large differences in asthma prevalence among different populations, with the highest prevalence found in Australia, New Zealand, and England. Data are insufficient to determine whether the differences between populations are the consequence of responses to the environment, to industrialization, or to different allergen loads. Although there is some evidence that asthma is less prevalent in children with high levels of parasitic infections[14], there have been no systematic studies relating parasitic infection to asthma where there has been adjustment for other environmental factors.

Figure 2-2, from the ISAAC study[1], shows the prevalence of wheezing in the last 12 months–documented by written questionnaires–among children 13 to 14 years old in a number of populations. The data show a wide range in the prevalence of wheezing in different populations (consistent with the data in **Figure 2-1**), but few conclusions can be drawn about the risk factors for wheezing in children from these data.

Figure 2-3 shows changes in the prevalence of asthma symptoms in children, young adults, and adults over time. Populations were studied with the same methods on two occasions at least 9 years apart. In all cases an increase in prevalence was documented.

This trend reflects a true increase in asthma prevalence, but is also affected by a recent tendency to label all episodes of wheezing as asthma. Thus, questionnaire estimates may not be regarded as reliable measures of the

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Figure 2-1. Prevalence of Asthma in Children[1]*

Country	Study year	Number	Age	Current asthma	Diagnosed asthma	Recent wheeze	AHR	Atopy (SPT)	Ref
Australia	82 86 91-93	1,487 1,217 6,394	8 to 10 8 to 11 8 to 11	5.4 6.7 10.3	11.1 17.3 30.2	21.7 26.5 24.3	10.1(H) 10.0(H) 18.0(H)	38.0 31.9 39.3	15 15 16
Australian Aborigines	91	215	7 to 12	0.1		8.4	2.8(H)	20.5	17
New Zealand	81 88 89	813 1,084 873	9 6 to 11 12	11.1# 9.1 8.1#	27.0 14.2 16.8	 22.0 17.9	22.0(M) 20.0(H) 12.0(E)	45.8+	18 19 20
England	93?	847	8 to 11		10.0	23.0	31.0(M)++		21
Germany	95-96 95-96 89-90	1,887 725 1,287	9 to 11 5 to 7 9 to 11	 3.4	7.9 4.1 5.9	8.1 	16.0(S) 8.4(C)	32.1 20.3 (RAST) 20.6	22 23 24
Denmark	92-93	744	8 to 10		6.6		2.3(E)		25
Spain		2,842	13 to 14	4.0	11.0	14.0	11.4(E)		26
China (San Bu)	92	647	12 to 20			1.1		49.0	27
Kenya	91	402	9 to 12	3.3	11.4		10.7(E)		28
Austria	95	507	12 to 15		42.2	32.8	14.0(S)		29
US (Tucson)	86-97	790	6			26.8		40.0	30

*Data are illustrative of the variation of childhood asthma prevalence and not a comprehensive list.
Current asthma: airway hyperresponsiveness (AHR) + wheeze in the last 12 months; #: indicates a figure calculated from published data; diagnosed asthma: asthma ever diagnosed; H: histamine; M: methacholine; E: exercise; S: saline; C: cold; SPT: skin prick test; +: 2 mm wheal; ++: >12.2 μmol.
All figures relating to asthma prevalence are expressed as a percentage of the population tested.

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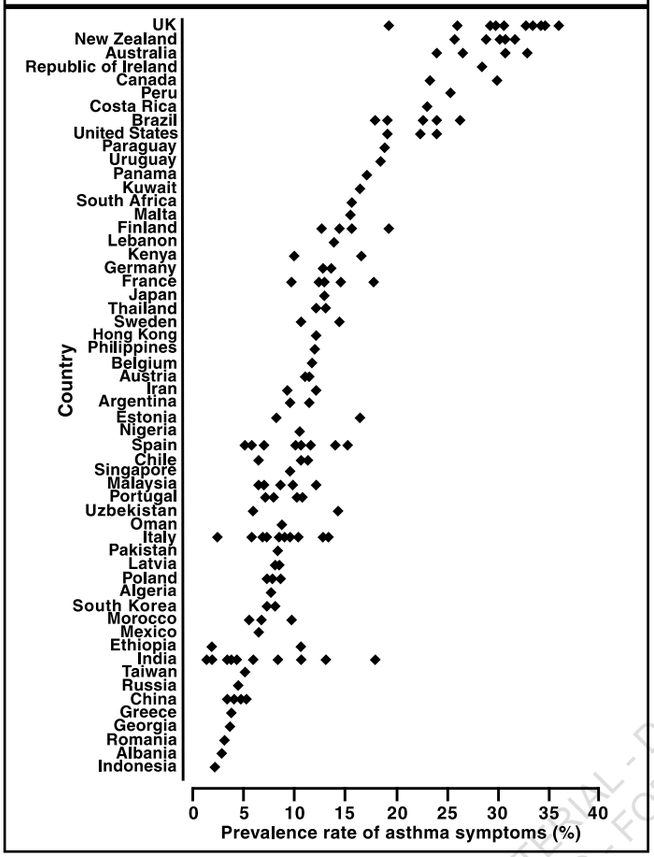
Figure 2-2. Twelve-Month Prevalence of Self-Reported Asthma Symptoms From Written Questionnaires[1].



true change in the prevalence of asthma over time. The reasons for the increase in the prevalence of asthma in children are poorly understood, but are discussed in the chapter on risk factors.

Adults

Data on the prevalence of asthma in adults are more controversial[31]. As can be seen in **Figure 2-3**, there has been some increase in asthma in adults, but the increase is not as striking as that in children. **Figure 2-4** shows data from studies of various Australian populations and from the adult population in the ECRHS in which airway hyperresponsiveness was measured. However, in many of these studies, the relationship between symptoms and airway hyperresponsiveness has not been reported so it is difficult to define clinically relevant asthma, especially as there was no video questionnaire to document the prevalence of wheezing in the last year that was likely to be due to asthma.

There are few data on asthma in older adults. Although some studies have demonstrated that asthma prevalence among the elderly is equal to that in younger age groups[49], it is acknowledged that asthma in the elderly is underdiagnosed[50]. Diagnosis of asthma in older adults is often confounded by similar symptoms from cardiac failure and chronic obstructive pulmonary disease, and normal age-related changes in respiratory function[51]. It is also more difficult because lung function testing is

Figure 2-3. Changes in Prevalence of Asthma in Children and Adults

Country	Study year	Number	Age	Current asthma	Diagnosed asthma	Ref
CHILDREN						
Australia	82	769	8 to 11	6.5	12.9	32
	92	795	8 to 11	9.9	19.3	33
New Zealand	75		12 to 18		26.2*	6
	89	435	12 to 18		34.0	6
Finland	77	4,335	12 to 18	0.1 (self-reported)		34
	91	3,059	12 to 18	2.8 (self-reported)		34
England	66	1,655	6 to 7	3.9 (self-reported)		35
	90	2,323	6 to 7	6.1 (self-reported)		35
	82	5,556	5 to 11	3.45 (self-reported)		36
	92	5,801	5 to 11	9.4 (self-reported)		36
	89	3,403	9 to 11		10.2	37
	94	4,034	9 to 11		19.6	37
Israel	80	834	7 to 12	9.0 (asthma ever)		38
	89	802	7 to 12	13.0 (asthma ever)		38
ADULTS						
Australia	81	553	18 to 55	5.4	9.0	39
	90	1,028	18 to 55	6.3	16.3	39
Belgium	78	605	17 to 31	1.2	2.4	40
	91	1,650	17 to 31	3.7	7.2	40
Finland	75	14,468	33 to 59		2.0	41
	81	15,317	33 to 59		2.1	41
	90	12,219	33 to 59		3.0	41

*Cumulative prevalence of asthma and/or wheeze.

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limited in this age group[52] and elderly people are less likely to complain about asthma symptoms and have poorer perceptions of shortness of breath than younger patients[53].

MORTALITY

Mortality data are of limited value because they are available for relatively few countries, and they are rarely available for different populations within the countries. However, trends in mortality may give an indication of the way a country is responding to the increasing burden of asthma.

Many factors lead to the uncertain reliability of mortality data. The code of the International Classification of Diseases (ICD-8) was revised in 1979, and the new code (ICD-9) artificially increased the mortality rate in older subjects in some countries. Diagnostic habit has a large influence because the clinical criteria for diagnosing asthma may have changed with time, and asthma may now be better recognized than in the past. In older subjects, the cause of death may be miscoded if the patient had coexisting asthma and chronic obstructive pulmonary disease. Misclassification of asthma at the time of death has led to inaccuracies in mortality figures for asthma in the elderly[54], but relatively high asthma mortality rates are reported in this age group[55,56].

When making international comparisons of asthma mortality, asthma prevalence rates in the countries being compared must also be considered. This has recently been made possible with the release of data from the ECHRS[57] and the ISAAC[1,13,58]. These data are depicted in **Figure 2-5** to provide a comparison of asthma mortality rates with prevalence rates of severe asthma in 12 countries[59].

In spite of the general unreliability of asthma mortality data, it is thought that for patients under 35 years of age the accuracy of diagnosis on death certificates is over 85 percent[60,61]. Death rates in the 5- to 34-year age group are therefore the most reliable although based on a small number of deaths. However, according to a US study, death certificate diagnosis of asthma as an underlying cause of death has a low sensitivity but a high specificity[62], suggesting that increases in mortality due to asthma are not likely to be caused by false-positive diagnosis of asthma and that there may be an underestimation of actual asthma-related mortality, at least in the United States.

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Figure 2-4. Prevalence of Asthma and Related Symptoms in Adults

Country	Study year	Number	Age	Current asthma	Diagnosed asthma	Recent wheeze	AHR (M)	Atopy	Ref
Australia	92-93	745	20-44	25.5	11.9	28.1	35.6	56.4	42
(Lismore)	91-92	814	18-55	5.4	17.9	18.8	7.4 {5.6-9.2}	44.0	42
(Wagga Wagga)	91-92	711	18-55	5.6	18.9	18.6	8.6 {6.5-10.7}	44.3	42
(Busselton)	81	553	18-55	5.4	9.5	17.5	10.6	38.5	39
(Busselton)	90	1,028	18-55	6.3	16.3	28.8	7.9 (H)	41.2	39
Australian Aborigines	90-91	715	20-84	3.3		11.1	7.4	35.0	43
New Zealand	92-93	1,254	20-44		10.5		26.6(M) {22.7-27.6}	44.0 {42.0-45.0}	5, 44, 45
Belgium	78 91	51,107 44,305	17-31 17-31	1.2 3.7	2.4 7.2		1.2 3.7		40 40
England	92-93 92-93	1,198 1,802	20-44 20-44		12.0 12.0	±27.0 30.3	19.9 {15.5-27.6} 16.5	40.0 {38.0-43.0} 28.0	5, 44, 45 46
Germany	92-93	1,608	20-44		2.7	17.0	14.0 {12.0-17.5}	35.0 {34.0-36.0}	5, 44, 45
Spain	92-93	1,331	20-44		4.0	22.0	10.5 {3.4-21.3}	34.2 {15.0-43.0}	5, 44, 45
France	92-93	1,750	20-44		4.0	14.4	18.5 {16.3-22.8}	35.0 {28.0-42.0}	5, 44, 45
US	92-93	337	20-44		7.1	25.7	18.3	42.0	5, 44, 45
Italy	92-93	717	20-44		4.0	9.5	10.0 {9.3-11.6}	26.0 {24.0-30.0}	5, 44, 45
Iceland	92-93	469	20-44		3.4	18.0	7.2	22.0	5, 44, 45
Greece	92-93	309	20-44		2.9	16.0		25.0	5, 44, 45
Tristan da Cunha	93	282	3-94		56.0		46.9	47.0	47
Switzerland	91	9,651	18-60		6.9		16.4	24.3	48

Current asthma: airway hyperresponsiveness (AHR) + wheeze in the last 12 months; Diagnosed asthma: asthma ever diagnosed;
H: histamine; M: methacholine.
Data are presented as percentage prevalence, with 95% confidence interval in brackets.

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Figure 2-5. Comparison of Asthma Mortality Rates With Prevalence of Severe Asthma in 12 Countries[59]

Country	Asthma Mortality Rate[a]	Prevalence of Severe Asthma[b]	Ratio
Australia	0.86	8.3	0.10
Canada	0.25	8.0	0.03
England and Wales	0.52	8.7	0.06
Finland	0.21	3.1	0.07
France	0.40	2.8	0.14
Italy	0.23	2.0	0.12
Japan	0.73	2.1	0.35
New Zealand	0.50	8.0	0.06
Sweden	0.12	2.0	0.06
United States	0.47	10.0	0.05
West Germany	0.44	5.0	0.08

[a]Asthma mortality rate (per 100,000) in persons aged 5 to 34 in 1993.
[b]Severe asthma defined as self-reported episodes of wheezing sufficient to limit speech in previous 12 months, in 13- to 14-year-old children, 1993-1995.
NB: Mortality and prevalence data are not available in the same age group.

When the mortality rates are high (as in older adults in Japan and Germany), the numbers are probably much less accurate because many patients suffering from chronic obstructive pulmonary disease may be described as having asthma on the death certificate.

Studies of asthma mortality since 1960 show that mortality rates in the United States and Canada are lower than in other countries, although there are wide variations in mortality rates within the United States[63]. In the 1990s asthma deaths increased in selected subpopulations in the United States, primarily among Blacks in inner-city areas[63]. In the 1960s there was an increase in death rates in New Zealand, Australia, and the United Kingdom, and a decade later a second epidemic of deaths was observed in New Zealand[64]. The increase in asthma deaths in New Zealand has primarily been observed among the Maori[64]. Death rates in Japan have been relatively stable since the 1960s. In most countries asthma deaths occur predominantly outside the hospital.

Several hypotheses in addition to artifacts in methodology have been proposed to explain the failure of most countries to decrease asthma mortality below about 0.4 to 0.6 per 100,000[65]. These include:

- Increasing severity of asthma. An overall increase in the severity of asthma increases the pool of patients at risk for death.
- Failure of management. A failure in management is often observed among young patients who die from asthma and may be due to the failure to use anti-inflammatory agents, poor compliance, or an inadequate evaluation of the severity of the asthma (by patients or health care professionals). It is surprising that death rates are not decreasing more significantly in young people in most countries despite the recognition of the therapeutic benefits of inhaled corticosteroids. There are ethnic differences in mortality in New Zealand[64] and in the United States[63] that may indicate racial trends in the severity of asthma, but more probably the trends are due to the low income of these populations which implies inability or reluctance to seek medical care and reduced ability to afford inhaled glucocorticosteriods.
- Reactions to asthma medications. The use of isoprenaline forte may have been associated with the increase in deaths in the 1960s in at least six countries. Also, retrospective studies carried out in New Zealand[66] and Canada[67] suggest that high doses of the short-acting inhaled β_2-agonist fenoterol may have been associated with increased asthma deaths, and responsible for the increased mortality in New Zealand in the 1970s and 1980s. Association of asthma deaths with other β_2-agonists is not supported by good evidence. It remains to be seen whether beta-adrenergic receptor polymorphisms are significant risk factors for these deaths.

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MORBIDITY

Morbidity refers to the impact of a disease (hospitalization, etc.) and the degree to which it impairs a person's quality of life. The factors underlying increased asthma morbidity may include increased severity of the disease, under-treatment of patients with anti-inflammatory therapy, over-reliance on bronchodilators, and delay in seeking medical help during an exacerbation. Poverty in affluent countries also appears to be a risk factor for increased morbidity[63].

Some data exist concerning the severity of asthma and the degree to which it affects individuals' lifestyle in various populations. Australian studies have shown that although 8 to 11 percent of children and 6 to 7 percent of adults have current asthma, about 4 percent of all age groups have moderate or severe asthma that requires regular medications[42]. A comprehensive, multinational survey in Europe[68] and surveys from the United States[69,70] provide data on the effects of asthma management and treatment on a variety of asthma outcomes.

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Quality of Life

More accurate methods of measuring morbidity, such as measurements of quality of life, are needed. Asthma is a chronic disorder that can place considerable restrictions on the physical, emotional, and social aspects of the lives of patients and may have an impact on their careers. There may be considerable absence from school or work[68,71,72]. The importance of emotional factors and restriction on social life may be greater when symptoms are not adequately controlled. The underlying disorder by itself may cause distress, especially when its natural history is unpredictable. Inappropriate medical care can increase these difficulties. Many people with asthma do not completely appreciate the impact of the disease on their social life and claim they lead "normal" lives either because normality may be based on adjustments and restrictions that they have already incorporated into their lifestyles or because they deny their restrictions, wanting to "live like others."

General health status scales such as the Sickness Impact Profile with 136 items[73] have been used in the assessment of asthma. A compromise between lengthy questionnaires and single-item measures of health has also been proposed. The Nottingham Health Profile with 45 items and the SF-36 (a Measures of Sickness short-form general health survey) are now widely used and validated. The SF-36 Health Status Questionnaire is based on 36 items selected to represent eight health concepts (physical, social, and role functioning; mental health; health perceptions; energy/fatigue; pain; and general health)[74]. A study was carried out using the SF-36 in patients with asthma of variable severity, and it was shown that most items correlated with the severity of asthma[75], suggesting that such scales may be used to compare different populations. Specific quality-of-life scales include questions targeted to asthma; many have been employed in clinical trials[76-78]. The Tayside Asthma Assessment Stamp (for patient's medical records) can be used in routine consultations to document morning, night-time, and exercise symptoms; peak flow; inhaler compliance; and "days lost" from work, school, or play due to asthma[79,80]. An electronic version of this stamp is displayed at http://www.srs.org.uk.

Hospital Admissions

The relationships among changes in prevalence, hospitalization rates, and mortality are unclear[31,56]. Increased hospital admission rates seen in some countries during the 1980s[81,82] do not appear to be due to a change in diagnosis, or to admission of patients with less severe asthma, but may be related to an increased prevalence of asthma as well as to a greater severity of asthma.

It is also important to note that changes in parents' attitudes or in health care practices may influence the rate of hospital admissions, and this may explain some reports of declining hospitalization rates. In Finland, asthma has been more frequently treated in outpatient clinics since 1985, leading to a decrease in hospital admissions. In Sweden, although the prevalence of asthma in school children increased between 1985 and 1993, hospital admissions decreased 45 percent in children aged 2 to 18, and a decreasing trend in the total number of hospital days has also been recorded. Increased use of anti-inflammatory medications, largely in the form of inhaled glucocorticosteroids, is thought to be the major reason for these decreased hospitalization rates[83]. Data from Norway indicate a significant decrease in readmission rates for children with asthma between 1980 and 1995, also attributed to increased use of anti-inflammatory medications[84].

NATURAL HISTORY OF ASTHMA

Infancy

Asthma may develop during the first few months of life, but it is often difficult to make a definite diagnosis until the child is older. In infants, the condition most commonly associated with wheezing is thought to be respiratory viral infection. Wheezing illness in infancy has recently been classified[85]. There is a correlation of early wheeze with reduced lung function before the development of symptoms, suggesting that small lungs may be responsible for some infant wheezing that resolves with the child's growth. Wheezing in the first year of life is not a prognostic indicator for asthma or for more severe asthma later in childhood. Those children who continue to wheeze in later childhood apparently have asthma related to atopy. Recurring exacerbations of asthma may be associated with exposure to allergens. In the susceptible infant, atopy appears to predispose the airways to sensitization by environmental allergens or irritants, and thus the infant may experience recurrent episodes of wheezing. Some episodes of asthma appear to be mainly allergen-related, others appear to be virus-related[86], and many may be attributable to some interplay of these causes. While viruses appear to be more important than allergens in infancy, allergens take on a greater role as children approach school age.

One study demonstrated that the majority of 7-year-olds with airway hyperresponsiveness suffered from atopy as infants[87]. Another study concerning pulmonary

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development showed that asthma in infancy can result in a decrease in lung function of approximately 20 percent in adulthood, indicating the possible deleterious effect of asthma on the development of the lung[88]. However, a subsequent study did not confirm this finding[89], and the Childhood Asthma Management Program (CAMP) Study showed that FEV_1 was well maintained[90] between the ages of 5 and 15. However, diminishing FEV_1 was associated with greater duration of asthma before enrollment in the study (at age 5)[91].

Childhood

The predominant feature associated with asthma in children is allergy. An Australian study, for example, indicated that sensitivity and exposure to domestic mites represents the major predictor of asthma[92]. The role of viral infections in the etiology of asthma is not clear. In atopic children, viral infections are clearly important in asthma exacerbations, but there are few data that suggest they directly cause the onset of asthma. By age 8, a proportion of children develop airway hyperresponsiveness and the associated symptoms of moderate to severe persistent asthma, while others continue to have mild intermittent asthma[93]. Many children with asthma also suffer from allergic rhinitis as documented in the ISAAC Study[1].

Lung growth appears to be relatively normal in most children with asthma, but it can be reduced throughout childhood and adolescence in those with severe and persistent symptoms. A longitudinal study of children in New Zealand concluded that growth as measured by spirometric tests of lung function was impaired among those children with airway hyperresponsiveness and/or allergy to domestic mite or cat allergen[94]. Similar studies in Australia showed that airway hyperresponsiveness in children resulted in reduced lung function as measured by spirometry at the age of 18[95]. Whether this reflects a failure to reach full growth because of asthma or simply the presence of congenitally small lungs is unknown. It must be noted that most of the studies performed to date that have shown reduced lung growth in children with asthma have measured lung function prior to bronchodilator therapy, and therefore have simply measured reversible airways obstruction. Most studies that have measured post-bronchodilator airway function have shown very little long-term effect of asthma on growth of lung function.

The long-term prognosis of childhood asthma is now of major concern. It has often been suggested that childhood asthma will "disappear" when the patient reaches adulthood. Epidemiological evidence gives less cause for optimism[89,96,97]. Despite methodological difficulties in the longitudinal studies, it has been estimated that asthma disappears in 30 to 50 percent of children (especially males) at puberty, but often reappears in adult life. Up to two-thirds of children with asthma continue to suffer from the disorder through puberty and adulthood. Moreover, even when asthma has clinically disappeared, the lung function of the patient frequently remains altered, or airway hyperresponsiveness or cough persists. The prognosis of asthma appears to be worse when the child has eczema or a family history of eczema.

It should also be noted that 5 to 10 percent of children with asthma that is considered to be trivial have severe asthma in later life. Childhood asthma must never be neglected in the hope that the child will simply grow out of it. Children with mild asthma are likely to have a good prognosis, but children with moderate or severe asthma probably continue to have some degree of airway hyperresponsiveness and will be at risk for the long-term effects of asthma throughout life[97].

Adulthood

Asthma can begin in adult life in response to sensitizing agents at the workplace and, perhaps, from the development of atopy later in life. Viral infections may still, in adult life, be a trigger of asthma exacerbations, but there is no published evidence that they cause the onset of asthma. The proportion of patients with late-onset asthma that come from the group with past asthma is unknown. In a long-term study of asthma from childhood[97,98], it was found that the more severe the asthma in childhood, the more severe the asthma in adult life, and many of those who "lost" their symptoms continued to have either abnormal lung function or airway hyperresponsiveness. Those with the worst asthma were also the most atopic. While confirmatory studies are required, data from the Nurses Health Study suggest a higher incidence of asthma in postmenopausal women taking estrogen[99].

The natural history of lung growth and senescence in adults with asthma has been given less attention than the natural history of chronic airflow limitation. During adulthood, clinical asthma may be associated with an increase in the rate of decline in FEV_1[100-102]. In middle-aged and elderly smokers, it is virtually impossible to separate chronic obstructive pulmonary disease and asthma by means of FEV_1. Airway hyperresponsiveness appears to be associated with an increase in the rate of decline of lung function. However, the effect of asthma is variable, and not all subjects with asthma have steep rates of decline. It appears that asthma starting after the age of 50 elicits a steeper rate of decline than asthma with an earlier onset[103]. Permanent airflow limitation is not rare in adults

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with asthma, as demonstrated by lung function measurements and computed tomography (CT) scans, on which permanent abnormalities of the airways can be observed[104]. Many elderly people with asthma have severe airways disease and lung function impairment[105].

SOCIOECONOMICS

Socioeconomic factors are integral to asthma care, whether viewed from the perspective of the individual sufferer, the health care professional, or organizations that provide health care. While a global perspective on socioeconomic factors is the ultimate goal, most of the literature currently available reflects knowledge gained from developed rather than developing countries.

Data from the United States Centers for Disease Control and Prevention (CDC) provide an indication of the burden of illness experienced by children with asthma compared to children without asthma. In a 1988 National Health Interview Survey, children with asthma missed 10.1 million days from school (2 times the number of days missed by children without asthma), and had 12.9 million contacts with medical doctors and 200,000 hospitalizations[106]. In the same survey, it was determined that almost 30 percent of children with asthma experienced some limitation of physical activity, compared to only 5 percent of children without asthma[107].

Absence from school has been documented as an adverse consequence of asthma in studies from India, Australia, the United States, and the United Kingdom[108-111], and may impair long-term educational achievement[104]. School absence rates may be a proxy marker of asthma severity and may correlate with treatment outcomes[112]. Subtler educational effects, although difficult to measure, may be the loss of learning time due to asthma symptoms and disruption of class work while obtaining treatments such as inhalers.

Restriction of physical activity has been reported in studies from the United States and India[107,108]. Preschool learning and socializing opportunities are likely to be impaired in young children unable to join in normal activities as a consequence of asthma. Suboptimum control of asthma can lead to missed recreation opportunities throughout childhood and adult life.

Asthma has been documented as a major cause of absence from work in many countries, including Australia, Sweden, and the United Kingdom[106,112-114]. It is likely that reports underestimate the true level of absence due to asthma as employees concerned about job security may opt to report episodes of work absence as due to respiratory infections rather than declare a chronic health problem such as asthma. The choice of occupation can be influenced by asthma[114], and in some regions the sole source of employment may be in an occupation clearly unsuited to people with asthma.

Uncontrolled asthma in one family member can impede the economic effectiveness of other family members[115]. Time spent caring for the person with asthma and obtaining medicines, as well as high medical bills, can cause substantial burden for entire families. Effective medical treatment for a person with asthma can not only restore the individual to a normal lifestyle but also provide an economic benefit to the entire family unit.

Socioeconomic "Cause and Effect"

Socioeconomic factors are relevant to the causes of asthma, access to treatment, and clinical outcomes[116], although the precise relationships between socioeconomic factors and asthma may vary from country to country. A study from Zimbabwe demonstrated that urban living and higher material standards of living appeared to be associated with a higher prevalence of reversible airways obstruction in children[117]. This could in part be due to better access to health care and increased diagnosis rates, but also represents a true increase in the prevalence of asthma-related symptoms. In developed countries, inner-city living is associated with a greater prevalence of asthma-related symptoms[110]. Damp, poorly ventilated houses with house-dust mite colonization are adverse environmental factors associated with lower socio economic status and inner-city living in developed countries.

Studies in Mexico[111], the United States[70], the United Kingdom[113], Germany[114], and Australia[115] indicate that low-income and minority populations experience a substantially higher prevalence of asthma, higher rates of asthma mortality, and greater morbidity as measured by hospital admissions and emergency room visits. Similarly, the higher rates of asthma morbidity among Pacific Islander minority populations in New Zealand vividly illustrate the link between socioeconomic status, access to health care, and clinical outcomes[19]. Reviews[118,119] discuss the complex links between poverty and asthma.

Costs of Asthma

The cost of asthma has been documented in several different health care systems in developed countries, including

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the United States[115,120,121], the United Kingdom[113], Australia, and Sweden[111,112]. A detailed review of treatment costs in the Republic of Transkei, South Africa, provides a working model for the study of asthma costs in developing countries[122]. Analyses have emphasized the need to differentiate between direct and indirect costs[123]. Direct costs are relatively easy to measure and include the costs of medication, medical bills, and documented episodes of health service utilization such as clinic visits and hospital admissions. Indirect costs include the adverse economic impact of the disease on an individual, family, and society. This includes the "cost" of premature mortality and productivity loss. For the purpose of regional comparison direct costs are used.

The cost of medical treatments for asthma can represent a substantial proportion of family income. In the United States, estimates of this cost range from 5.5 percent to 14.5 percent of total family income[123,124]. A comparable figure for the cost of asthma treatment in India is 9 percent of per capita annual income[108].

Comparisons of the cost of asthma in different regions lead to a clear set of conclusions:

- Primary care is less expensive than hospital care
- Emergency treatment is more expensive than planned treatment
- Nurse-led treatment can be cost effective
- Families can suffer from the financial burden of treating asthma.

Several studies in the United Kingdom have looked closely at the links between the process of clinical care and economic outcomes. One study showed that integrated primary and secondary care was cost effective[125]. Another study found that nurse-led intervention to improve the diagnosis and treatment of childhood asthma in primary care led to a reduction in hospital care costs[126]. It should be noted, however, that these positive outcomes tend to diminish over time, indicating a need to sustain the intensity of the intervention. Primary care of asthma by a trained asthma nurse may be associated with a favorable clinical outcome and, by implication, reduced health service costs[127]. The cost of treating acute asthma attacks is far greater than the cost of providing preventive drug treatment[128].

Health Policy

Asthma is a treatable disease with preventable morbidity[129,130]. Although the cost of preventive asthma treatment seems high, the cost of not treating asthma correctly is even higher[129,131-134]. Proper treatment of the disease poses a challenge for individuals, health care professionals, health care organizations, and governments. Other chapters in this document focus on strategies for asthma care that can by adopted by individuals and health care professionals, but to truly minimize the social and economic burden of asthma also requires action by health care organizations and public agencies. Some ways in which health care organizations and governments might address this problem include:

- Encourage primary care management of asthma
- Subsidize or encourage the use of preventive medications
- Maintain surveillance on key asthma processes and outcomes
- Make asthma a health service priority.

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.

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CHAPTER

3

RISK FACTORS

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KEY POINTS:

- Risk factors for asthma may be classified as host factors that predispose individuals to or protect them from developing asthma, and environmental factors that influence the susceptibility to the development of asthma in predisposed individuals, precipitate asthma exacerbations, and/or cause symptoms to persist.
- Host factors include the genetic predisposition to the development of either asthma or atopy, airway hyperresponsiveness, gender, and race.
- Exposure to allergens and occupational sensitizers, viral and bacterial infections, diet, tobacco smoke, socioeconomic status, and family size are the main environmental factors that influence the susceptibility to the development of asthma in predisposed individuals.
- Exposure to allergens and respiratory (viral) infections are the main factors responsible for causing exacerbations of asthma and/or the persistence of symptoms.

Asthma is a chronic inflammatory disorder of the airways. This chronic inflammation is associated with increased airway responsiveness to a variety of stimuli and with recurrent symptoms and reversible airflow limitation that are characteristic of asthma. This chapter discusses risk factors for asthma (**Figure 3-1**), in particular, (1) host factors involved in the development of asthma, and (2) environmental factors that may influence the susceptibility to the development of asthma in predisposed individuals, cause exacerbations of asthma, and/or cause symptoms to persist.

Host factors include the genetic predisposition to the development of either asthma or allergic sensitization, (i.e., atopy, defined as the production of abnormal amounts of IgE in response to environmental allergens), airway hyperresponiveness, gender, and race.

Environmental factors modify the likelihood that asthma will develop in predisposed individuals. These factors include allergens, occupational sensitizers, tobacco smoke, air pollution, respiratory (viral) infections, diet, socioeconomic status, and family size. Some environmental factors can also exacerbate asthma; these are also called precipitating factors.

Figure 3-1. Potential Risk Factors for Asthma

HOST FACTORS

- Genetic predisposition
- Atopy
- Airway hyperresponsiveness
- Gender
- Race/ethnicity

ENVIRONMENTAL FACTORS

Factors that influence the susceptibility to the development of asthma in predisposed individuals

Indoor allergens
- Domestic mites
- Animal allergens
- Cockroach allergen
- Fungi, molds, yeasts

Outdoor allergens
- Pollens
- Fungi, molds, yeasts

Occupational sensitizers

Tobacco smoke
- Passive smoking
- Active smoking

Air pollution
- Outdoor pollutants
- Indoor pollutants

Respiratory infections
- Hygiene hypothesis

Parasitic infections

Socioeconomic status

Family size

Diet and drugs

Obesity

Factors that precipitate asthma exacerbations and/or cause symptoms to persist

Indoor and outdoor allergens (see above)

Indoor and outdoor air pollutants

Respiratory infections

Exercise and hyperventilation

Weather changes

Sulfur dioxide

Foods, additives, drugs

Extreme emotional expression

Tobacco smoke (active and passive)

Irritants such as household sprays, paint fumes

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HOST FACTORS

Genetic Predisposition to the Development of Asthma

There is good evidence to indicate that asthma is a heritable disease. A number of studies have shown an increased prevalence of asthma and the phenotype associated with asthma among the offspring of subjects with asthma compared to the offspring of subjects without asthma[1-4]. The phenotype associated with asthma can be defined by subjective measures (e.g., symptoms), objective measures (e.g., airway hyperresponsiveness or serum IgE level), or both. Because of the complex clinical presentation of asthma, the genetic basis of the disease is

Figure 3-2. Summary of Genetic Linkage and Association Studies for Asthma, Allergic Rhinitis, Atopic Dermatitis, and Atopy[6]

Locus*	Candidate genes	Asthma^	Allergic rhinitis	Atopic dermatitis	Atopy°
2 pter	Unknown	8			8
2q33	CD28, IGBP5	9			
3p24.2-p22	CCR4	10			
4q35	IRF2	11			11
5p15	Unknown	9			
5q23-q33	IL-3, IL-4, IL-5, IL-13, IL-9, CSF 2, GRL1, ADRB2, CD14	9 10 12, 13		14	15 16 13, 17, 18, 19
6p21.1-p23	HLAD, TNFA	8, 9			8, 11, 19, 20
7p15.2	TCRG, IL-6	11			11
7q35	TCRB				13
9q31.1	TMOD	8			8
11p15	Unknown	9			
11q13	FCER1B, CC16/CC10	11 16, 20		21	11 15, 16, 22, 23, 24, 25, 26
12q14- q24.33	STAT 6, IFNG, SCF, IGF1, LTA4H, NFYB, BTG1	8 27 28 9, 10, 29	27		8 28
13q14.3-qter	TPT1	9, 30			11, 19, 31
14q11.2-q13	TCRA/D, MCC	9		32	33, 34
14q32	IgHG				35
16p12.1	IL4R				36
16q22.1-q24.2	Unknown	11			11
17p11.1-q11.2	C-C chemokine cluster	9			
19q13	CD22	9, 10			
21q21	Unknown	9, 10			
Xq28/Yq28	IL9R	37			
12q	NOS1	38			
5q31	β_2-agonist receptor	39			
11q13	GSTP1	40			

CD, Cell differentation antigen; IGBP, insulin-like growth factor-binding protein; CCR, C-C chemokine receptor; IRF, interferon regulatory factor; CSF, colony-stimulating factor; GRL, glucocorticoid receptor; ADR, adrenergic receptor; TCR, T-cell receptor; TMOD, tropomyosin-binding protein; STAT6, signal transducer and activator of transcription 6; SCF, stem-cell factor; IGF, insulin-like growth factor; LTA4H, leukotriene A4 hydrolase; NFYB, the β subunit of nuclear factor-Y; BTG, B-cell translocation gene; TPT1, tumor protein, translationally controlled 1; IgHG, immunoglobulin heavy chain G.
*Includes the full regions for which evidence of linkage has been observed.
^In general, asthma was defined as a qualitative (yes/no) trait in most studies; the definition of asthma included airway hyperresponsiveness as either a qualitative or a quantitative trait (e.g., $\log_e$ slope).
° The definition of atopy includes individual measurements or a composite measurement of total IgE, spIgE (RAST or skin-prick test). The study by Hizawa et al. reported novel evidence for linkage of spIgE response to Der p to 2 novel regions, 2q21-q23 and 8p23-p21; however, these findings have not been replicated by others.
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often studied through intermediate phenotypes that can be measured objectively, such as the presence of atopy or airway hyperresponsiveness, although these conditions are not specific to asthma. This lack of a clear definition of the asthma phenotype presents the biggest problem when reviewing studies of the genetic basis of asthma and atopy, because multiple definitions of the same intermediate phenotype are used in different studies[4].

Family studies have convincingly shown that atopy (as measured by allergen skin tests, total IgE, and/or specific IgE), airway hyperresponsiveness, and asthma as diagnosed by questionnaire are at least partly under genetic control[2,4]. Numerous studies of twins have demonstrated that concordance rates for asthma, eczema, and hay fever are all substantially higher for monozygotic than for dizygotic twins, suggesting a strong genetic contribution. In population-based studies of twins, the estimated effect of genetic factors is about 35 to 70 percent, depending on the population and the design of the study[4,5].

Despite intensive effort and advances in molecular biology and genetics, no gene (or genes) involved in the heritability of atopy or asthma has been identified with any

certainty[4,5]. The results of several studies provide an indication that multiple genes may be involved in the pathogenesis of asthma, and chromosomal regions likely to harbor asthma susceptibility genes have been identified (**Figure 3-2**)[4-6].

Genetic control of the immune response. Genes located in the human leukocyte antigen (HLA) complex may govern the specificity of the immune response to common aeroallergens in some individuals[7]. The HLA gene complex is located on chromosome 6p and consists of the class I, class II, and class III genes (including the highly polymorphic genes for HLA class I and II molecules), and others such as the gene for tumor necrosis factor-α (TNF-α). Many population studies have investigated associations between IgE responses to specific allergens and both HLA class II genes and T cell receptor (TCR) genes. The strongest reported association is that between the HLA allele DRB1*15 and the response to Amb a v allergen[4,5].

Genetic control of proinflammatory cytokines. Chromosomes 11, 12, and 13 contain several genes that may be important in the development of atopy and asthma[5]. Evidence for linkage of a broadly defined allergic phenotype to markers on chromosome 11 was detected in the early genetic studies of asthma[8,9]. Chromosome 12 contains the genes encoding interferon-γ, mast cell growth factor, insulin-like growth factor, and the constitutive form of nitric oxide synthase. A series of studies has identified a positive linkage between markers on 12q, asthma, and IgE[4]. Initial data are now also available for chromosomes 14 and 19[10].

Mutations of the cytokine gene cluster on chromosome 5 have been hypothesized to predispose subjects to asthma[4,5]. Several genes on chromosome 5q may be important in the development or progression of inflammation associated with asthma and atopy, including genes encoding the cytokines interleukin (IL)-3, IL-4, IL-5, IL-9, IL-12 (β-chain), IL-13, and granulocyte-macrophage colony-stimulating factor[4,5]. IL-4 in particular plays an essential role in the atopic immune response, both by causing differentiation of Th2-like cells and by inducing IgE production by B cells. This makes the IL-4 gene, or genes for the factors that regulate its expression, strong candidate genes for predisposition to atopy and asthma[4,5].

Atopy

Atopy, defined as the production of abnormal amounts of IgE antibodies in response to contact with environmental allergens, is demonstrated by increased total or specific serum IgE and by a positive response to skin-prick tests using a battery of standardized allergens, specific to each geographic zone. Atopy appears to be an important host factor that predisposes individuals to developing asthma. The available epidemiological evidence suggests that the population-based proportion of asthma cases attributable to atopy is about 50 percent[11]. The association between allergic sensitization and asthma is age dependent. In fact, the majority of children who become sensitized to aeroallergens during the first 3 years of life develop asthma later in life, whereas children who become sensitized after the age of 8 to 10 have a risk of developing asthma that is not much higher than that of children who do not become sensitized[12].

Figure 3-3 shows the prevalence of skin-prick-test positivity and asthma in population-based studies comparing different populations or the same population over time[11]. The proportion of people with asthma who are skin-prick-test positive varies considerably between different studies. Although population-based studies suggest an association between the prevalence of atopy and asthma[13] or between the levels of IgE and asthma[14,15], most studies report an inconsistent association between the increase of atopy and the increase of asthma. This suggests that the importance of atopy as a cause of asthma may have been overemphasized[44] and that it should be considered only one of the factors, even if a very important one, needed for disease expression.

Atopic diseases occur in families. Significant familial aggregation of asthma and associated phenotypes such as airway hyperresponsiveness and total IgE levels have been described in numerous studies[4,5]. Family studies have suggested that the atopic status of subjects without asthma does not influence the risk of asthma in their relatives, but the presence of atopy in subjects with asthma further enhances the likelihood of the relatives developing asthma. Thus, although asthma and atopy may be inherited independently[25,26], the coincidence of asthma and atopy or atopic manifestations such as eczema in one individual greatly increases the risk of asthma in her or his relatives. A family history of hay fever or atopic dermatitis, excluding asthma, is unrelated to asthma in the offspring. In contrast, the prevalence of asthma alone, i.e., without concomitant hay fever or atopic eczema, increases strongly if nearest of kin suffer from asthma alone, suggesting a separate genetic factor controlling the development of asthma[27]. However, the risk of atopic parents with asthma having a child with asthma further increases when a family history of asthma is accompanied by a history of atopy[28]. Similarly, when both airway hyperresponsiveness and atopy are present in the parents, the prevalence of asthma increases in the offspring[28].

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Figure 3-3. Prevalence of Skin-Prick-Test Positivity and Asthma in Population-Based Studies Comparing Different Populations or the Same Population Over Time

Reference	Population origin	Number of subjects	Age	Percent with positive skin-prick test	Percent with doctor-diagnosed asthma
Comparisons of different populations					
16	Marseilles	4,008	18-65	28*	4
	Briancon	1,055	18-65	10*	2
17	Munich	4,451	9-11	37	9
	Leipzig/Halle	2,335	9-11	18	7
18	Malaysia	321	16	64	3
	Hong Kong	471	14	58	7
	China	647	16	49	2
19	Sydney	1,339	8-11	42	24
	West Sydney	904	8-11	42	28
	Moree/Narrabi	770	8-11	40	31
	Wagga Wagga	850	8-11	40	29
	Belmont	926	8-11	39	38
	Broken Hill	794	8-11	37	30
	Lismore	805	8-11	35	31
20	Hamburg	1,159	20-44	36	2
	Erfurt	731	20-44	30	1
21	Rural Ethiopia	861	5-70+	12*	1
	Urban Ethiopia	2,194	5-70+	4*	4
13	Urban Antwerp	319	20-44	26*	7
	Suburban Antwerp	337	20-44	17*	4
Comparisons of the same population over time					
22	Busselton 1981	553	18-55	39	9
	Busselton 1990	1,028	18-55	41	16
23	Belmont 1982	718	8-10	28	9
	Belmont 1992	873	8-10	29	38
	Wagga Wagga 1982	769	8-10	30	13
	Wagga Wagga 1992	795	8-10	35	30
24	Leipzig/Halle	1,492	9-11	19	4
	Leipzig/Halle	2,311	9-11	27	4

* Skin-prick-test-positive to house dust mites.

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Airway Hyperresponsiveness

Airway hyperresponsiveness, a state in which the airways narrow too easily and too much in response to provoking stimuli, is a risk factor for asthma. The condition has a heritable component and is closely related to serum IgE levels and airway inflammation. A tendency to produce an elevated level of total serum IgE is co-inherited with airway hyperresponsiveness, and a gene governing airway hyperresponsiveness is located near a major locus that regulates serum IgE levels on chromosome 5q[29].

Asymptomatic airway hyperresponsiveness to histamine is a risk factor for asthma[30]. However, it is not yet clear whether the development of airway hyperresponsiveness precedes, coincides with, or follows the development of symptoms of asthma. Interestingly, asymptomatic airway hyperresponsiveness is associated with airway inflammation and remodeling[30,31], suggesting that airway inflammation may precede the onset of asthma.

Gender and Asthma

Childhood asthma is more prevalent in boys than in girls[32]. The increased risk for males in childhood is probably related to narrower airways, increased airway tone[32-34], and possibly higher IgE[35] in boys, which predispose them to enhanced airflow limitation in response to a variety of insults. Further support for this hypothesis comes from the observation that the difference disappears after age 10, when the airway diameter/length ratio is the same in both sexes, probably because of changes in thoracic size that occur with puberty in males but not in females[36-38]. More females than males develop asthma during puberty and thereafter, so the prevalence of adult asthma becomes higher in females than in males. Interestingly, aspirin-induced asthma[39] is more frequent in women.

Race/Ethnicity and Asthma

The majority of data indicate that socioeconomic and

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environmental factors are primarily responsible for apparent racial and ethnic differences in the prevalence of asthma. Migrant studies suggest that subjects of different races may acquire the risk of the population they move to. The prevalence of wheezing is the same among children of different racial descent living in London or Australia[40]. The much higher prevalence of wheezing in black than white children living in the United States seems likely to be due to socioeconomic and environmental factors[41]. Thus, even though slight differences in asthma prevalence between different races living in the same region have been found in some studies[42], these differences may be attributable to socioeconomic conditions, allergen exposures, and dietary factors rather than to racial predisposition.

ENVIRONMENTAL FACTORS THAT INFLUENCE THE SUSCEPTIBILITY TO THE DEVELOPMENT OF ASTHMA IN PREDISPOSED INDIVIDUALS

Allergens and occupational sensitizers have been considered the most important causes of asthma, with the understanding that they could first sensitize the airways and then keep asthma active by precipitating asthma attacks or leading to the persistence of symptoms.

Exposure to an allergen is an important risk factor for the development of atopic sensitization to that specific allergen[43,44], and exposure to allergens in sensitized individuals is a risk factor for asthma exacerbations and/or the persistence of asthma symptoms[45]. Thus, it has been speculated that exposure to an allergen is the cause of asthma or at least of its manifestation and persistence. However, a major unresolved question is whether exposure to allergens and occupational sensitizers is indeed the primary cause of the development of new asthma, or if this exposure merely triggers asthma attacks or leads to the persistence of symptoms in subjects who already have asthma[46].

Several studies have suggested a correlation between allergen exposure and the prevalence of asthma[47-49], and have documented an improvement of asthma after exposure to allergens ceases[17,50]. However, no longitudinal study has firmly demonstrated that the level of allergen exposure during infancy is related to asthma risk later in life[46]. Indeed, even if exposure to allergens early in life is related to allergen sensitization, many factors may contribute to the expression of asthma symptoms later in life, current exposure to allergens being just one such factor. Two recent studies clearly show that early allergen exposure is indeed a risk factor for the development of allergen sensitization but not for asthma, confirming that allergy and asthma develop through separate pathways and mechanisms[51,52]. Some cross-sectional[13] and prospective[51] studies have shown that exposure to some allergens may actually be negatively associated with current expression of asthma[11].

If the level of exposure to allergens, and particularly to mites, in early life is indeed crucial for allergic sensitization and for the expression of asthma[53], children brought up in a mite-free environment at high altitude should have a significantly lower prevalence of asthma and wheeze than children from a humid, mite-infested area. However, two independent studies performed in the Alps and New Mexico failed to document a significant effect of a mite-free environment on the occurrence of asthma[16,54]. Other allergens (e.g., pet-derived allergens or *Alternaria*) found in both environments may have played a role in producing these results[55].

The fact that allergen exposure may exacerbate asthma or cause symptoms to persist may lead to an increased estimate of asthma prevalence (number of cases in a given population) in epidemiological studies, even if allergen exposure does not influence asthma incidence (new cases over time). Indeed, the allergen-specific IgE-mediated reaction may simply represent one of several mechanisms that contribute to triggering acute exacerbations of asthma or to maintaining chronic airway inflammation and asthma symptoms without necessarily causing new asthma.

The presence of at least some form of occupational asthma or environmental asthma only in exposed subjects suggests that some substances to which a subject becomes sensitized can cause the development of asthma. The studies in Barcelona, where epidemics of asthma exacerbations were traced to days when soybeans were being unloaded at a specific silo without a filter, increased the awareness that small amounts of airborne allergen can cause major changes in the lungs of sensitized people[56]. The fact that those who came to the hospital were already atopic and allergic to the dust suggested that sensitization can occur at low atmospheric concentrations if the allergen is potent enough[57]. In addition, the fact that most of those who came to the hospital already had asthma suggests that the primary effect of exposure to a sensitizing agent is most likely triggering asthma exacerbations rather than causing the onset of new asthma.

It has not been firmly established whether the exposure and sensitization to an occupational sensitizer is actually the cause of occupational asthma, or just one additional

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trigger of asthma exacerbations. Most of the studies conducted in occupational asthma have involved small groups of subjects without proper controls, and the cause-effect relationship between the sensitizing agent and the development of asthma has been based on a positive response after bronchoprovocation challenges. Asthma may persist after long-term avoidance of the sensitizing agent in a significant proportion of subjects with occupational asthma[58,59], but this observation does not illuminate the cause of occupational asthma, as it may suggest either that asthma and occupational sensitization are two independent events, or that once asthma is induced by an occupational sensitizer it may persist even in the absence of the causative agent.

On the other hand, there is evidence that exposure to allergens and/or chemicals may indeed cause asthma, at least in some subjects, particularly if the sensitizing agent is potent enough. Historical examples show asthma developing in most, if not all, subjects exposed to bees, platinum salts, and biological enzymes on the job[60]. In a 5-year study of 277 workers employed in a new toluene diisocyanate manufacturing plant, an incidence of new cases of occupational asthma of up to 5 percent was identified[61]. In another study, a 2.7 percent incidence of new cases of occupational asthma caused by animal allergens was found in previously healthy apprentices in animal health technology[62].

Indoor Allergens

Indoor allergens include domestic (house dust) mites, animal allergens, cockroach allergen, and fungi. Indoor allergens today have increased in developed countries where homes have been insulated for energy efficiency, carpeted, heated, cooled, and humidified–changes that have also made homes ideal habitat for domestic mites, cockroaches, other insects, molds, and bacteria[63,64].

Domestic mites. Although mite allergens are carried in particles too large to penetrate the airways, there is evidence to suggest that domestic mites are the most common indoor allergen associated with asthma worldwide[48,65,66]. However, as previously mentioned, early allergen exposure is a risk factor for the development of allergen sensitization but not for asthma[51,52].

House dust is composed of several organic and inorganic compounds, including fibers, mold spores, pollen grains, insects and insect feces, mammalian danders, and mites and mite feces. Domestic mite allergens are present in various parts of mite bodies[67-69], secreta, and excreta and constitute the main source of dust-derived allergens. The principal domestic mite species are the pyroglyphid mites *Dermatophagoides pteronyssinus, D. farinae, D. microceras*, and *Euroglyphus mainei*, which usually account for 90 percent of the mite species in house dust from temperate regions[70]. Mites feed on human and animal scales colonized by microfungi, yeasts, and bacteria. Mites can be found in floors and tend to bury themselves deep in carpets, mattresses, and soft furnishings. Conditions for growth are a temperature between 22 and 26° C and a relative humidity greater than 55 percent (or an absolute humidity less than 8 g/kg).

D. pteronyssinus is the dominant mite in constantly damp climates (Northern Europe, Brazil, and the Pacific Northwest). *D. farinae* survives better in drier climates and is the most prominent mite species in areas with prolonged dry winters. Another domestic mite of importance is *Blomia tropicalis,* commonly found in houses in tropical and subtropical areas, such as Brazil and Florida.

In addition to the pyroglyphid mites, other mite species are found in house dust, cause development of IgE antibody responses, and may also be termed domestic mites. These include storage mites, which inhabit stored food products and hay and require abundant food and high humidity for survival. The most common species belong to the genera *Tyrophagus, Glycyphagus, Acarus, Lepidoglyphus, Cortoglyphus,* and *Tarsonemus*.

The allergens of domestic mites have been identified as cysteine proteases (group I allergens: *D. pteronyssinus* I, *D. farinae* I, and *D. microceras* I); serine proteases (group III allergens); and amylase (group IV[71] allergens). These allergenic enzymes have been found in mite fecal pellets. The group II allergens are derived mainly from mite bodies rather than from mite feces (*D. pteronyssinus* II, *D. farinae* II). The predominant allergens in house dust are from groups I and III; very little group II allergen has been found in dust. Interestingly, the most important mite allergens have proteolytic activity, and thus they might have easier access to the immunocompetent cells.

A concentration of mite allergen above 0.5 μg of *D. pteronyssinus* I per gram of dust seems to be a significant risk factor for mite allergy, but a similar threshold level for provocation of asthma symptoms has not been clearly defined[72-74].

Animal allergens. Household warm-blooded animals release allergens in secretions (saliva), excretions (e.g., urine), and danders.
Cats. Cat allergens are potent airway-sensitizing agents. The main allergenic protein (Fel d1) is found in cat pelt (especially in the facial area), sebaceous secretions, and urine, but not in saliva[75]. This allergen is carried on small

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particles of about 3 to 4 microns in diameter, which easily become airborne and are responsible for the rapid onset of respiratory symptoms in cat-sensitized persons entering an indoor environment containing a cat[72,76]. While early exposure to cats may decrease rather than increase a child's risk of developing asthma[77], cat allergens may constitute a relevant risk factor for asthma exacerbations and emergency room visits. Although households with a cat contain higher quantities of cat allergen, private homes without a cat and public places (such as hospitals, cinemas, and public transport) may contain sufficient allergenic protein to induce clinical symptoms in highly sensitized subjects[73,78]. The clothes of cat owners constitute the vehicle of passive transport of Fel d1 to cat-free environments[79].

Dogs. Dogs produce two important allergenic proteins, Can f1 and Can f2. The characteristics of dog allergens (allergen-carrying particles, ubiquity, etc.) are similar to those of cat allergens. Although a slight degree of cross-reactivity between cat and dog allergenic materials has been demonstrated[71], allergic sensitivity to dogs is not as common as sensitivity to other mammals. Nevertheless, up to 30 percent of allergic individuals have positive skin tests to dog extracts. Although the many breeds of dog (over 100) and the diversity of dog allergens create problems in the randomization of extracts, a dog allergen has been purified from dog hair and dander[80].

Rodents. Many children keep rodents as pets, and there are inner-city areas where wild mice or rats are present. The allergenicity of rodent antigens is well known in animal handlers, who become sensitized to urinary proteins[81].

Cockroach allergen. In some locations and among some ethnic groups, sensitization to cockroach allergen may be as common as sensitization to domestic mite allergens. Most species of cockroaches live in tropical climates; however, central heating has enabled them to thrive outside their normal habitat. The most common species are the American cockroach *(Periplaneta americana)*, German cockroach *(Blatella germanica)*, Asian cockroach *(B. orientalis)*, Australian cockroach *(P. australasiae)*, and brown-banded cockroach *(Supella supulledium)*. Allergens from the German and American cockroaches have been characterized, and their presence in house dust can be measured by using specific monoclonal antibodies[82].

Fungi. Molds and yeasts can act as indoor airborne allergens. Among these is *Alternaria,* which is an established risk factor for asthma in various populations and has been associated with the risk of asthma death in the United States[83,84]. Dark, humid, and poorly ventilated areas are optimal for indoor fungal growth. Fungi grow well within the systems used for cooling, heating, and humidification, with house humidifiers providing a special risk for indoor fungal growth and air contamination. Unfortunately, there are as yet no reliable methods of measuring the concentration of indoor fungi. The most common indoor fungi are *Penicillium, Aspergillus, Alternaria, Cladosporium,* and *Candida*[85,86].

Outdoor Allergens

The most common outdoor allergens that may lead to asthma in susceptible people are pollens and fungi.

Pollens. Pollen allergens associated with asthma come mainly from trees, grasses, and weeds. Pollen allergens are carried in large particles, and it is not clear how they reach the bronchi. Micron-sized particles of starch granules are released from pollens, particularly after rainfall, and seem to be responsible for pollen-induced asthma exacerbations[87,88].

The air concentration of pollens varies with location and atmospheric condition, but in general, tree pollens predominate in the early spring, grass pollens in the late spring and summer, and weed pollens during summer and fall. Clinical and aerobiological studies show that the pollen maps are changing as a result of cultural factors (e.g., importation of plants for urban parklands) and greater international travel. Concentrations of Lol p1 (the major allergen from rye grass, *Lolium perenne*) above 10 μg/g in house dust are associated with epidemics of pollen-induced exacerbations of asthma[89], increase of symptoms, increase of airway hyperresponsiveness, and airway inflammation[90].

While there is strong evidence that exposure to pollens may trigger asthma exacerbations, there is yet no evidence that sensitization to pollens increases the risk of developing asthma[91].

Fungi. Molds and yeasts can be outdoor airborne allergens. *Alternaria* and *Cladosporium* (which are also indoor fungi) are the only fungi that have been established as risk factors for asthma. Fungi tend to be seasonal allergens in temperate zones, where some fungi sporulate on warm, dry summer days, and others prefer the rainy nights of fall[92,93].

Occupational Sensitizers

An extensive list of occupational sensitizing agents has been reported[94]; **Figure 3-4** provides an abbreviated

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listing. A continuously updated list on the Asmanet website (http://asmanet.com) currently includes at least 361 occupational agents shown to be involved in occupational asthma.

Occupational sensitizers are usually classified according to molecular weight. The mechanism of action of low-molecular-weight sensitizers remains largely unknown[95]. High-molecular-weight sensitizers probably sensitize subjects and cause asthma exacerbations by the same mechanisms as allergens. For example, acute exposure to irritant gases in the workplace or during accidents may induce a long-lasting airway hyperresponsiveness, which was formerly named reactive airway dysfunction syndrome and is now known as irritant-induced asthma.

Irritant-induced asthma shares most of the clinical and physiologic characteristics of other forms of asthma[96]. Its pathology is similar but not identical, being characterized by increased airway mucosal mononuclear cells and subepithelial fibrosis but not by an increased number of mast cells and eosinophils[97].

Figure 3-4. Agents Causing Asthma in Selected Occupations

Occupation or occupational field	Agent
	Animal proteins
Laboratory animal workers, veterinarians	Dander and urine proteins
Food processing	Shellfish, egg proteins, pancreatic enzymes, papain, amylase
Dairy farmers	Storage mites
Poultry farmers	Poultry mites, droppings, feathers
Granary workers	Storage mites, *Aspergillus*, indoor ragweed, grass
Research workers	Locusts
Fish food manufacturing	Midges
Detergent manufacturing	*Bacillus subtilis* enzymes
Silk workers	Silkworm moths and larvae
	Plant proteins
Bakers	Flour, amylase
Food processing	Coffee bean dust, meat tenderizer (papain), tea
Farmers	Soybean dust
Shipping workers	Grain dust (molds, insects, grain)
Laxative manufacturing	Ispaghula, psyllium
Sawmill workers, carpenters	Wood dust (western red cedar, oak, mahogany, zebrawood, redwood, Lebanon cedar, African maple, eastern white cedar)
Electric soldering	Colophony (pine resin)
Nurses	Psyllium, latex
	Inorganic chemicals
Refinery workers	Platinum salts, vanadium
Plating	Nickel salts
Diamond polishing	Cobalt salts
Manufacturing	Aluminum fluoride
Beauticians	Persulfate
Welding	Stainless steel fumes, chromium salts
	Organic chemicals
Manufacturing	Antibiotics, piperazine, methyldopa, salbutamol, cimetidine
Hospital workers	Disinfectants (sulfathiazole, chloramine, formaldehyde, glutaraldehyde), latex
Anesthesiology	Enflurane
Poultry workers	Aprolium
Fur dyeing	Fur dye
Rubber processing	Formaldehyde, ethylene diamine, phthalic anhydride
Plastics industry	Toluene diisocyanate, hexamethyl diisocyanate, dephenylmethyl isocyanate, phthalic anhydride, triethylene tetramines, trimellitic anhydride, hexamethyl tetramine, acrylates
Automobile painting	Ethanolamine, diisocyanates
Foundry workers	Reaction product of furan binder

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Tobacco Smoke

Tobacco burning, which is a ubiquitous source of indoor irritants, produces a large and complex mixture of gases, vapors, and particulate matter. More than 4,500 compounds and contaminants have been identified in tobacco smoke, among them respirable particles, polycyclic hydrocarbons, carbon monoxide, carbon dioxide, nitric oxide, nitrogen oxides, nicotine, and acrolein.

Passive smoking. There is evidence that exposure to environmental tobacco smoke (i.e., passive smoking) increases the risk of lower respiratory tract illnesses *in utero*[98], in infancy[99], and in childhood[100,101]. Sidestream smoke, which burns hotter and is more toxic than the smoke inhaled by the tobacco user, is particularly irritating to the respiratory mucosa. Smoking by a child's mother during pregnancy plus smoking by any member of the household after the child is born increases the child's risk of developing asthma and wheeze[102,103]. The effects of environmental tobacco smoke exposure on adult asthma have not yet been investigated extensively and the available data are limited[104].

Active smoking. While active smoking may increase the risk of developing occupational asthma in workers exposed to some occupational sensitizers (e.g., acid anhydrides)[105], there is still limited evidence that active smoking is a risk factor for the development of asthma. However, active smoking is associated with accelerated decline of lung function in people with asthma, greater asthma severity[106], and poor response to asthma treatment[107, 190], supporting the concept that active smoking may contribute to asthma severity even without contributing to the development of asthma[106].

Air Pollution

Air pollution is defined as the atmospheric accumulation of irritants to a degree that becomes injurious to humans, animals, or plants. Both outdoor and indoor irritants contribute to air pollution.

Outdoor pollutants. There are two main types of outdoor pollution: industrial smog (sulfur dioxide particulate complex) and photochemical smog (ozone and nitrogen oxides), and they can coexist in a given area. Levels of air pollutants are affected by weather conditions and local geographic features. Several studies have implicated various pollutants as aggravating asthma[108], mainly in experiments with controlled chamber exposure. However, because of the great number of variables, epidemiological studies trying to link the rising trend of asthma with ambient pollution have been inconclusive. Some studies have shown a significant association of air pollutants such as ozone, nitrogen oxides, acidic aerosols, and particulate matter with symptoms and exacerbations of asthma. It is possible that chronic exposure to pollution may predispose to respiratory disease in a more subtle and complicated manner.

Environmental pollutants such as sulfur dioxide, ozone, and nitrogen oxides can, at concentrations found in heavily polluted cities, trigger bronchoconstriction, transiently increase airway responsiveness, and enhance allergic responses. Thus, in theory, pollution might indeed contribute to the development of asthma. However, although asthma seems to be more frequent in industrialized countries, there is little, if any, evidence that air pollution is directly responsible for the increased prevalence of asthma in these countries[44].

The role of air pollution in the development of asthma and allergy was studied by comparing the prevalence of respiratory disorders in school children living in two German cities: the eastern city of Leipzig, with its heavy industrial pollution, and the western city of Munich, with its heavy automobile traffic. Asthma and allergy were significantly more prevalent in Munich, while bronchitis was more prevalent in Leipzig[109]. This difference was related, among various factors, to the type of air pollution: in Munich, vehicle emissions (nitrogen dioxide and respirable particulate matter) predominated, whereas in Leipzig the air pollution contained high concentrations of sulfur dioxide from high-sulfur coal burned for heating and energy production. Subsequent studies[24] demonstrated that the prevalence of hay fever in Leipzig schoolchildren increased from 2 to 3 percent in 1991-92 to 5.1 percent in 1995-96 (i.e., 6 to 7 years after the reunification of Germany), while the prevalence of all IgE-mediated sensitizations increased from 19.3 percent in 1991-92 to 26.7 percent in 1995-96. Thus, the difference in prevalence of allergic disorders formerly observed between eastern and western Germany is progressively decreasing as motor vehicle traffic and the consequent forms of air pollution increase in the former East Germany.

Exposure to traffic, particularly to diesel exhaust, may exacerbate preexisting allergic conditions but does not necessarily induce the development of new cases of asthma and atopy[110]. Diesel particles have also been shown to absorb allergens from grass pollen onto their surface and may therefore act as potential carriers to increase deposition of pollen allergens in the lung[111-113]. In this way, both the allergen dose and the antigenicity of the pollen allergen may be enhanced by automobile-related pollution[114].

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Indoor pollutants. The contaminants and atmospheric dynamics of indoor air pollution are different from those of outdoor air pollution. Modern construction techniques possibly contribute to greater indoor pollution by lowering the turnover of indoor air. An increased indoor pollutant load may be in addition to the increased antigen load (in particular, from the feces of domestic mites) produced by changes in house design and forms of heating and furnishing (especially the use of carpets and upholstered furniture). Because very young children spend most of their time indoors, and because residents of developed countries also spend 90 to 95 percent of their time indoors, indoor pollutants are important to consider. However, each home indoor environment is unique, and air quality may vary from house to house and even from room to room.

Major indoor pollutants are nitric oxide, nitrogen oxides, carbon monoxide, carbon dioxide, sulfur dioxide, formaldehyde, and biologicals such as endotoxin[115]. Sources of these indoor pollutants include the following:

- Cooking with natural gas or liquid propane, which produces carbon monoxide, carbon dioxide, sulfur dioxide, nitric oxide, and nitrogen oxides
- Cooking on wood, kerosene, or coal-burning stoves, which produces carbon monoxide, nitrogen oxides, and sulfur dioxide as well as respirable particles
- Heating with gas, wood, coal, and kerosene units and fireplaces, which produces carbon monoxide, carbon dioxide, nitric oxide, nitrogen oxides, respirable particles, and particulate soot[116]
- Building and furnishing with foam installations, glues, fireboard, pressed board, plywood, particle board, carpet backing, and fabrics that contain the volatile organic compound formaldehyde, and using paints or other materials that release isocyanates.

Some data suggest that indoor pollutants may contribute to the development of asthma, but further studies are needed. Among the problems related to indoor pollution are nose irritation, respiratory infections and bronchitis, and lung cancer as a result of respirable particles; nose irritation, impaired lung function, and increased infections in children as a result of nitrogen oxides; and difficulty in breathing and asthma symptoms as a result of formaldehyde[117].

Respiratory Infections

Respiratory infections have a complex relationship with asthma. Such infections early in life have been associated with both increased and decreased risk for the development of asthma, and infections at any time of life are associated with the onset of exacerbations.

Epidemiologic evidence confirms that acute respiratory viral infections cause asthma exacerbations in both adults and children[118,119]. The major respiratory virus types and the conditions they are most associated with are listed in **Figure 3-5**[118]. Each respiratory virus is capable of causing almost any respiratory condition, depending on the site and dose of virus inoculated and the degree of host predisposition[118]. The most common respiratory viruses in infancy are respiratory syncytial viruses (RSV), which cause approximately 50 percent of all wheezing illnesses and 80 percent of cases of bronchiolitis in this age group[118]. Parainfluenza virus is also an important cause of bronchiolitis and croup in infancy, while common cold viruses such as rhinoviruses are the principal triggers of wheezing in older children and adults with asthma[120].

Bacterial infections, particularly with *Chlamydia pneumoniae*, in infancy have been suggested to play a role in the development of asthma later in life, although the available evidence only demonstrates associations between chronic bacterial infection of the airways and severe asthma and between bacterial infections and exacerbations of asthma[120-122]. Several studies have demonstrated an association between viral respiratory infections, particularly RSV bronchiolitis, in early life and

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Figure 3-5. Respiratory Viruses and Respiratory Conditions Associated With Them[118]

Virus type	Serotypes	Common cold	Asthma exacerbation	Pneumonia	Bronchitis	Bronchiolitis
Rhinovirus	1-100 (plus)	+++	+++		+	+
Coronavirus	229E and OC43	++	++	–	–	–
Influenza	A, B, and C	+	+	++	+	
Parainfluenza	1, 2, 3, and 4	+	+		++ (Laryngotracheobronchitis)	+
Respiratory syncytial virus	A and B	+	+	+	+	+++
Adenovirus	1-43	+	+	++	+	+

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later development of asthma or pulmonary function abnormalities, including airway hyperresponsiveness[123,124]. One study confirmed that RSV bronchiolitis is the most important risk factor for the development of wheezing, asthma, and atopic sensitization in children followed up to 7 years of age[125]. Another study has clearly shown that not only RSV infections but also other severe respiratory viral infections in the first 3 years of life are associated with increased risk of wheeze during childhood up to 13 years of age[119]. There is increasing evidence that infants with RSV bronchiolitis have impaired type 1 immunity and augmented type 2 immunity, thus putting them at risk for the development of allergic sensitization and development of severe respiratory tract infections (due to impaired antiviral immunity) early in life. These infants are also at risk for the development of wheezing illness and asthma later in life on reexposure to allergens and viral infections.

There is thus a clear association between severe viral respiratory infections early in life and the development of asthma in childhood. There is also evidence that this association is mediated by a common preexisting imbalance in immunity (deficient type 1 and augmented type 2 immunity). However, it is not yet clear whether viral infections early in childhood can affect the development of the immune system and thereby modify the risk for the subsequent development of allergies and asthma[119].

In contrast to the above evidence, a recent large epidemiologic study completed in Germany[126] has clearly shown a protective effect of frequent upper respiratory infections (sniffles) during the first year of life on the risk of later development of atopy and asthma, even in children with a family history of atopic diseases.

Similar data from the United States (Tucson, Arizona) also show that conditions associated with increased respiratory infections early in life (having a larger number of siblings and attending day care) also protect against the development of asthma[127]. These data are in accordance with the hygiene hypothesis (see below) but appear to contradict the positive associations between respiratory infections and asthma discussed above. This apparent contradiction can be resolved by understanding that individual severe infections early in life (such as RSV bronchiolitis) are a marker of impaired type 1 immunity and are therefore associated with increased risk for the development of asthma later in life. In contrast, measures reflecting an increased overall load of infectious disease (such as frequent sniffles[121] or day care attendance[128]) identify children whose immune systems are more likely to develop successfully with type 1 responses as a result of environmental stimulation, placing these children at reduced risk of developing asthma later in life.

A possible link between mycobacterial infection and reduced risk of allergy was suggested by a study of 867 Japanese children who underwent routine tuberculin tests prior to *Mycobacterium bovis* BCG vaccination at ages 6 and 12 years. An inverse relationship was observed between delayed hypersensitivity to tuberculin at the age of 12 and both total and allergen-specific serum IgE levels at the same age[129]. The authors interpreted this as evidence that prior infection with tuberculosis or environmental mycobacteria might protect against the development of allergy. However, the same data may simply suggest that atopic/asthmatic subjects may have a less prominent tuberculin response. Conflicting data have been reported on the relationship between BCG vaccination and the development of atopy and asthma[130]. The role of other vaccinations, including those for measles and pertussis[131], has been questioned.

The hygiene hypothesis. Improvement in hygiene and reduced recirculation of common infections is strongly associated with the increasing prevalence of atopy and atopic diseases in Western countries[132].

Respiratory allergy is less frequent in people heavily exposed to orofecal and foodborne microbes. Hygiene and a Westernized, semisterile diet may facilitate atopy by influencing the overall pattern of commensals and pathogens that stimulate the gut-associated lymphoid tissue, thus contributing to the epidemic of allergic asthma and rhinitis in developed countries[132]. The most consistent evidence of an inverse relationship between infection and allergy is known from studies of hepatitis A[133].

Another factor that confers protection against the development of atopy and asthma is growing up on a farm[134]. Living conditions of farming families differ in many respects from those of other families: larger family size, more pets, frequent heating with wood or coal, less maternal smoking, more dampness, and different dietary habits. None of these factors, however, explains the strong inverse association between atopy and growing up on a farm. Instead, contact with livestock and poultry has been found to explain much of the relationship between farming and reduced prevalence of atopy[135].

The prevalence of atopy is lower in children from anthroposophic families than in children from other families. (Anthroposophy is a 20th century religious system growing out of theosophy.) This suggests that some factors associated with an anthroposophic lifestyle (e.g., restricted use of antibiotics, few vaccinations, and a diet containing live lactobacilli) may lessen the risk of atopy in childhood[136].

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Parasitic Infections

The results of studies that include egg counts suggest that subjects with asthma have a lower parasitic burden than normal subjects. Similarly, African children with urinary schistosomiasis have been reported to have a lower prevalence of atopy than those free of this infection[137]. Although epidemiological studies suggest that asthma is less common where intestinal parasitism is endemic, case-control studies show either no association or an increase in parasitism in people with asthma[138]. Overall, the available data neither refute nor support the theories that parasitic disease either protects against or causes asthma[128].

Socioeconomic Status

Another feature of the epidemiology of allergic disease for which the hygiene hypothesis offers an explanation is the socioeconomic gradient–that is, the higher prevalence of childhood asthma and atopic diseases found in developed nations than in developing nations, and the greater prevalence of these diseases in affluent than poor regions in the developing world[139]. The socioeconomic status of families may be a surrogate measure of lifestyle characteristics rather than a measure of risk factors *per se*. These lifestyle characteristics may include dietary habits, family size, access to health care, passive smoking, allergen exposure, or other, yet-unknown determinants[44].

Family Size

Studies have indicated an inverse relationship between asthma and family size: having no siblings or one sibling is associated with an increased risk of asthma compared with having more than one sibling[140,141]. Many authors have shown that the number of siblings is also inversely related to the prevalence of inhalant allergy[142], hay fever[143], and asthma, suggesting that exposure of young children to older children at home protects against the development of asthma and frequent wheezing later in childhood[127].

Diet and Drugs

A Cochrane review concluded that an antigen-avoidance diet during pregnancy is unlikely to substantially reduce the risk of giving birth to an atopic child. Moreover, such a diet may have an adverse effect on maternal and/or fetal nutrition[144]. Conflicting data have been reported about the protective role of breast feeding in the development of asthma.

Although the relationship between food sensitivity and the development of asthma is still uncertain, there is some evidence that food allergy in infancy is followed by asthma. Children with food-sensitive enteropathies and colitis have a higher subsequent prevalence of asthma, which is probably more indicative of a predisposition to develop allergies than of the food actually causing asthma.

Because omega-3 polyunsaturated fatty acids have been shown to have anti-inflammatory effects *in vitro*, there have been several studies to determine whether fish in the diet is associated with a lower prevalence of asthma[145,146]. However, a Cochrane analysis[147] indicated there is little evidence to recommend that people with asthma supplement or modify their dietary intake of fish oil in order to improve their asthma control. Equally, there is no evidence that they are at risk if they do so.

The consumption of fruit rich in vitamin C, even at a low level, may reduce wheezing symptoms in childhood, especially among already susceptible individuals[147,148]. The severity of asthma, though not its development, has been linked to increased salt intake, but only in men[149].

It is widely believed that allergic reactions to foods or drugs may cause asthma and particularly that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may be an important cause of adult-onset asthma. While there is solid evidence that NSAIDs may cause asthma exacerbations in a significant proportion of people with asthma, there is so far no convincing evidence that these drugs can actually cause the development of asthma[150,151].

Obesity

Despite the inherent difficulty in associating two common disorders, there is some evidence of a correlation between higher body mass index (BMI) and greater risk of developing asthma[152-154]. In addition, there is some evidence that weight loss improves lung function (particularly PEF variability)[155], symptoms, morbidity, and health status[156] in obese patients with asthma, suggesting that obesity might contribute to the worsening of respiratory symptoms and quality of life in people with asthma.

FACTORS THAT PRECIPITATE ASTHMA EXACERBATIONS AND/OR CAUSE SYMPTOMS TO PERSIST

Triggers are risk factors that cause asthma exacerbations by inducing inflammation or provoking acute bronchoconstriction, or both. Triggers vary from person to person and from time to time. They include further exposures to causal factors (allergens and occupational

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agents) that have already sensitized the airways of the person with asthma.

Triggers also include exercise, cold air, drugs, irritant gases, weather changes, and extreme emotional expression. These triggers cannot cause asthma to develop initially but can exacerbate asthma once it is present. Taking a careful history is necessary in attempting to identify each individual's triggers.

In this section, allergens, air pollutants, respiratory infections, exercise and hyperventilation, weather changes, sulfur dioxide, foods, additives, and drugs, and extreme emotional expression are briefly discussed in their role as asthma triggers. Other factors that may cause exacerbations, including rhinitis, sinusitis, polyposis, gastroesophageal reflux, menstruation, and pregnancy, are also briefly examined.

Allergens

Once the subject is sensitized, indoor and outdoor allergens can cause asthma exacerbations. Recent studies have proved that very small amounts of airborne allergens are able to cause asthma exacerbations and major changes in the lungs of sensitized people[157]. The mechanisms by which subsequent exposure to allergens may cause asthma exacerbations and maintain chronic airway inflammation in asthma are described in the chapter on mechanisms of asthma.

Air Pollutants

Children with asthma who are exposed to maternal smoking have higher requirements for medication and more frequent emergency department visits[158,159]. Other irritants, such as wood smoke, household sprays, volatile organic compounds (e.g., polishes and cooking oils), and air pollutants, may also exacerbate asthma.

Increased air stagnation was shown to be a surrogate for accumulation of the products of incomplete combustion, including carbon monoxide and fine particulate levels of organic and elemental carbon, and is strongly associated with asthma exacerbations[160].

An important factor that can act as a trigger is exposure to vehicle traffic, particularly diesel exhaust, which might exacerbate preexisting allergic conditions. The role of diesel exhaust in the development of new cases of atopy and asthma is still uncertain[161]. Finally, the airway responses to allergen may be enhanced by simultaneous exposure to air pollutants, constituting a potential amplifying mechanism[44,162].

Respiratory Infections

In contrast to the slight evidence of a pathogenetic role of viral infections in the development of asthma, it is well established that viral respiratory infections can exacerbate asthma[163]. RSV, rhinovirus[164], and influenza virus have been implicated[123], with rhinovirus being implicated in the majority of the exacerbations of asthma in children[165]. The role of infections as triggers also appears to be important in adults[163].

Respiratory viruses may exacerbate asthma through various mechanisms. Viral infections may cause epithelial damage and airway inflammation, both of which may lead to asthma symptoms. Virus-specific IgE antibody has been identified for RSV and for the parainfluenza virus, and these viruses may be responsible for the generation and release of allergic mediators from human lung cells[166]. In addition, at least one virus has been shown to potentiate the allergic response to allergens by increasing the release of inflammatory mediators and the cascade of inflammatory events characteristic of asthma[167].

Exercise and Hyperventilation

Exercise is probably the most common trigger of brief episodes of symptoms. Exercise incites airflow limitation in most children and young adults who have asthma[168]. The mechanisms of exercise-induced airflow limitation are mainly related to changes in the airway mucosa induced by the associated hyperventilation, to either cooling or rewarming, or to changes in the osmolarity of fluid lining the airway mucosa. Exercise appears to be a specific stimulus for people with asthma, because it seldom leads to airflow limitation in people without asthma, even those with other airway diseases, such as chronic bronchitis, cystic fibrosis, or bronchiectasis[169]. Hyperventilation with cold, dry, or even hot air can cause asthma exacerbations through unknown mechanisms. Like exercise, hyperventilation seems to be a specific trigger for asthma[170,171].

Weather Changes

Adverse weather conditions, such as freezing temperatures, high humidity, and episodes of acute pollution brought on by weather conditions have been associated with asthma exacerbations, but these factors have not been examined systematically and in depth[172,173]. Epidemics of asthma exacerbations associated with thunderstorms may be related to increased concentrations of allergenic particles associated with the downdraft of the storm, which sweeps up pollen grains and particles and concentrates them in a shallow band of air at ground level[174].

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Sulfur Dioxide

Sulfur dioxide can trigger a dose-dependent airflow limitation in patients with asthma, although it has no effect on the airways of normal subjects up to very high concentrations[175]. Airflow limitation may be incited by sulfur dioxide at concentrations as low as 1 ppm, a level easily encountered in the workplace or elsewhere in the environment[176,177].

Foods, Additives, and Drugs

It is widely believed that allergic reactions to foods are common asthma triggers, but documented evidence is difficult to find. Some ingested substances, including salicylates, food preservatives, monosodium glutamate, and some food-coloring agents, cause asthma symptoms in some patients. Preservatives in many beverages (including wine and beer) and in some foods contain metabisulfite, which may release sufficient sulfur dioxide to provoke bronchoconstriction[178].

In about 4 to 28 percent (depending on the study methodology) of adults with asthma–particularly in those with nasal polyps and sinusitis–but rarely in children with asthma, NSAIDs may cause asthma exacerbations. The majority of these patients first experience symptoms during the third to fourth decade of life, but it is still unclear what proportion of them have preexisting asthma rather than newly developed asthma. Thus, it remains to be established whether aspirin and related drugs cause the development of asthma or, more likely, simply act as triggers of asthma albeit through highly specific mechanisms. Once NSAID intolerance develops, it is present for life[150,151].

Beta blockers can provoke bronchoconstriction in asthma patients by blocking beta-receptors to endogenous catecholamine[179]. In a few subjects, the inhalation of heroin has triggered the development of status asthmaticus[180]. Drugs or agents that can induce bronchospasm are listed in **Figure 3-6**.

Extreme Emotional Expression

Emotional stress may be a trigger for asthma exacerbations, primarily because extreme expressions of laughing, crying, anger, or fear can lead to hyperventilation and hypocapnia, which can cause airway narrowing[181,182]. Panic attacks, which are rare but not exceptional in some patients with asthma, have a similar effect[183,184]. However, it is important to note that asthma is not a psychosomatic disorder.

Figure 3-6. Drugs or Agents Associated With the Induction of Bronchospasm

Acetylsalicylic acid
Beta blockers
Cocaine
Contrast agents
Dipyridamole
Heroin
Hydrocortisone
IL-2
Nebulized drugs Beclomethasone Pentamidine Propellants
Nitrofurantoin (acute)
NSAIDs
Propafenone
Protamine
Vinblastine/mitomycin

Other Factors That May Exacerbate Asthma

Rhinitis, sinusitis, and polyposis are sometimes associated with asthma, and the treatment of each of these conditions is often associated with improvement of asthma[185]. For example, there is indirect evidence that bacterial sinusitis may have a role in asthma exacerbations, because antibiotic treatment of bacterial sinusitis is shown to reduce the severity of asthma[185]. However, sinusitis and asthma may simply coexist. Apart from sinusitis, there is little evidence that bacterial infections can exacerbate asthma. Gastroesophageal reflux can exacerbate asthma, especially in children, and asthma sometimes improves when the reflux is corrected[186,187]. Many women complain that their asthma is worse at the time of menstruation, and premenstrual exacerbations have been documented[188]. Similarly, asthma may improve, worsen, or remain unchanged during pregnancy[189].

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CHAPTER

4

MECHANISMS OF ASTHMA

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KEY POINTS:

- Asthma is a chronic inflammatory disorder of the airways with recurrent exacerbations.
- Chronic airway inflammation is invariably associated with injury and repair of the bronchial epithelium, which results in structural and functional changes known as remodeling.
- Inflammation, remodeling, and altered neural control of the airways are responsible for both recurrent exacerbations of asthma and more permanent airflow obstruction.
- The potential to develop excessive airway narrowing is the major functional abnormality in asthma.
- Excessive airway narrowing is caused by altered smooth muscle behavior, in close interaction with airway wall swelling, parenchymal retractile forces, and intraluminal secretions.
- Exacerbations of asthma are associated with an increase in airway inflammation and, in susceptible individuals, can be induced by respiratory infections, allergen exposure, or exposure to occupational sensitizers.
- Respiratory failure in asthma is a consequence of airway closure, ventilation/perfusion mismatch, and respiratory muscle exhaustion.

INTRODUCTION

The current concept of asthma pathogenesis is that a characteristic chronic inflammatory process involving the airway wall causes the development of airflow limitation and increased airway responsiveness, the latter of which predisposes the airways to narrow in response to a variety of stimuli (**Figure 1-9** and **Figure 4-1**). Characteristic features of the airway inflammation are increased numbers of activated eosinophils, mast cells, macrophages, and T lymphocytes in the airway mucosa and lumen. These changes may be present even when asthma is asymptomatic, and their extent appears to be broadly related to the clinical severity of the disease[1,2]. In parallel with the chronic inflammatory process, injury of the bronchial epithelium stimulates processes of repair that result in structural and functional changes referred to as "remodeling"[3]. The recurrent episodes of symptoms and reversible airflow limitation that characterize asthma represent an acute inflammatory response acting upon structurally and functionally altered airways.

AIRWAY INFLAMMATION IN ASTHMA

Airway inflammation in asthma is extremely complex in origin, regulation, and outcome. The mechanisms involve a cascade of events involving many different kinds of cells, factors, and mediators that interact to create the characteristic inflammatory and tissue remodeling processes of asthma.

Immunologic Mechanisms of Airway Inflammation

The immune system is separable into antibody-mediated and cell-mediated processes[4]. Antibody-mediated processes are characterized by production and secretion of specific antibodies by B lymphocytes, while cell-mediated processes depend on T lymphocytes. T cells control B lymphocyte function and also exert proinflammatory actions through cytotoxic activity (by CD8+ "killer" T cells) and the secretion of cytokines.

In many cases, especially in children and young adults, asthma is associated with atopy manifesting through immunoglobulin E (IgE)-dependent mechanisms[5]. At a population level, the contribution of atopy to the asthma phenotype has been estimated to be 40 percent in both children and adults[6]. Nonanaphylactogenic anti-IgE monoclonal antibody (E-25) is able to markedly attenuate the early and late airway responses, the increase in airway hyperresponsiveness, and the influx of eosinophils into the airway lumen that follow inhaled allergen challenge. This anti-IgE antibody is also effective in improving asthma control in clinical trials. These observations provide unequivocal evidence for a pivotal role of IgE in a proportion of asthma patients[7,8].

At least two distinct T-helper (Th), $CD4^+$ lymphocyte subtypes have been characterized on the basis of their profile of cytokine production[9-11]. Although both T lymphocyte subtypes secrete IL-3 and GM-CSF, the Th1 subtype preferentially produces IL-2, stimulating T lymphocyte proliferation, interferon-γ (IFN-γ) (which inhibits B lymphocyte activation and IgE synthesis), and tumor necrosis factor-β (TNF-β)[9-11] (**Figure 4-1**). The Th2 subtype, the primary subtype involved in asthma, secretes the cytokines IL-4, IL-5, IL-9, IL-13, and IL-16. Th2 cytokines are responsible for the development of the classic delayed-type or cell-mediated hypersensitivity reaction.

IL-4 is a cytokine central to the allergic response, promoting isotype switching of B cells to IgE synthesis,

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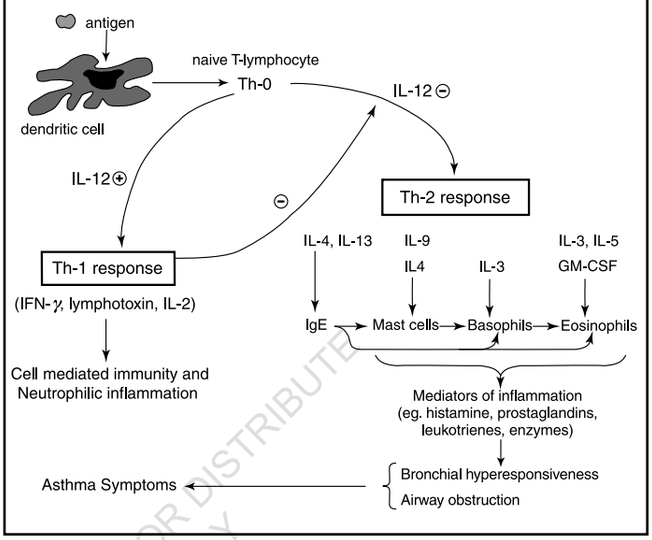
directing T cells along the Th2 differentiation pathway, upregulating the expression of vascular cell adhesion molecule-1 (VCAM-1), and controlling the level of expression of IgE Fcϵ, cytokine and chemokine receptors, and leukocytes involved in the allergic cascade. Administration of soluble IL-4 receptor (which binds to free IL-4, preventing it from binding to cell-associated IL-4 receptors) has shown beneficial anti-inflammatory effects both in animal models and in preliminary human asthma trials[12,13]. IL-13, another Th2 cytokine that has multiple effects on immune and structural components involved in asthma, may also prove a target for therapy[14].

A pivotal step in the generation of an immune response is the activation of T lymphocytes by antigen appropriately presented to them by accessory cells, a process that involves major histocompatibility complex (MHC) molecules (MHC class II molecules on $CD4^+$ T cells and MHC class I molecules on $CD8^+$ T cells). Dendritic cells are the primary antigen presenting cells in the airways. They originate from precursors in the bone marrow[15] and form an extensive network of interdigitating cells beneath the airway epithelium. From this location they migrate to local lymphoid collections under the influence of granulocyte-macrophage colony-stimulating factor (GM-CSF), a cytokine released from activated epithelial cells, fibroblasts, T cells, macrophages, and mast cells. Following antigen uptake, which is enhanced by cell-surface IgE, dendritic cells move into lymphocyte-enriched regions. There, under the influence of additional cytokines, they mature into effective antigen presenting cells[16]. Dendritic cells can also drive the polarization of naive T-helper cells (Th0) towards the Th2 subtype that coordinately secretes cytokines encoded in a cluster on chromosome 5q31-33 (IL-4 gene cluster) (**Figure 4-1**).

The presence of activated lymphocytes and eosinophils in bronchial biopsies of atopic and nonatopic patients with asthma suggests that a T-lymphocyte-eosinophil interaction is important, a hypothesis further supported by the finding of cells expressing IL-5 in bronchial biopsies of atopic patients with asthma[17,18]. IL-5 is an important cytokine for eosinophil regulation, its level of expression in the airway mucosa of patients with asthma correlating with markers of both T lymphocyte and eosinophil activation[11,17].

Figure 4-1. Pathogenesis of Asthma



Intrinsic Nonallergic Asthma

People with intrinsic asthma show negative skin tests and have no clinical or family history of atopy. Their serum total IgE concentrations frequently fall within the normal range and there is no evidence of specific IgE antibodies directed against common allergens. This form of asthma is associated with nasal polyps and aspirin sensitivity, its onset is often preceded by a history of respiratory virus infection, and it disproportionately affects females. Patients with intrinsic asthma are usually older than their allergic counterparts and their clinical course is often more severe. The Swiss SAPALDIA survey of 8,357 adults between the ages of 18 and 60 revealed that up to a third of all cases of asthma could be categorized as nonallergic[19].

Ever since the first description of intrinsic asthma, there has been debate about the relationship of this variant of the disease to atopy. One suggestion is that intrinsic asthma represents a form of autoimmunity, or autoallergy, triggered by infection. Others have suggested that people with intrinsic asthma are simply sensitized to an as-yet undetected allergen[20]. Although intrinsic asthma has a different clinical profile than atopic asthma, it is not a distinct immunopathological entity. Airway biopsies of subjects with intrinsic asthma show a Th2 cytokine profile with accompanying inflammatory cells, just as in atopic asthma[21]. A small proportion of intrinsic asthma cases may have their origins in the workplace with unrecognized IgE or non-IgE sensitization to reactive chemicals *(vide infra)*.

Acute Inflammation

Inhaled allergen challenge in allergic patients leads to an early allergic response, and in some cases this is followed by a late-phase response. The early response results from the activation of cells bearing allergen-specific IgE, especially mast cells[22] and macrophages[23]. In patients with a strong allergic component to their asthma, basophils

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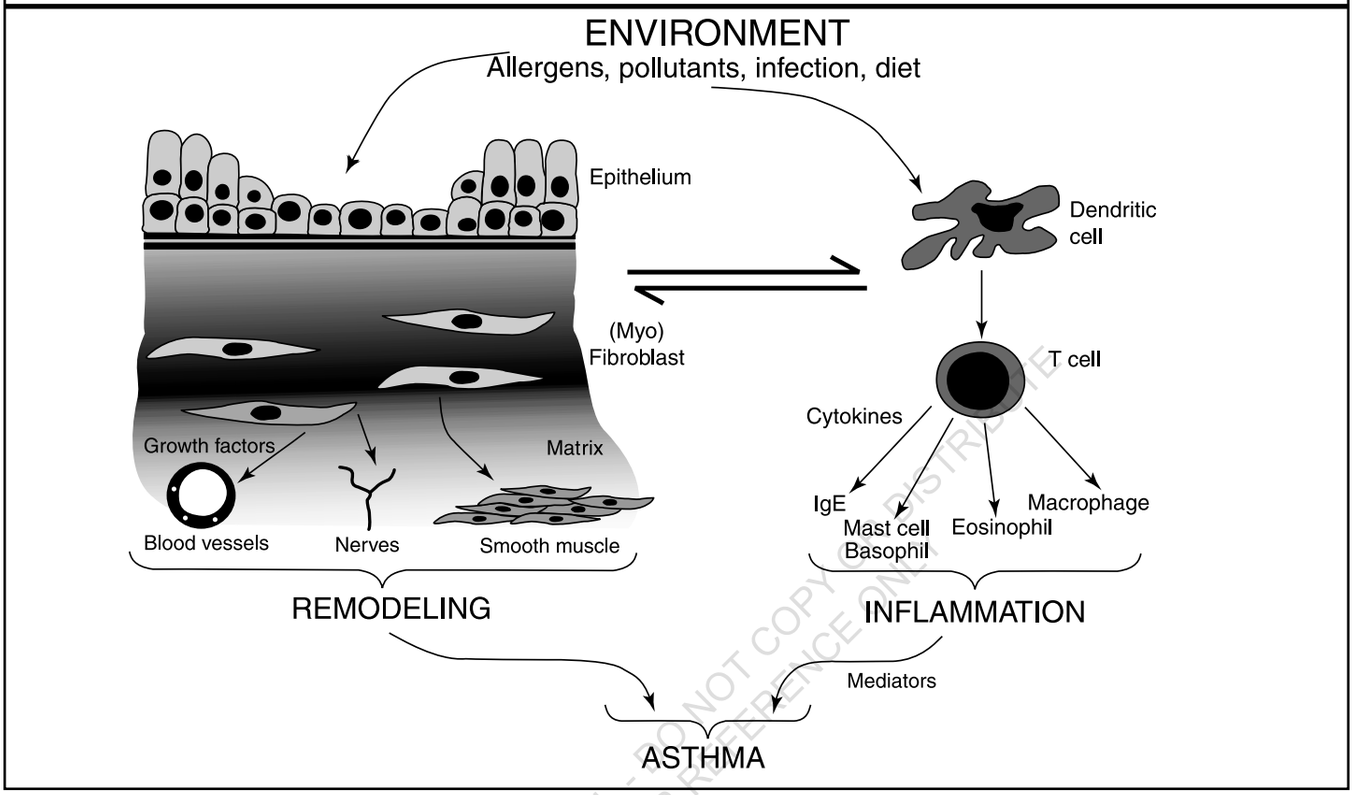
Figure 4-2. Inflammation and Remodeling in Asthma



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may also contribute. Cross linkage of cell-bound IgE initiates a series of biochemical events that results in the noncytotoxic secretion of granule-derived mediators such as histamine, proteolytic and glycolytic enzymes, and heparin, and the generation of newly formed mediators including prostaglandin PGD2, leukotriene C4[24], adenosine, and reactive oxygen[25]. Together, these mediators induce contraction of airway smooth muscle and stimulate afferent nerves, mucus hypersecretion, vasodilation, and microvascular leakage[26] (**Figure 4-2**).

The late-phase response has been considered a model system to study the mechanisms of inflammation in asthma[27,28]. During the late-phase response and during natural allergen exposure, activated airway cells release cytokines and chemokines into the circulation, stimulating the release of inflammatory leukocytes, especially eosinophils and their precursors, from the bone marrow into the circulation[29,30].

Recruitment of Inflammatory Cells Into the Airways

Peripheral blood cells including eosinophils, basophils, lymphocytes, and monocytes are recruited into inflamed airways. This process begins with the upregulation of a series of endothelial adhesion molecules by selective inflammatory mediators. These adhesion molecules attach to their ligands expressed on the rolling leukocytes, resulting in firm adhesion of the leukocytes to microvascular endothelial cells[31], then migration across the endothelium and into the perivascular space. Cell-associated chemokines also play a key role in these processes, interacting with receptors on leukocytes and cooperating with the eosinophilopoietic cytokines IL-5 and GM-CSF to help initiate and direct migration and prime leukocytes for enhanced mediator secretion[32,33].

Cell Survival in Airway Tissues

The survival of inflammatory cells in airway tissues depends on exogenous factors. Under normal circumstances, apoptosis (programmed cell death) of inflammatory cells limits inflammatory tissue injury and promotes resolution rather than progression of inflammation[34,35]. In asthma, survival of activated inflammatory cells such as eosinophils is greatly increased as a consequence of reduced apoptosis[36-38]. Many of the cytokines and chemokines, and certain of the matrix molecules, that are overexpressed in the airways of people with asthma enhance inflammatory cell survival[39].

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Site of the Inflammation in Asthma

In nocturnal asthma the peribronchial airways and alveoli may be the site of inflammation[40,41], but asthma is predominantly a disorder that affects the conducting airways. It is accepted that both central and peripheral airways are inflamed and that inflammation occurs both inside and outside the smooth muscle layer, a fact that has implications for the optimal delivery of anti-inflammatory drugs. The reason for the preferential involvement of the conducting airways in asthma inflammation is not known, but most likely relates to specific properties of the airway epithelium.

In addition to being a physiological barrier, the bronchial epithelium has an important role in directing the inflammatory response (**Figure 4-2**). It is still customary to consider allergic asthma as primarily an immune disorder, but an equally valid model is one of epithelial malfunction in which the response to injury or stress (e.g., viruses, pollutants, allergens) induces the microenvironment that facilitates the development of a Th2 response. Epithelial cells are a source of cytokines and chemokines (e.g., GM-CSF, eotaxin, RANTES) that are capable of sustaining eosinophilic inflammation and of secreting mast cell growth factors such as IL-6 and stem cell factor. Increased communication between an activated epithelium and submucosal mesenchymal cells also has the capacity to cause the release of large quantities of eosinophilic and mast-cell-promoting cytokines. Considering epithelial malfunction a primary abnormality in asthma also enables an explanation of asthma that is not linked to IgE, such as intrinsic (late-onset) asthma, aspirin-intolerant asthma (due to defective PGE2 production), and occupational asthma arising from exposure to reactive chemicals, such as isocyanates, where epithelial conjugates have been demonstrated.

Constitutive Cells of Airway Inflammation

In asthma normal resident cells of the airways (fibroblasts, myofibroblasts, epithelial cells, and smooth muscle cells) release an array of cytokines and growth factors that may contribute to the chronic nature of airway inflammation.

Fibroblasts play a key role in the remodeling and inflammatory processes. They produce collagen, reticular and elastic fibers, proteoglycans, and glycoproteins of the amorphous extracellular matrix (ECM)[42]. Their biological activity is regulated by a range of cytokines and growth factors. Although fibroblasts are regarded as fixed cells of the ECM, they retain the capacity for growth and regeneration and may evolve into various cell types, including smooth muscle cells, becoming myofibroblasts[43] and possibly smooth muscle.

Myofibroblasts contribute to tissue remodeling by releasing ECM components such as interstitial collagens, fibronectin, and laminin[44], and by producing growth factors for blood vessels, nerves, and smooth muscle. Increased numbers of myofibroblasts are found in the airways of people with asthma and their number has been correlated with the thickness of the reticular basement membrane[45]. Following bronchial allergen challenge, myofibroblasts increase in numbers in airway biopsies, raising the possibility of their migration towards the basement membrane from deeper in the airway wall[46].

The ability of myofibroblasts to promote tissue remodeling is influenced by bronchial epithelial cells, which when activated or damaged release profibrogenic growth factors such as transforming growth factor-β (TGF-β)[47,48]. One explanation for the promotion of remodeling by myofibroblasts is that the altered epithelial phenotype renders the epithelium unable to respond to injury or stress by appropriate epidermal growth factor receptor (EGFR)-mediated repair, leading to increased cytokine and profibrogenic growth factor production[49,50]. While there is evidence for impaired epithelial proliferative responses in asthma and increased expression of inhibitors of cell cycling, the precise molecular mechanisms that result in remodeling have yet to be elucidated[51].

In vitro studies suggest that smooth muscle cells are an important source of proinflammatory cytokines in asthma[52]. In addition to their capacity for contraction, airway smooth muscle cells have cytokine and mediator synthetic and secretory potential *in vitro*[53]. They participate in chronic airway inflammation by interacting with mast cells, eosinophils, activated T lymphocytes, and monocytes/macrophages. Smooth muscle cells also have the potential to alter the composition of the ECM microenvironment and to orchestrate key events in airway remodeling[54]. Whether these events occur *in vivo* in the airways of people with asthma is not known, since the majority of observations on smooth muscle cells have relied on cultures, most frequently obtained from resected lung specimens.

Inflammatory Cells

Eosinophils. In chronic asthma, an increased number of activated eosinophils are found in bronchial biopsies[2], most frequently beneath the basement membrane. Most people with allergic or nonallergic asthma, including those with mild asthma, have eosinophils in their bronchi, and there is a significant although variable association between the activation of eosinophils and the severity of asthma[2] and airway hyperresponsiveness[55].

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Eosinophils possess a wide array of biological properties, including a capacity to release toxic granule proteins, oxygen free radicals, eicosanoids (sulfido-peptide leukotrienes)[56], platelet activating factor (PAF), Th2 cytokines[57,58], and a range of growth factors[59-61]. They can be activated for mediator secretion by both immune and non-immune mechanisms[62]. Activated eosinophils may initiate contraction of human airway smooth muscle[63], increase microvascular permeability[64], and induce airway hyperresponsiveness[65]. However, in a preliminary study an IL-5-blocking monoclonal antibody administered for up to 16 weeks reduced blood and sputum eosinophils to almost undetectable levels, but had no effect on the allergen-induced early- and late-phase responses, nor on airway hyperresponsiveness[66]. These findings may call into question the role of the eosinophil as a proinflammatory cell in all cases of asthma, especially because similar reductions in the eosinophil count are produced by exogenous IL-12 or IFN-γ without any evidence of physiological or clinical benefit[67]. Further studies are needed to determine whether these findings can be extrapolated to eosinophil functions in chronic asthma.

Mast cells. Mast cells are found in the bronchi of normal subjects and people with asthma[55,68-70]. They are often in a degranulated state in the airways of people with asthma, both in the stable phase of the disease and–to a greater extent–following allergen challenge[71,72]. In addition to releasing autacoid mediators, airway mast cells are an important source of neutral proteases, especially tryptase, which has a range of effects on protein substrates including protease-activated receptors.

Neutrophils. Polymorphonuclear neutrophils have long been regarded as terminal differentiated cells, incapable of protein synthesis and fulfilling only a passive effector role in inflammation via phagocytosis and the release of preformed enzymes and cytotoxic compounds. However, neutrophils can release a wide variety of enzymes including ECM-degrading proteases (e.g., MMP-9 and elastase), reactive oxygen species, and cytokines and chemokines such as IL-1β, TNF-α, IL-6, and IL-8[73-75]. Neutrophils are increased in the airways of patients with chronic and severe asthma during respiratory virus exacerbations or after exposure to air pollutants, but their role in the pathophysiologic changes of severe asthma requires elucidation[76].

Macrophages. Tissue macrophages have the potential to secrete a wide variety of products, many of which play a major role in the processes of injury and repair[77-79]. They synthesize and secrete plasminogen activator and a group of metallopreoteinases that can degrade various extracellular matrix macromolecules including elastin[80]. Macrophages may also be involved in airway remodeling through the secretion of growth factors such as platelet-derived growth factor (PDGF), basic fibroblast growth factor (b-FGF), and TGF-β[81].

Neural Control of Airways

Several irritant stimuli (such as fog, sulfur dioxide, dust, and cold air) provoke reflex bronchoconstriction by stimulating the sensory receptors in the airways. In both normal subjects and subjects with asthma, this physiologic defense mechanism is able to provoke bronchoconstriction. However, the bronchoconstrictor response in subjects with asthma develops at a lower level of stimulation and is more intense compared to that in normal subjects. It has been proposed that increased activity of the parasympathetic autonomic nervous system is responsible for some of the airway hyperresponsiveness present in asthma[82]. While this mechanism may be involved, it does not seem to be a major cause of airflow limitation in this disease[83]. The system of innervation of the airways is much more complex. In addition to the classic cholinergic and adrenergic mechanisms, a network of nonadrenergic, noncholinergic neural pathways has been described in human airways[83]. The demonstration of an extensive network of nerve fibers containing potent neuropeptides and neuroregulators (EGF-like growth factors), in addition to classic neurotransmitters, has revived interest in the possible role of abnormalities of the neural control of airways in the pathogenesis of asthma[83].

Nitric oxide (NO) is a reactive gas formed from arginine in both neuronal and nonneuronal tissue through the action of nitric oxide synthase. In asthma, there is some evidence to suggest that the inducible (glucocortiocosteroid-suppressible) form of this enzyme is upregulated in the epithelium[84]. NO is a potent vasodilator and a bronchodilator and most likely serves as a neuroregulator released from non-adrenergic, non-cholinergic inhibitory nerves[85], which regulate airway smooth muscle tone, pulmonary blood flow, and local immune responses. Thus, an abnormality of NO production and/or breakdown may be relevant to asthma pathophysiology[86].

The observation that mast cells and eosinophils have the propensity to aggregate in airway nerve ganglia and that their mediators are able to interfere with neurotransmission creates further sites at which neuroeffector mechanisms may contribute to the asthma phenotype. The availability of potent and selective inhibitors and antagonists of these inflammatory cell mediators should help resolve some of these issues.

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AIRWAY REMODELING

Airway remodeling is a heterogeneous process leading to changes in connective tissue deposition and to altered airways structure through a dynamic process of dedifferentiation, migration, differentiation, and maturation of structural cells[3] (**Figure 4-2**). Several structural features are characteristically involved in airway remodeling in asthma.

In the bronchi the subepithelial basement membrane is of normal thickness, but thickening and an increase in the density of the *lamina reticularis* typically occur early in the disease process. This thickening is brought about by a plexiform deposition of interstitial collagens I, III, and V and fibronectin[87] produced by activated myofibroblasts, which themselves derive from the attenuated fibroblast sheath lying immediately beneath the epithelium[45]. The observation that increased collagen deposition in the *lamina reticularis* occurs only in asthma suggests that this change is a fundamental abnormality linked to pathogenesis of the disease.

The combination of epithelial damage, prolonged epithelial repair, overproduction of profibrotic growth factors (e.g., TGF-β), and proliferation and differentiation of fibroblasts into myofibroblasts is thought to be central to the remodeling process. Activated myofibroblasts produce a range of growth factors, chemokines, and cytokines that promote proliferation of airway smooth muscle cells and increases in microvascular permeability and neural networks. Since these changes have been observed in children before the onset of asthma, it has been suggested that activation or reactivation of the epithelial mesenchymal trophic unit, in addition to inflammation, is fundamental to asthma and differentiates the human disease from the relatively acute allergen-induced inflammation observed in many animal “models” of the disease. Increased deposition of matrix molecules, including complex proteoglycans, deeper in the airway wall has been observed in patients who have died of asthma, and its extent is directly related to disease duration.

The ECM is a dynamic structure, characterized under normal circumstances by an equilibrium between synthesis and controlled degradation of ECM components. Matrix metalloproteases (MMPs) that selectively degrade ECM components (MMP-2 and MMP-9) are of special significance in this process, as are their respective inhibitors, tissue inhibitor of metalloprotease (TIMP)-1 and TIMP-2. MMPs have also been implicated in angiogenesis and smooth muscle hyperplasia through their release of active forms of growth factors, and they also play a crucial role in the trafficking of inflammatory and structural cells.

Components of the ECM also interact with inflammatory cells[88] (**Figure 4-2**). Proteoglycans can serve as a reservoir for cytokines and growth factors[89,90], as “traps” for water causing persistent tissue swelling, as ligands for cell adhesion molecules on inflammatory cells[91,92], and as promoters of leukocyte mediator release and cell survival[93-95]. Cytokines and growth factors cause the proliferation of airway smooth muscle and induce the synthesis of ECM proteins[48,96].

Hypertrophy and hyperplasia of airway smooth muscle, goblet cells, and submucosal glands[97,98] occur in the bronchi of people with asthma, especially in those with chronic and severe disease. Overall, the airways in asthma display various structural alterations that can all contribute to an overall increase in airway wall thickness. For decades, asthma has been considered a condition of reversible airflow obstruction. In the majority of patients, complete reversiblity of longstanding abnormalities in spirometric measurements such as FEV_1 may be observed after treatment with inhaled glucocorticosteroids. However, many people with asthma have evidence of residual airway obstruction after such treatment, which can even exist in asymptomatic patients, and this likely represents remodeling. Remodeling may also be important in the pathogenesis of nonspecific airway hyperresponsiveness, especially the component that reverses slowly (over 1 to 2 years) or incompletely with inhaled glucocorticosteroid treatment[99,100].

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PATHOPHYSIOLOGY OF ASTHMA

Airways Obstruction

Inflammatory changes in the airways of people with asthma are thought to underlie the disorder's defining pattern of disturbances in function: airways obstruction causing airflow limitation that varies spontaneously or as a result of treatment. These functional changes are associated with the characteristic symptoms of asthma–cough, chest tightness, and wheezing–and with airway hyperresponsiveness to bronchoconstrictor stimuli. Cough is probably caused by stimulation of sensory nerves in the airways by inflammatory mediators, and recurrent cough may be the only symptom of asthma, especially in children (“cough variant asthma”)[101-103]. Inflammatory mediators may also affect the perception of breathlessness through their effects on afferent nerves. At one extreme, afferent nerve stimulation may contribute, sometimes with hypercapnia or hypoxemia, to the disproportionately great drive to breathing that accounts for the alveolar hyperventilation and possibly also for some of the distress of acute asthma attacks. At the other extreme, changes in afferent

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receptor function are thought to be responsible for a reduced ability to sense bronchial narrowing in some patients, especially those with chronic severe asthma, the so-called "poor perceivers"[104-107].

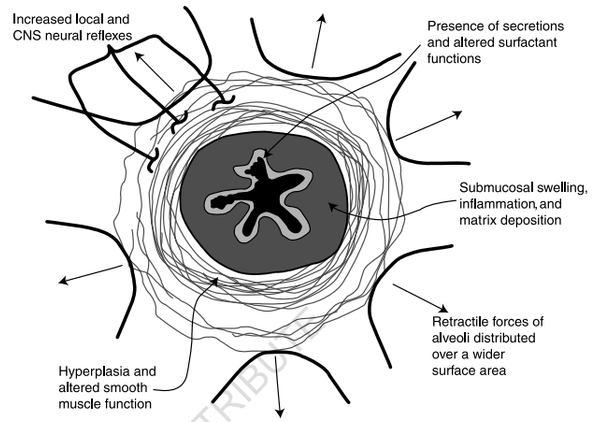
The airway narrowing of asthma is multifactorial. The major cause is contraction of bronchial smooth muscle provoked by agonists released from inflammatory cells. These agonists include histamine, tryptase, prostaglandin D2, and leukotriene C4 from mast cells; neuropeptides from local afferent nerves; and acetylcholine from postganglionic efferent nerves. The consequences of airway smooth muscle contraction are exaggerated by thickening of the airway wall due to acute edema, cellular infiltration, and remodeling–the chronic hyperplasia of smooth muscle, vascular, and secretory cells and deposition of matrix in the airway wall[108]. Still greater airflow limitation may arise if the lumen of the airways becomes filled with copious, thick, viscous secretions produced by goblet cells and submucosal glands, leakage of plasma proteins from the bronchial microvasculature, and cellular debris[108-113].

Virtually all of the functional disturbances of asthma derive from this airway narrowing, which affects all parts of the tracheobronchial tree but is probably maximal in small bronchi 2 to 5 mm in diameter[114-116]. Airway resistance is increased, and maximal expiratory flow is reduced at all lung volumes. Narrowed peripheral airways close at higher lung volumes, causing marked increases in residual volume[117]. Also contributing to thoracic hyperinflation is the tendency to breathe at a higher lung volume, as an adaptive mechanism to reduce excessive airway narrowing by increasing circumferential traction on intrapulmonary airways[118]. These changes greatly increase the work of breathing: resistive work is increased because of the high pressures required to move air through narrowed airways, and elastic work is increased because of the lower compliance of both the lungs and the thoracic cage at high volumes. Overinflation of the thorax places the diaphragm and intercostal muscles at a mechanical disadvantage, so that they must function over a suboptimal range of their length-tension curve[119]. The increase in the work of breathing and the loss in muscle efficiency cause fatigue and can lead to exhaustion and respiratory failure.

Airway Hyperresponsiveness

Asthma is almost invariably associated with airways that narrow too easily and/or too much in response to provocative stimuli[120,121]. The potential for excessive airway narrowing is clinically the most relevant physiological

Figure 4-3. Mechanisms of Airway Hyperresponsiveness



abnormality in this disease. The mechanisms responsible for this exaggerated reactivity or "hyperresponsiveness" are not known, but may be related to altered behavior of airway smooth muscle secondary to changes in its contractility or phenotype[122]. In addition, inflammatory changes in the airway wall, particularly in the peribronchial region, could strongly enhance airway narrowing during smooth muscle contraction[123] (**Figure 4-3**).

Airway hyperresponsiveness is most often assessed clinically by delivering progressively increasing doses of an aerosol of a pharmacologic stimulant–such as histamine or methacholine–until a measure of lung function changes by a predetermined amount[120,121] (**Figure 1-5**). The most commonly used endpoint is a fall in FEV_1, and airway hyperresponsiveness is expressed in terms of the "provocative concentration" or "provocative dose" causing a 20 percent fall, the "PC_{20}" or "PD_{20}". A PC_{20} of < 8 mg/ml for either histamine or methacholine confirms airway hyperresponsiveness and is characteristic of asthma[120,121], but may be found in other disorders such as COPD, cystic fibrosis, and allergic rhinitis. In asthma, there is a rough inverse correlation between the PC_{20} or PD_{20} and the severity of the disease[120,121]. Airway hyperresponsiveness can also be demonstrated by an increase or even absence of a maximal response plateau on the dose-response curve[120]. Other provocative stimuli such as exercise; eucapnic hyperpnea of cold, dry air; and aerosols of hypertonic saline, distilled water, and adenosine have no direct action on airway smooth muscle (unlike histamine and methacholine). Instead, they are presumed to stimulate release of mediators from mast cells, nerve endings, or other cells resident in the airways[120,121] (**Figure 1-2**), and thus have an advantage in that they act through a mechanism more closely

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resembling that of the triggers of bronchoconstriction encountered in day-to-day life. Comparison of airway responsiveness to histamine, a direct smooth muscle agonist, and to adenosine, which acts through the activation of airway mast cells, has been used to infer whether changes in measurements of responsiveness are due primarily to a change in the release of mediators from airway mast cells or to a change in the airway's responsiveness to them.

Airway Smooth Muscle

Some measurements of isotonic contraction of airway smooth muscle in subjects with asthma have shown increased shortening[124,125]. This change in contractile function could result from alterations in the contractile apparatus[126], in smooth muscle tissue elasticity, or in the extracellular matrix[127]. The enhanced contractility seen in asthma seems to be associated with increased velocity of shortening[127]. This may be accompanied by smooth muscle growth[128] and/or changes in smooth muscle cell phenotype, with cells varying between contractile, secretory, and proliferative phenotypes in interaction with airways inflammation[129]. In addition, there is evidence that changes in the organization of contractile filaments or in the plasticity of smooth muscle cells can underlie the maintenance of chronic airway hyperresponsiveness[130]. This illustrates that the functional properties of airway smooth muscle are fundamental to the properties of airways *in vivo*.

The role of airway dynamics is further underlined by the "perturbed equilibrium" hypothesis, suggesting that airway smooth muscle in asthma becomes stiffened when it is not periodically stretched, leading to a latch-state causing persistent airway narrowing[131]. Such a "frozen," contractile state might occur secondarily to airway inflammation, which leads to adventitial swelling and thereby to mechanical uncoupling of elastic recoil pressure and airway smooth muscle[123,131].

Inflammatory mediators released from the mast cell–such as tryptase and eosinophil cationic protein–have been shown to increase the contractile response of smooth muscle to other inflammatory mediators such as histamine[132]. These findings provide a link between a mast-cell-derived product and *in vitro* human airway hyperresponsiveness. The inflammatory milieu may affect smooth muscle contractility directly[133], and will also have secondary effects through changes in airway geometry and mechanics[123,134].

Mucus Hypersecretion

Chronic excessive production of sputum is the defining symptom of chronic bronchitis, but is also characteristic of patients with asthma who have never smoked cigarettes or worked in a dusty occupation. Surveys have shown that as many as 30 percent of people with asthma report sputum production on a daily basis and 70 percent report it as an important symptom during attacks[135]. In fact, asthma is often misdiagnosed as "recurrent acute bronchitis." Goblet cell and submucosal gland cell hyperplasia are consistently found in the airways of people with asthma[131,132], and are features of the airway wall remodeling characteristic of chronic asthma. Widespread obstruction of the airways by mucus plugs is almost invariably found in fatal asthma[111-113,136,137] and is likely an important cause of the airflow obstruction that often persists despite maximal bronchodilator treatment of severe attacks.

Airway secretions in subjects with asthma are not simply increased in volume compared to normal subjects; they differ in viscoelastic and rheologic properties as well. These quantitative and qualitative differences are thought to arise from both the infiltration of the airway wall by inflammatory cells and the pathologic changes in secretory cells and blood vessels in the airway epithelium and submucosa. The abnormal thickness and "stickiness" of these secretions are due not simply to an excess of mucin production[138], but also to clumps of sloughed epithelial cells, albumin leaked from the bronchial microvasculature, eosinophil-derived basic proteins, and DNA from lysed inflammatory cells[138,139]. These changes account for the occasional finding of bronchial casts of inspissated mucus (Curschmann's spirals) in sputum from patients with asthma[140].

The hypersecretion of mucus in asthma reflects two distinct types of pathophysiologic mechanisms: those responsible for secretory cell metaplasia and hyperplasia, and those responsible for secretory cell degranulation. Important mediators of goblet cell metaplasia and hyperplasia are released in the inflammatory cascade characteristic of asthma and include epidermal and other growth factors[141], IL-4, IL-9, and IL-13[14,142,143]. Goblet cell degranulation is triggered by environmental stimuli (such as smoke, sulfur dioxide, chlorine, and ammonia), possibly through the local release of neuropeptides or the activation of cholinergic reflex pathways. Possibly more important is the degranulation provoked by inflammatory mediators with secretagogue activity, such as neutrophil elastase, mast cell chymase, leukotrienes, histamine, and non-protease neutrophil products[113,144,145]. The finding of free neutrophil elastase in sputum produced during acute exacerbations of asthma suggests that this may be an especially important secretagogue in severe attacks[146,147].

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Irreversible Airflow Limitation

The thickening of the airway wall characteristic of remodeling takes place in both cartilaginous (large) airways and membranous (small) airways and is evident in both pathologic and radiographic studies[115,116,148]. Together with changes in the elastic properties of the airways and loss of the interdependence between the airways and the surrounding parenchyma, airway wall thickening may explain the occurrence of persistent and incompletely reversible airway narrowing in a subgroup of patients with asthma[149-151]. The mechanisms responsible for remodeling are the focus of active research but are not yet defined[99]. They are presumed to be linked to chronic or recurrent airway inflammation, and there is some evidence that loss of airway function, again presumed to reflect remodeling, occurs even in mild asthma of recent onset but can be prevented by early introduction of regular therapy with an inhaled glucocorticosteroid[152-154]. Furthermore, smooth muscle stiffening also contributes to the development of irreversible airflow limitation in asthma[131]. The proportion of patients with mild asthma who are at risk for developing clinically important, chronic, irreversible airflow limitation is not known.

Exacerbations

Episodic worsening is a major feature of asthma[155]. There are multiple triggers for exacerbations, including stimuli that produce bronchoconstriction only ("inciters"), such as cold air, fog, or exercise, and stimuli that promote airways inflammation ("inducers"), such as exposure to allergens, occupational sensitizers, ozone, or respiratory virus infection[120,156]. Exercise and hyperventilation with cold and dry air[157] cause bronchoconstriction in asthma by cooling and drying of the airways, leading to the release from airway resident cells and inflammatory cells of mediators such as histamine or cysteinyl leukotrienes, which stimulate smooth muscle contraction[158]. These "inciters" do not worsen bronchial responsiveness to other stimuli, and so have only transient effects.

Asthma exacerbations may develop over a number of days. Most are associated with respiratory virus infections, particularly the common cold virus (rhinovirus)[159]. Rhinovirus can induce an inflammatory response in the intrapulmonary airways[160], and in patients with asthma this inflammation is associated with an episode of variable airways obstruction and worsened bronchial hyperresponsiveness[161]. The inflammatory response involves eosinophil and/or neutrophil influx and activation, which may be mediated by cytokines or chemokines released by T cells and/or bronchial epithelial cells[162,163].

It is highly likely that allergen exposure can also induce exacerbations in sensitized subjects with asthma[164]. In particular, patients with late asthmatic responses demonstrate a flare-up of eosinophilic airways inflammation after allergen challenge, which is followed by an episode of aggravated airway hyperresponsiveness[56]. Repeated allergen challenge at a sub-bronchoconstrictor level, which probably better mimicks natural, seasonal exposures[57], can also induce such responses. The possibility cannot be excluded that such repeated, sub-bronchoconstrictor exposures can actually induce persistent airways inflammation and some aspects of airway remodeling, such as collagen deposition in the subepithelial reticular layer[165].

Persistent abnormalities occur after exposure to occupational sensitizers in patients with occupational asthma[166]. Even several months after cessation of exposure, airway hyperresponsiveness and some aspects of airways inflammation (mucosal eosinophils and macrophages) can persist, while other features (including subepithelial collagen deposition) usually show some reversal[167]. Such findings illustrate that there is a complex interaction between the pathophysiological mechanisms involved in exacerbations and those involved in the persistence of asthma. This interaction is further complicated by potential interactions between different "inducers," for example, between occupational sensitizers and air pollutants[168].

In about 10 percent of adult patients with asthma, nonsteroidal anti-inflammatory drugs that inhibit cyclooxygenase-1 precipitate asthma attacks[169]. These attacks may be dangerous. In a large retrospective survey of adult asthma patients who underwent mechanical ventilation for a near-fatal attack of asthma, 24 percent had a history of intolerance to aspirin[170].

Nocturnal Asthma

Nocturnal worsening of asthma is a well recognized clinical characteristic in a considerable number of patients[171]. Bronchial biopsy specimens do not demonstrate increases in T cell, eosinophil, or mast cell numbers at 4:00 a.m. in people who have asthma with nocturnal airways obstruction[172]. However, transbronchial biopsies have provided some evidence of nighttime accumulation of eosinophils and macrophages in alveolar and peribronchial tissue in patients with nocturnal asthma[40]. The latter findings are of special interest, given the proposed role of adventitial inflammation in the peripheral airways in the development of excessive airway narrowing[123,134]. Altered airway-parenchymal interdependence may be extremely important in nocturnal asthma, a hypothesis also supported by recent

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observations showing loss of such interdependence in people with asthma during sleep in a supine position as opposed to awake in a supine position[173].

Blood Gas Abnormalities

Asthma causes important impairments of gas exchange only during severe attacks. The degree of arterial hypoxemia roughly correlates with the severity of airways obstruction that is not homogeneous throughout the lungs. Often, some airways are completely occluded, others severely narrowed, and still others unobstructed. The resulting mismatch of ventilation and perfusion widens the alveolar-arterial oxygen difference ($(A\text{-}a)dO_2$), accounting for the oxygen tensions of 60-69 mm Hg (8.0-9.2 kPa) typically found during severe attacks of asthma[174]. The hypocapnia that is almost invariably found in mild to moderate attacks reflects an increase in respiratory drive. An elevated arterial PCO_2 indicates that airways obstruction is so severe that the muscles of respiration cannot maintain the ventilation rate set by the respiratory drive (alveolar hypoventilation). Any worsening of airways obstruction or muscle fatigue, or any decline in respiratory drive (as from administration of a narcotic or sedative drug), can then cause a further fall in alveolar ventilation. The rise in arterial PCO_2 then further inhibits muscle performance and respiratory drive ("CO_2 narcosis"), precipitating respiratory failure and death[175,176]. Arterial hypercapnia thus indicates an attack of extreme severity that requires aggressive management.

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CHAPTER

5

DIAGNOSIS

AND

CLASSIFICATION

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KEY POINTS:

- Asthma is underdiagnosed throughout the world.
- Asthma can often be diagnosed on the basis of symptoms. However, measurements of lung function, and particularly the reversibility of lung function abnormalities, greatly enhance diagnostic confidence.
- Lung function measurements that are most helpful for the diagnosis of asthma (in patients over 5 years of age) include forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), and airway hyperresponsiveness.
- Asthma severity is classified by the presence of clinical features before treatment is started and/or by the amount of daily medication required for optimal treatment.
- Measurements of allergic status add little to the diagnosis of asthma but can help in the identification of risk factors so that appropriate environmental control measures can be recommended.
- Special care should be given to diagnosing asthma in children, in individuals with recurrent cough, in the elderly, and in individuals exposed to occupational agents known to cause asthma.

Epidemiological studies both in children and adults (especially the elderly) consistently suggest that asthma is underdiagnosed and as a consequence undertreated[1]. Part of the problem is that many patients tolerate intermittent respiratory symptoms (though not, for example, chest pains) before obtaining a medical opinion. The transient nature of asthma symptoms serves to reinforce the acceptance of symptoms. Another important factor resulting in underdiagnosis of asthma is the nonspecific nature of the symptoms, which can lead to alternative diagnoses by the attending health care professional. It should be remembered that establishing a correct diagnosis of asthma is essential if appropriate drug therapy is to be given. Not infrequently asthma in children is diagnosed as variant forms of bronchitis[2] and, as a consequence, treated inappropriately and ineffectively with successive courses of antibiotics and cough medications[3]. Although the adage “all that wheezes is not asthma” is frequently cited, asthma as a cause of wheeze and related symptoms is so common that a more appropriate view might be “all that wheezes is asthma until proven otherwise.”

CLINICAL DIAGNOSIS

History and Measurements of Symptoms

A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, and chest tightness. Seasonal variability of symptoms and a positive family history of asthma and atopic disease are also helpful diagnostic guides.

Figure 5-1 highlights questions that are useful when considering a diagnosis of asthma. **Figure 5-2** presents a questionnaire that has been used and validated for the diagnosis of asthma in epidemiological studies[4,5]. Measurements of symptoms and lung function are important parameters for assessing the characteristics of the patient's asthma. Various symptom scores have been developed and validated in order to quantify asthma control[6] and quality of life[7,8]. Symptom scores should be adapted to the age and the cultural background of the patient.

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. However, some people with asthma may

Figure 5-1. Questions to Consider in 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 have a wheeze or cough after exercise?
- Does the patient have wheeze, 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 antiasthma treatment?

Figure 5-2. International Union Against Tuberculosis and Lung Disease (IUATLD) Asthma Questionnaire[4,5]

- Have you had wheezing or whistling in your chest at any time?
- Have you had an attack of shortness of breath that came on following strenuous activity at any time?
- Have you woken up with an attack of wheezing at any time?
- Have you woken up with an attack of coughing at any time?
- Have you had an attack of shortness of breath that came on during the day when you were at rest at any time?

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have normal auscultation but significant airflow limitation when measured objectively.

Clinical signs such as dyspnea, airflow limitation (wheeze), and hyperinflation are more likely to be present if patients are examined during symptomatic periods. During an exacerbation of asthma, contraction of airway smooth muscle, edema, and hypersecretion tend to close the smaller (noncartilaginous) airways. To compensate, the patient breathes at a higher lung volume to increase outward retraction of the airways, thereby helping to maintain their patency. Thus the more severe the airflow limitation, the greater the tendency for airway closure to occur, and the higher the lung volume must be to keep airways open. The combination of hyperinflation and advanced airflow limitation in an asthma exacerbation also markedly increases the work of breathing.

Although wheezing is the most typical physical finding in asthma, this sign may be absent in severe asthma exacerbations. However, patients in this state usually have other physical signs reflecting severity, such as cyanosis, drowsiness, difficulty speaking, tachycardia, hyperinflated chest, use of accessory muscles, and intercostal recession.

Measurements of Lung Function

Patients with asthma frequently have poor recognition of their symptoms and poor perception of the severity, especially if their asthma is severe and longstanding[9]. Assessment of symptoms such as dyspnea and wheezing by physicians may also be inaccurate. Measurements of lung function, particularly the reversibility of lung function abnormalities, provide a direct assessment of airflow limitation. Measuring the variability in lung function provides an indirect assessment of airway hyperresponsiveness. However, although some relationship has been established between laboratory indices of airway hyperresponsiveness and peak expiratory flow (PEF) variability[10], they are not interchangeable. For example, PEF variability may respond rapidly to glucocorticosteroid treatment[11], whereas histamine or methacholine airway responsiveness improves over a slower time course[12]. Nevertheless, measurements of airflow limitation, its reversibility (**Figure 1-5** and **Figure 1-7**), and its variability (**Figure 1-6**) are considered critical in establishing a clear diagnosis of asthma. These measurements underlie the new asthma management strategies advocated in established asthma guidelines. Measurement of lung function for diagnosing and monitoring asthma is analogous to measurement in other chronic diseases. For example, blood pressure measured with a sphygmomanometer is used for diagnosing and monitoring hypertension, and blood glucose measured with reagent strips or digital read-out meters is used for diagnosing and monitoring diabetes.

A wide range of different methods to assess the level of airflow limitation exists, but two methods have found widespread acceptance for use in patients over 5 years of age. These are the measurement of forced expiratory volume in 1 second (FEV_1) and its accompanying forced vital capacity (FVC), and the measurement of peak expiratory flow (PEF). Both of these measurements depend on the concept of airflow limitation relating directly to the luminal size of the airways (airway caliber) and the elastic properties of the surrounding lung tissue (alveoli).

Spirometry. Measurement of FEV_1 and FVC is undertaken during a forced expiratory maneuver using a spirometer. Recommendations for the standardization of spirometry have been published[13,14]. The procedure is repeatable, but effort dependent; therefore, proper instructions on how to perform the forced expiratory maneuver must be given to patients, and the highest values of two or three recordings taken. The test begins to lose its reliability at values of FEV_1 less than 1 liter. Predicted values of FEV_1, FVC, and PEF based on age, gender, and height have been obtained from population studies, and although these are being continually revised, they form some useful bases against which to judge whether a given value is abnormal or not. It is important that predicted values of FEV_1, FVC, and PEF take into account ethnic characteristics and extremes of age. Because diseases other than those causing airflow limitation may result in reduced FEV_1, a useful assessment of airflow limitation can be obtained as the ratio of FEV_1 to FVC. In the normal lung, flow limitation on forced expiration results in FEV_1/FVC ratios of greater than 80 percent and in children possibly greater than 90 percent. Any values less than these are suggestive of airflow limitation.

Spirometry is helpful for the diagnosis of asthma, where at least a 12 percent improvement in FEV_1 either spontaneously, after inhalation of a bronchodilator, or in response to a trial of glucocorticosteroid therapy favors a diagnosis of asthma[15]. Spirometry is also helpful for monitoring the activity of the asthma, although primarily in a clinic health care setting because the apparatus is cumbersome and moderately expensive. Small electronic spirometers have been developed for portable use, but expense is likely to limit their widespread acceptance. Nevertheless, spirometry recordings are helpful in diagnosing asthma and assessing its severity, and

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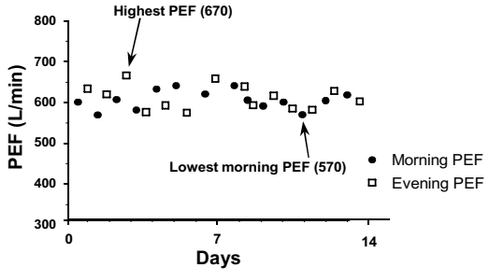
Figure 5-3. A Simple Index of PEF Variation[25]



(Minimum morning PEF (% recent best) = 570/670 = 85%)

recordings at regular intervals (dependent upon the severity of the disease) assist in monitoring the long-term progress of asthma and its long-term response to therapeutic interventions. Spirometry, as opposed to PEF monitoring, is particularly helpful in assessing progress in patients with greatly compromised lung function (e.g., the elderly person with asthma and chronic obstructive pulmonary disease) because PEF measurements can be relatively well preserved in such patients in the presence of greatly reduced spirometric values.

Peak expiratory flow. An important aid in the diagnosis and subsequent treatment of asthma is the PEF meter. In some countries, PEF meters are becoming available on health service prescription. Recent versions of the PEF meter are relatively inexpensive (at least in affluent countries), portable, plastic, and ideal for patients to use in home settings for day-to-day objective monitoring of asthma.

PEF meters are useful in clinic and primary health care settings to help in the diagnosis of asthma, where at least a 15 percent improvement after inhalation of a bronchodilator or in response to a trial of glucocorticosteroid therapy favors a diagnosis of asthma[16]. PEF meters are also useful for ongoing supervision of asthma if spirometry is impractical (**Figure 1-6**). Finally, regular home monitoring of PEF is sometimes useful because it can help patients detect early signs of asthma deterioration. Several studies have demonstrated that patients' symptom reports are unreliable indicators of airflow limitation[17,18]. Poor perception of the severity of asthma on the part of the patient and health care professional has been cited as a major factor causing delay in treatment and thus may contribute to increased severity and mortality from asthma exacerbations[19]. However, this is not the case with all patients. One study showed that symptoms preceded the onset of declines in lung function[20].

It is important to note that measurements of PEF do not always correlate with other measurements of lung function in asthma and are not necessarily interchangeable in evaluating asthma severity[21]. For example, in children with asthma, PEF can be normal as airflow obstruction and gas trapping worsens. Therefore PEF can underestimate the degree of airflow obstruction[22]. Also, in children, measurements of PEF do not always correlate with symptoms or other measures of disease severity[23]. For these reasons, PEF measurements are ideally compared to the patient's own previous best measurements.

Careful instruction is required if patients are to reliably measure PEF because PEF measurements, like FEV_1 and FVC measurements, are effort dependent. A PEF meter may be used regularly throughout the day and over weeks and months to aid in the assessment of asthma severity and monitor the response to treatment. The severity of asthma is reflected not only in the level of baseline airflow limitation, but also in its variability, particularly across 24 hours (**Figure 1-6**). Ideally PEF should be measured first thing in the morning when values are usually close to their lowest and last thing at night when values are usually at their highest.

One method of describing diurnal PEF variability is as the amplitude (the difference between the prebronchodilator morning value and the postbronchodilator value from the evening before), expressed as a percentage of the mean daily PEF value[24]. Another method is the minimum morning prebronchodilator PEF over 1 week, expressed as a percent of the recent best (Min%Max)[25] (**Figure 5-3**). This latter method has been suggested to be the best PEF index of airway lability because it requires only a once-daily reading, it correlates better than any other index with airway hyperresponsiveness, and the calculation is simple[25].

A diurnal variation in PEF of more than 20 percent is considered to be diagnostic of asthma, the magnitude of the variability being broadly proportional to disease severity (**Figure 1-6**)[24]. However, it should be noted that in mild intermittent asthma or in severe intractable disease, variability in PEF may not be present or may be lost. In more severe asthma, diurnal variation and reversibility may not be a feature until after a trial of glucocorticosteroids. Even then, the more severe intransigent forms of the disorder may take many weeks of treatment before reversibility becomes apparent.

By using a combination of regular symptom recording and PEF measurement, patients can be provided with

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treatment plans that are responsive to asthma severity, and the course of asthma can be effectively monitored[26]. Furthermore, it is conceivable that a patient's adherence to treatment may be enhanced by observing objectively his/her responses to therapy.

Although long-term PEF monitoring for most patients with persistent asthma can be valuable and may be ideal, this is not always possible for reasons of cost, cooperation, and availability of peak flow meters. However, short-term monitoring is particularly recommended for establishing a diagnosis, identifying possible environmental triggers, and evaluating changes in therapy. Long-term monitoring is particularly recommended for those patients with severe asthma, for those with poor perception of severity, and for those who have ever been hospitalized.

PEF measurement may be of use not only in establishing a diagnosis of asthma and assessing its severity but also in uncovering an occupational cause for asthma. When used in this way, PEF should be measured more frequently than twice daily and special attention paid to changes occurring inside and outside the workplace[27].

If, in the presence of infrequent symptoms, these tests fail to support a diagnosis of asthma, it is usually advisable to maintain surveillance with periodic reevaluation until the diagnostic situation becomes clearer. In these circumstances, the health care professional should take special consideration of the patient's family history, age, and asthma triggers before deciding on a diagnostic or therapeutic course of action. When there is doubt, a trial of treatment with short-acting β_2-agonists as needed and inhaled glucocorticosteroids is considered one of the surest ways of establishing a diagnosis of asthma, especially if combined with PEF monitoring. A clear knowledge of the degree of lung dysfunction (such as with daily measurements of PEF) over a period of time not only offers the opportunity for detecting environmentally related causes of the asthma but also provides the criteria for assessing asthma severity and environmental influences, and for observing the response to treatment.

The clinician must always feel confident that the diagnosis of asthma is fully established because the consequences for the patient are considerable and frequently lifelong. The requirements for diagnostic confirmation in patients presenting with severe symptoms and gross lung dysfunction differ from those for asymptomatic patients.

Airway hyperresponsiveness. For patients with symptoms consistent with asthma, but normal lung function, measurements of airway responsiveness to methacholine, histamine, or exercise challenge may help establish a diagnosis of asthma[28]. These measurements are sensitive for a diagnosis of asthma, but have low specificity[29]. This means that a negative test can be useful to exclude a diagnosis of persistent asthma, but a positive test does not always mean that a patient has asthma. This is because airway hyperresponsiveness has been described in patients with allergic rhinitis[30] and in those with airflow limitation caused by conditions other than asthma, such as cystic fibrosis[31], bronchiectasis, and chronic obstructive pulmonary disease[32].

Measuring Noninvasive 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 eosinophils and metachromatic cells[33]. In addition, levels of exhaled nitric oxide (NO)[34] or carbon monoxide (CO)[35] have been suggested as noninvasive markers of airway inflammation in asthma. Levels of exhaled NO and CO 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 exhaled gases has yet been evaluated prospectively as an aid in asthma diagnosis. There is a need to develop further noninvasive discriminate measurements of airway inflammation.

Measurements of Allergic Status

The presence of an allergic component in asthma can be identified by skin testing or measurement of specific IgE in serum. While these tests add little to the diagnosis of asthma, they can help in identifying its risk factors or triggers so that appropriate environmental control measures can be recommended. Deliberate provocation of the airways with a suspected allergen or sensitizing agent may also be helpful in establishing causality, especially in the occupational setting[27], but is not routinely recommended, because it is not often useful in establishing a diagnosis and on the grounds of safety.

Skin tests with allergens represent the primary diagnostic tool in determining atopic status. Prick tests are the most commonly used for diagnostic purposes. Their characteristics–simplicity, rapidity of performance, low cost, and high sensitivity–explain their key position. However, when improperly performed, skin tests can lead to falsely positive or negative results. Measurement of specific IgE in serum does not surpass skin tests and is more expensive. The main limitation of methods to assess allergic status is that a positive test does not necessarily

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mean that the disease is allergic in nature, as some individuals have specific IgE antibodies without any symptoms. The relevant exposure and its relation to symptoms must be confirmed by the patient history. Measurement of total IgE in serum has no value as a diagnostic test for atopy.

PARTICULARLY DIFFICULT DIAGNOSTIC GROUPS

In this section emphasis is given to the difficult problems in diagnosing asthma in children, in the elderly, in relation to occupational exposure to risk factors, in seasonal asthma, and in cough variant asthma. For these patient groups measurements of airflow limitation and variability are extremely useful for establishing a diagnosis of asthma.

Childhood Asthma

Diagnosis of asthma in children can present a particularly difficult problem, largely because episodic wheezing and cough are among the most common symptoms encountered in childhood illnesses, particularly in children under 3 years old[3]. Although health care professionals are increasingly encouraged to make a positive diagnosis of asthma whenever recurrent wheezing, breathlessness, and cough occur (particularly if these symptoms occur at night and in the early morning), the disorder's underlying process may be different in infants than in older children and adults[36]. The use of the label "asthma" to describe such children has important clinical consequences. It implies a syndrome in which there is airway inflammation and for which there is a specific protocol of management.

The younger the child, the greater the likelihood that an alternative diagnosis may explain recurrent wheeze. Alternative causes of recurrent wheezing in infancy include cystic fibrosis, recurrent milk inhalation, primary ciliary dyskinesia syndrome, primary immune deficiency, congenital heart disease, congenital malformation causing narrowing of the intrathoracic airways, and foreign body aspiration. Features such as a neonatal onset of symptoms, associated failure to thrive, vomiting-associated symptoms, and focal lung or cardiovascular signs all suggest an alternative diagnosis and indicate the need for further investigations, such as a sweat test to exclude cystic fibrosis, measurements of immune function, and reflux studies. Chest radiography is an important diagnostic test to exclude such alternative causes of wheezing.

Among those children in whom an alternative diagnosis has been excluded, there is the possibility that recurrent wheezing does not have a uniform underlying pathogenesis[3]. Nonetheless, there are two general patterns of wheezing in infancy. Some infants who have recurrent episodes of wheeze associated with acute viral respiratory infections, often with a first episode in association with respiratory syncytial virus bronchiolitis, come from nonatopic families and have no evidence of atopy themselves[37,38]. These infants usually outgrow their symptoms in the preschool years and have no evidence of subsequent asthma, though they may have minor defects of lung function and airway hyperresponsiveness. This syndrome may have more to do with airway geometry than airway inflammation[39], and thus may differ mechanistically from the more established chronic inflammatory condition that underlies asthma in older children and adults.

Other infants with asthma have an atopic background often associated with eczema and develop symptoms later in infancy that persist through childhood and into adult life[40]. In these children, characteristic features of airway inflammation can be found even in infancy. However, there are no practical, clinical tests that can be done to establish the presence of airway inflammation. Also, there are no clear markers to predict the prognosis for an individual child. However, in young children with frequent wheezing, a parental history of asthma along with the presence of other atopic manifestations in the child are significantly associated with the presence of asthma at age 6[41]. The onset of wheeze at an early age (under 2 years) is a poor predictor of whether asthma will persist in later childhood[3,37,38].

It is likely that the relationship between wheezing associated with recurrent viral infections and the later development of persistent asthma requires further study. Not only are the etiological mechanisms of asthma in childhood unclear, but there is also considerable reluctance on the part of doctors to establish a diagnosis and, therefore, to initiate appropriate therapy. Because lower respiratory tract symptoms similar to symptoms of asthma are so common in childhood (and frequently occur in association with upper respiratory tract symptoms), often either a correct diagnosis is not made or an inappropriate diagnosis is given, thereby depriving the child of antiasthma medication. Although in these young children there is the possibility of overtreatment, the episodes of wheezing may be foreshortened and reduced in intensity by the effective use of anti-inflammatory medications and bronchodilators rather than antibiotics. It is for this reason that health care professionals are encouraged to use the word "asthma" rather than other terminology to describe recurrent viral-associated wheezing in early childhood.

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Asthma in all age groups may present only as repeated coughing, especially at night, with exercise, and with viral illness, but these are particularly common patterns of presentation of the disease in childhood. The presence of recurrent nocturnal cough in an otherwise healthy child should raise asthma as a probable diagnosis.

In children under the age of 5, the diagnosis of asthma has to be based largely on clinical judgment and an assessment of symptoms and physical findings. Because the measurement of airflow limitation and airway hyperresponsiveness in infants and small children requires complex equipment and is difficult[42], these measurements can only be recommended as a research tool. A trial of treatment is probably the most confident way to make a diagnosis of asthma in children (and in many adults as well). Prognostic features include a family history of asthma or eczema and the presence of eczema in a young child with respiratory symptoms[38]. Children 4 to 5 years old can be taught to use a PEF meter and obtain reliable readings. However, unless there is careful parental supervision of when and how the measurements are made, PEF recording in childhood can be unreliable[43]. The use of diary cards to record symptoms, PEF, and treatment has proved an invaluable part of asthma management strategies.

Some children with asthma present only with exercise-induced symptoms. In this group, or when there is doubt over the presence of mild asthma in a child, exercise testing is helpful. A 6-minute running protocol is easily performed in clinical practice. When used in conjunction with measurements of airflow limitation (FEV_1 or PEF), this can be most helpful in establishing a firm diagnosis of asthma[44], especially if the cough produced by the exercise is similar to that occurring spontaneously at night.

Asthma in the Elderly

A group of patients in which the diagnosis of asthma is often not made or is missed is the elderly[45]. Although lung damage from smoking or extensive exposure to inhaled environmental insults results in such diseases as bronchitis, emphysema, or fibrosing lung disease in this age group, it is now becoming increasingly recognized that undiagnosed asthma is a frequent cause of treatable respiratory symptoms. A further complicating factor is the difficulty that some older people have in performing lung function tests, including PEF. This means that making a diagnosis of asthma or chronic bronchitis based purely on symptoms is fraught with difficulties.

Late-onset asthma occasionally occurs in association with vasculitis and marked eosinophilia (Churg-Strauss syndrome). In the older patient, longstanding asthma may enter a severe destructive phase associated with allergic bronchopulmonary aspergillosis. Characteristically, however, late-onset asthma is not associated with evidence for specific allergen sensitization.

Later in life, smoking and elevated serum IgE levels appear to be independent determinants of chronic airflow limitation, although they may interact[46]. This has led to a growing body of opinion that chronic obstructive pulmonary disease (COPD), associated with a long history of smoking, may have an important inflammatory component that is responsive to anti-inflammatory drug intervention, thus blurring the boundary between asthma and other forms of obstructive lung disease[47]. When doubt exists, a trial of oral glucocorticosteroids in which a greater than 12 percent improvement in FEV_1 or 15 percent improvement in PEF occurs, accompanied by improvement in symptoms and reduced bronchodilator requirement, usually confirms asthma as a cause of chronic respiratory symptoms.

The elderly are susceptible to episodes of wheezing, breathlessness, and cough caused by left ventricular failure (sometimes mistakenly labeled cardiac asthma)[45]. The presence of increased symptoms with exercise and at night may add to the diagnostic confusion. A careful history and physical examination looking for features of ischemic heart disease and cardiac dysfunction, together with an ECG and chest x ray usually clarify the picture, but if after this doubt still persists, a trial of diuretic treatment is helpful.

Not only is the diagnosis of asthma difficult in the elderly, but the assessment of severity also presents a particular problem because the perception of symptoms and their severity is reduced in this age group when compared to young adults and also as a consequence of lifestyle adaptation.

Occupational Asthma

Asthma acquired in the workplace is a diagnosis that is frequently missed unless the health care professional is made aware of the possibility. Many inhalant chemicals are now known to produce asthma in the occupational environment (**Figure 3-4**). They range from highly reactive small molecular weight chemicals such as isocyanates, to known immunogens such as platinum salts, as well as to complex plant and animal biological products. Because of its insidious onset, occupational asthma is often misdiagnosed as chronic bronchitis or some form of COPD and is therefore either not treated at all or treated inappropriately. The diagnosis requires a defined occupational history, especially in relation to exposure to

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Figure 5-4. Overview of Lung Diseases

LUNG DISEASES

consist of

INFECTIONS

Simple colds, bronchiolitis, pneumonia, tuberculosis, and HIV/AIDS and related opportunistic infections

and

OBSTRUCTIVE DISEASES	**RESTRICTIVE DISORDERS**
Localized	Lung disease
Vocal cord paresis	Extrinsic allergic alveolitis
Laryngeal carcinoma	Sarcoidosis
Tracheal carcinoma	Fibrosing alveolitis
Bronchial carcinoma	Asbestosis
Foreign bodies	Eosinophilic pneumonia
Bronchopulmonary dysplasia	
	Pleural disease
Generalized	Pleural effusion
Chronic obstructive pulmonary disease	Pneumothorax
Asthma	Chest wall deformity
Obliterative bronchiolitis	Kyphoscoliosis
Cystic fibrosis	
Bronchiectasis	Respiratory muscle weakness
	Subdiaphragmatic problems
	Obesity
	Ascites

sensitizing agents; absence of asthma symptoms before beginning employment; and a documented relationship between development of symptoms at the workplace and reduction of these on withdrawal from the workplace. A confirmation of occupational asthma may be successfully achieved by lung function measurement, such as serial measurement of PEF at work and away from work (single measurements are less sensitive than serial measurements), and specific bronchial provocation testing[48]. The increasing recognition that occupational asthma can persist, or continue to deteriorate, even in the absence of continued exposure to the offending agent[49], emphasizes the need for an early diagnosis, appropriate strict avoidance of further exposure, and pharmacologic intervention.

Seasonal Asthma

In some sensitized individuals, asthma may be exacerbated by seasonal increases in specific aeroallergens. Examples include birch[50], grass[51], *Alternaria*[52], and ragweed pollens[53]. Seasonal asthma is usually associated with allergic rhinitis. This type of asthma may occur only intermittently, with the patient being entirely asymptomatic between seasons. Alternatively, it may occur as a seasonal worsening of asthma symptoms in a patient with persistent asthma.

Cough Variant Asthma

Another group of patients whose asthma can sometimes be missed are those with cough variant asthma[54]. These patients have chronic cough as their principal, if not only, symptom. Frequently this occurs at night; consequently 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. Within this group are patients who cough and have sputum eosinophils but who also have normal indices of lung function when assessed by spirometry and airway hyperresponsiveness[55].

Some patients with hypertension treated by angiotensin-converting-enzyme (ACE) inhibitors, or patients with gastroesophageal reflux, postnasal drip, or chronic sinusitis, may develop a cough that resembles cough variant asthma[56].

DIFFERENTIAL DIAGNOSIS

Asthma is one of the most common causes of respiratory symptoms, but it is only one cause of lung disease (**Figure 5-4**). An important step in ensuring diagnosis of asthma is the demonstration of reversible and variable airflow limitation, preferably by spirometry.

Although in children both asthma and acute respiratory infections produce wheezing as a consequence of widespread airway obstruction, respiratory symptoms may also arise from localized airway obstruction and inhaled foreign bodies[57], possibilities that must always be considered in the differential diagnosis (**Figure 5-5**). Another diagnosis to consider in both children and adults is pseudoasthma, most often caused by vocal cord dysfunction[58]. In adults, asthma superimposed on COPD is a common problem in past or present smokers.

CLASSIFICATION OF ASTHMA

Asthma may be classified on the basis of etiology, severity, and pattern of airflow limitation.

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Figure 5-5. Differential Diagnosis of Obstructive Airway Disease

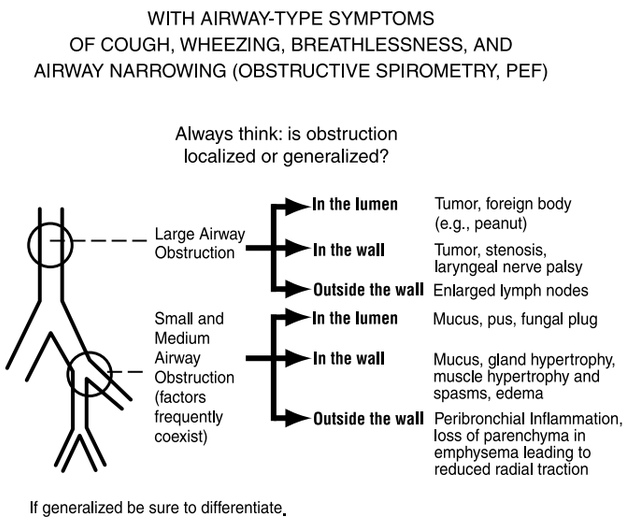

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Figure 5-6. Classification of Asthma Severity by Clinical Features Before Treatment

STEP 1: Intermittent
Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month • FEV_1 or PEF ≥ 80% predicted • PEF or FEV_1 variability < 20%
STEP 2: Mild Persistent
Symptoms more than once a week but less than once a day Exacerbations may affect activity and sleep Nocturnal symptoms more than twice a month • FEV_1 or PEF ≥ 80% predicted • PEF or FEV_1 variability 20-30%
STEP 3: Moderate Persistent
Symptoms daily Exacerbations may affect activity and sleep Nocturnal symptoms more than once a week Daily use of inhaled short-acting β_2-agonist • FEV_1 or PEF 60-80% predicted • PEF or FEV_1 variability > 30%
STEP 4: Severe Persistent
Symptoms daily Frequent exacerbations Frequent nocturnal asthma symptoms Limitation of physical activities • FEV_1 or PEF ≤ 60% predicted • PEF or FEV_1 variability > 30%

Etiology

Many attempts have been made to classify asthma according to etiology, particularly with regard to environmental sensitizing agents. Such a classification is, however, limited by the existence of patients in whom no environmental cause can be identified. Despite this, an effort to identify a specific environmental cause for asthma in an individual patient should be part of the initial clinical assessment, because it enables the use of avoidance strategies in asthma management.

Severity

Conventional assessments of asthma severity have combined assessments of symptoms, amounts of β_2-agonist used to treat symptoms, and lung function (**Figure 5-6**). An assessment of asthma based on clinical or symptom indices of disease severity over the preceding year has been shown to relate to pathological indices of airway inflammation[59]. Both the level of airflow limitation and its variability enable asthma to be subdivided by severity into four steps: Intermittent, Mild Persistent, Moderate Persistent, and Severe Persistent. This type of asthma classification, based on severity, is important when decisions must be made about management at the initial assessment of a patient. This is because asthma therapy involves a stepwise approach in which the level of therapy is increased as the severity of the asthma increases.

The severity of a patient's asthma may be classified into one of these four steps based on the clinical features present before treatment is begun (**Figure 5-6**). When the patient is already on treatment, the classification of severity should be based on the clinical features present and the step of the daily medication regimen that the patient is currently on[60] (**Figure 5-7**). Thus, a patient with ongoing symptoms of mild persistent asthma, despite being on the appropriate maintenance treatment for this step, should be regarded as having moderate persistent asthma. Similarly, a patient with ongoing symptoms of moderate persistent asthma, despite being on the appropriate maintenance treatment for this step, should be regarded as having severe persistent asthma. Thus, the combination of the current level of symptoms and the current maintenance treatment step should enable the establishment of the patient's asthma severity and the corresponding appropriate maintenance treatment. Once asthma control is achieved and maintained for a sufficient time, then a reduction in therapy should be tested. If control is maintained, then the patient should be reclassified according to the new maintenance treatment.

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Figure 5-7. Classification of Asthma Severity by Daily Medication Regimen and Response to Treatment

	Current Treatment Step*		
	Step 1: Intermittent	Step 2: Mild Persistent	Step 3: Moderate Persistent
Patient Symptoms and Lung Function on Current Therapy	**Level of Severity**		
Step 1: Intermittent Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month Normal lung function between episodes	Intermittent	Mild Persistent	Moderate Persistent
Step 2: Mild Persistent Symptoms more than once a week but less than once a day Nocturnal symptoms more than twice a month but less than once a week Normal lung function between episodes	Mild Persistent	Moderate Persistent	Severe Persistent
Step 3: Moderate Persistent Symptoms daily Exacerbations may affect activity and sleep Nocturnal symptoms at least once a week 60% < FEV_1 < 80% predicted OR 60% < PEF < 80% of personal best	Moderate Persistent	Severe Persistent	Severe Persistent
Step 4: Severe Persistent Symptoms daily Frequent exacerbations Frequent nocturnal asthma symptoms $FEV_1 \leq 60\%$ predicted OR PEF ≤ 60% of personal best	Severe Persistent	Severe Persistent	Severe Persistent

**Treatment as described in Chapter 7, Part 4A, Figure 7-5.*

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The severity of acute asthma exacerbations is often underestimated by patients, their relatives, and their health care professional. The reasons for this are complex, but include a failure to use measurements of lung function for assessment. If severe asthma exacerbations are not recognized and treated appropriately, such exacerbations can be fatal[61]. It is important to recognize that any patient with asthma, however mild on a chronic basis, may have a severe acute asthma exacerbation. Specific factors have been identified that are associated with a higher risk of asthma mortality[62]. These include a previous history of life-threatening acute attacks, hospitalization within the previous year, psychosocial problems, a history of intubation for asthma, recent reductions or cessation of glucocorticosteroid therapy, and noncompliance with recommended medical therapy.

Time Trends of Airflow Limitation

Asthma may also be classified according to time trend patterns of airflow limitation monitored by PEF measurements. This form of classification is likely to reflect the different pathological causes of airflow limitation and has therapeutic implications. Intermittent asthma may be defined as the presence of occasional episodes of respiratory symptoms and PEF reductions (in the last year) with normal PEF and normal or near-normal airway responsiveness in between episodes. By contrast, persistent asthma is characterized by daytime and nocturnal PEF variability, frequent symptoms, and airway hyperresponsiveness. Some patients with longstanding persistent asthma with an irreversible component to their disease fail to achieve normal lung function despite intensive therapy with glucocorticosteroids. The term “brittle asthma” is sometimes used to describe patients with airway hyperresponsiveness and extreme day-to-day variability in airway obstruction. These patients are particularly at risk for sudden, severe, and life-threatening exacerbations.

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CHAPTER

6

EDUCATION AND THE DELIVERY OF CARE

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KEY POINTS:

- Good asthma care requires sufficient numbers of well-educated health professionals organized so that they are available to the maximum number of patients. Guidelines on asthma management should be available but adapted and adopted for local use by local asthma planning teams consisting of both primary and secondary care health professionals (**Evidence D**).
- Implementation of guidelines is most likely to be effective and result in alteration of health professional behavior where there is practice-based education regarding the asthma guidelines, within-consultation prompting of behavior, and feedback to health care professionals regarding their management (**Evidence B**).
- Patient education involves a partnership between the patient and health care professional(s) with frequent revision and reinforcement. The aim is guided self-management–that is, giving patients the ability to control their own condition with guidance from the health care professionals. Interventions including the use of written self-management (action) plans have been shown to reduce morbidity in both adults (**Evidence A**) and children (**Evidence B**).
- Clear communication between health care professionals and asthma patients to meet patients' information needs is a key to enhancing compliance (**Evidence B**).

This chapter is concerned with the organization of health care professionals, the implementation of guidelines, patient education and self-management, and the education of family members, coaches, employers, and others who may come in contact with people who have asthma. It includes a number of tools that may be helpful in the education of both patients and health professionals.

The following conditions are essential to effective asthma care delivery:

- Sufficient numbers of well-educated health professionals should be organized effectively so that they are available to the maximum number of patients.
- Asthma should be correctly diagnosed, its severity assessed, and appropriate treatments prescribed.
- Adequate finances should be available to governments or individuals to ensure that asthma treatments are available (and means of providing less expensive medications need to be explored).
- Patients should understand how to use the asthma treatments to maximal advantage.

Although government officials make the decisions about health care financing and personnel requirements, health professionals should be consulted on these issues. Correct diagnosis and management of asthma and the correct use of appropriate treatments are issues directly concerned with the education of health care professionals and their patients. Some of the methods suggested in this chapter may initially appear more expensive, but may ultimately lead to significant cost savings.

Research has shown that currently there are deficiencies in most of the four essentials listed above. For example, delays in diagnosis are common[1] and lead to inappropriate (non-asthma) treatments being given. Underdiagnosis of asthma is mainly due to the failure of patients with

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Figure 6-1. Education: An Essential Part of the Management of Asthma

Why educate?
Good education should reduce morbidity and mortality, keep people at work and school, and reduce health costs (especially if it reduces hospitalization) and indirect costs.

Who needs education?
- Policy-makers and planners–so they make asthma a priority and effect good organization of care
- Health care professionals–doctors, nurses, pharmacists, medical students, and care assistants/field workers
- The wider public–teachers, employers, and coaches
- Patients (and their families and loved ones).

What topics should be covered in education?
- Information about the content of clinical practice guidelines
- Information about the diagnosis
- Information about prevention of exacerbations and deterioration of lung function
- Training in (guided) self-management
- Ability to recognize deteriorating asthma
- Knowledge about the different treatments
- Training in proper use of medication inhalers and peak flow meters.

How to educate?
- Educate the health care professionals and emphasize the importance of preventive management, i.e., managing asthma to prevent symptoms and exacerbations.
- Recognize that patient education involves:
  - giving information and acquisition of skills
  - altering behavior by the patient.
- Good communication and development of a partnership between patients and health care professionals are essential if barriers to education are to be overcome.
- Monitoring, auditing, and setting of standards are also essential parts of the process and the responsibility of officials and professional organizations.

Where to educate?
- Education of health care professionals is necessary in schools and colleges, and by continuing medical education.
- Education of the wider public is necessary by articles in newspapers and journals and by programs on television.
- Education of patients is a continual process involving revision and reinforcement at each meeting with a health care professional.

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bronchial symptoms to visit a health care provider, and this failure may be associated with a poor perception of asthma symptoms[2]. In other cases asthma severity is underestimated, with the result that regular preventive therapy is underused[3,4]. Studies of both adults and children have shown that only about 50 percent of patients take regular preventive therapies as previously advised by their doctor[5-7]. In large surveys, considerable numbers of asthma patients report regular sleep disturbance and limitation of daytime activities[8].

These deficiencies may have particularly serious consequences for patients with severe asthma. One study showed that 74 percent of those admitted to the hospital with severe asthma could have had the admission prevented by more appropriate prior care[9]. Surveys of deaths from asthma have shown that nearly 90 percent of cases involve avoidable factors[10]. Studies also show that 78 percent of those who die from asthma have previously been admitted to hospitals for asthma[11], and 40 percent have been admitted to the hospital in the 12 months prior to death[12]. Patients who have a history of hospital admission for asthma, especially if they required mechanical ventilation, should be considered at high risk for asthma-related death. Education and the teaching of self-management skills may be especially important to these patients, and lack of self-management education may increase the risk of emergency room visits among patients with poorly controlled asthma.

Education is clearly an essential part of the overall management of asthma. An outline summary of the relevance of education to asthma is shown in **Figure 6-1**. Education includes education about primary prevention, secondary prevention, and management of asthma.

THE ORGANIZATION AND EDUCATION OF HEALTH PROFESSIONALS

To ensure the proper organization of well-educated health professionals within a country or within a district within a country, an asthma planning team should be instituted (**Evidence D**). Likely members of such a team are shown in **Figure 6-2**. In some countries, such as Finland and Peru, asthma planning has been done at a national level with government health department collaboration; in other countries, such as Australia, a National Asthma Campaign has involved a coalition of health professional organizations, the government, pharmaceutical companies, and patient support organizations. Countries will vary so much for reasons of economics, culture, and environment that the priorities and problems presented to each planning team may vary considerably. Some of the issues that need to be considered are shown in **Figure 6-3**.

Figure 6-2. Likely Members of a National or District Asthma Planning Team

- Health planners
- Public health physicians
- Primary care physicians
- Pediatricians
- Respiratory physicians
- Pharmacists
- Allergists
- Nurses
- Health educational specialists
- Patient support groups

Figure 6-3. Checklist of Issues for National or District Asthma Planning Teams

- What is the size of the problem 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 our climatic conditions?
- Can we standardize inhaler devices and medicines 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, teenager, minority)?
- Whom can we enlist to help in education (community health workers/health-promotion facilitators/trained educators currently working on other programs/self-help patient groups)?
- Who will take responsibility for the education of health care professionals?
- Who will take responsibility for the education of patients?
- How can we integrate asthma education and treatment into other programs (e.g., child health)?

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Guidelines

Guidelines on asthma management should be adopted and adapted for local use by local asthma planning teams consisting of both primary and secondary care health professionals (**Evidence D**). Guidelines are used 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 act as a starting point for the education of health professionals. Sections on referral patterns may be used as a basis for

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deciding how different patients are cared for and working out shared care protocols.

However, whether guidelines are national or international in scope, it is unlikely that their production alone will reduce asthma morbidity. Guidelines seem to be most effectively introduced to health care providers through interactive methods[13], a time-consuming but necessary process. Simply reading guidelines generally does not change physicians' delivery of care because information is necessary but it is rarely sufficient by itself to produce changes in behavior. Furthermore, guidelines are often lengthy and contain multiple messages referring to different situations and to different severities of disease; health care professionals need to have learning situations in which they can consider how to adapt the guidelines to their clinical populations.

For successful dissemination and incorporation into clinical practice, comprehensive guidelines (such as the GINA guidelines) must be not only read by physicians but also discussed in peer groups. In addition, and probably most importantly, doctors should receive daily prompting and feedback to remind them to incorporate the content into their consultations. One study evaluating asthma care in general practice before and after the publication of national asthma guidelines showed that dissemination alone had hardly any effect on care, but direct feedback regarding physicians' actual patient care resulted in a clear improvement in accordance with guidelines[14].

Figure 6-4. Key Questions for Considering Asthma*

IS IT ASTHMA?
Ask patients or parents these key questions:

- Has the patient had an attack or recurrent attacks of wheezing?
  Consider asthma.
- Does the patient have a troublesome cough at night?
  Consider asthma.
- Does the patient have a cough or wheeze after exercise?
  Consider asthma.
- Does the patient have a cough, wheeze, or chest tightness after exposure to airborne allergens or pollutants?
  Consider asthma.
- Do the patient's colds "go to the chest" or take more than 10 days to clear up?
  Consider asthma.
- Does the patient use anti-asthma medication? (How often?)
  Consider asthma.

If the patient answers "yes" to any of the questions, a diagnosis of asthma may be likely. However, it is important to remember the possibility of pulmonary emboli, heart disease, and anemia as alternative causes of respiratory symptoms.

**These questions may be produced in poster form for clinics or as cartoons.*

Ideally, feedback should compare the behavior of individual health professionals not only with the (theoretical) behavior described in the guideline, but also with the actual behavior of their peers. Audit or providing the health professional with an assessment of the care he or she is providing can lead to an alteration in behavior[15], but audits alone may give only negative feedback. By contrast, when the care provided is compared with that provided by peers and subsequently discussed with these peers, the health professional also receives positive feedback. This creates a social learning situation, the best method for accomplishing clear changes in behavior.

When teaching health professionals about asthma, it may be helpful to see the condition within the whole context of respiratory medicine to avoid overdiagnosis or misdiagnosis. **Figure 6-4** provides key questions to ask about the patient's history. Several figures from other chapters in this report may be easily reproduced for use by health care professionals as teaching aids or as consultation room reminders or prompts.

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Monitoring Process and Outcome

In addition to setting up a system to deliver care to patients with asthma through trained health care professionals, it is also essential to set up a system for monitoring the effectiveness and quality of care. Such monitoring involves surveillance of traditional epidemiological parameters, such as morbidity and mortality, as well as the specific audit of both process and outcome within different sections of the health care system. *Process* parameters are defined as parameters that characterize asthma care in practice, while *outcome* parameters refer to the effects this care has on the patient with asthma. Effective assessment of these parameters requires the determination and definition of minimum sets of data that can be audited. Each country needs to determine its own minimum sets of data to audit. Examples include the following.

To audit **process** ask:

- Was a record kept of the patient's technique for taking medication (for example, using an inhaler or a nebulizer) and their understanding of when and how to take each medication?
- Was the patient on an appropriate step of therapy for the severity of his or her asthma?
- Was a record kept of advice given about how to recognize deteriorating asthma and how to handle exacerbations?

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The UK Royal College of Physicians of London has recently reviewed strategies for auditing **outcomes**, and concluded that at each consultation the patient's answers to the following questions should be recorded[16]:

In the last week or month:

- Have you had difficulty sleeping because of your asthma (including cough)?
- Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness, or breathlessness)?
- Has your asthma interfered with your usual activities (e.g., housework, work, school, etc.)?

A prompt stamp (a standardized note put into the patient's record) such as the Tayside Asthma Assessment Stamp may be used to help remind health care providers to ask these questions during consultations[16,17]. An electronic version of this stamp is displayed at http://www.srs.org.uk.

PATIENT EDUCATION

The aim of patient education, which is a continual process, is to provide the patient with asthma and the patient's family with suitable information and training so that the patient can keep well and adjust treatment according to a medication plan developed in advance with the health care professional. The emphasis must be on the development of an ongoing partnership among health care professionals, the patient, and the patient's family.

Patient education should aim to:

- Increase understanding
- Increase skills
- Increase satisfaction
- Increase confidence, and thereby to
- Increase compliance and self-management.

Basic education should be provided over several consultations or visits. Education should be provided to patients of all ages. Although the focus of education for small children will be on the parents, children as young as 3 years of age can be taught simple asthma management skills. Teenagers may have some unique difficulties regarding compliance that may be helped through peer support group education in addition to education provided by the health care professional. Revision and reinforcement are essential components of education provided by the health care professional. **Figure 6-5** outlines the basic features of a patient education program,

Figure 6-5. Individualizing Education in a Stepwise Manner

The goal: To provide the patient and his or her family with suitable information and training so that the patient can keep well and adjust treatment according to a medication plan developed with the health care professional.

Key components:
- The development of a partnership
- Acceptance that this is a continuing process
- A sharing of information
- Full discussion of expectations
- Expression of fears and concerns

The patient then requires information about:
- Diagnosis
- Difference between "relievers" and "controllers"
- Training in use of inhaler devices
- Advice regarding prevention
- Signs that suggest asthma is worsening and actions to take
- Training in monitoring asthma
- Advice about how and when to seek medical attention

The patient then requires:
- A guided self-management plan
- Regular supervision, revision, reward, and reinforcement

Figure 6-6. Prevention: A Patient Checklist

What should I avoid?
- Active smoking
- Passive smoking
- Beta-blockers (tablets and eye drops)
- Aspirin (and NSAIDs) where previously adversely affected
- Occupational agents (to which the patient has become sensitized)

What should I consider and avoid or modify exposure to, if relevant to me?
- Domestic mites
- Other common allergens
- Adverse occupational environments
- Foods and additives
- Adverse indoor environments

What should I always undertake, if necessary by adjusting treatment?
- Normal social activities
- Exercise (other than in certain very adverse environmental conditions)
- Sports

Always mention to the health care professional anything else that may affect your asthma (for example, menstruation, alcohol).

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and **Figure 6-6** provides a patient checklist of what to avoid to prevent an asthma exacerbation. The information and skill training required by individual patients vary, and each patient's 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 patient in a number of steps. Social and psychological support may also be required to maintain positive behavioral change. Further, the patient's understanding of the information and management skills should be assessed periodically so that educational steps may be repeated or added as appropriate.

Improving Compliance

Studies of adults and children[18] have shown noncompliance rates of around 50 percent with the taking of regular preventive therapies. Noncompliance 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. Noncompliance 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 compliance (e.g., "So that we may plan therapy, do you mind telling me how often you find that you actually take the medicine?"). Specific drug and nondrug factors involved in noncompliance are listed in **Figure 6-7**.

Figure 6-7. Factors Involved in Noncompliance

Drug factors
Difficulties with inhaler devices
Awkward regimes (e.g., four times daily or multiple drugs)
Side effects
Cost of medication
Dislike of medication
Distant pharmacies
Nondrug factors
Misunderstanding or lack of instruction
Fears about side effects
Dissatisfaction with health care professionals
Unexpressed/undiscussed fears or concerns
Inappropriate expectations
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

Compliance can usually be increased:

- If the patient accepts the diagnosis of asthma
- If the patient believes that his or her asthma may be dangerous or is a problem
- If the patient believes that he or she is at risk
- If the patient believes that the treatment is safe
- If the patient feels in control
- If there is good communication between patient and health care professional.

The importance of good communication as the basis for subsequent good compliance cannot be underestimated[1,19-21] (**Evidence B**). Key factors in good communication are[22]:

- 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 enhanced communication skills can result in measurably better patient 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[23]. Recent studies have also shown that patients can be trained to benefit more from consultations. In one study, patients taught how to give information to doctors in a clearer manner, information-seeking techniques, and methods of checking their understanding of what the doctor had told them gained significant improvements in compliance and overall health[24].

Methods of Delivery

Patients can acquire information about asthma and its treatment by:

- Listening to the health care professional
- Reading a book or cartoon, watching a video, or listening to an audiotape

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- Attending an asthma educational course
- Attending a public meeting or a patient support group to learn from other patients with asthma
- Reading articles in magazines or newspapers
- Watching television programs or listening to the radio
- Using the World Wide Web or interactive multimedia.

Several studies have evaluated the effectiveness of various methods of asthma education. One conclusion is that patient preference does not always equate with effectiveness. For example, one study showed patients preferring a book to an audiotape, but the latter was actually more effective in terms of knowledge gained[25]. Further, studies demonstrate that interventions involving the giving of information alone may improve patient knowledge, but do not necessarily lead to improvement in lung function or reduction in use of health service resources[26,27]. What can lead to improved control of asthma are more interactive educational interventions coupled with personalization of advice[28,29]. For example, three educational sessions on asthma conducted by a specially trained nurse may be sufficient to reduce the number of patients reattending emergency departments with out-of-control asthma. Attendance at an "asthma class" has also produced reduced hospitalization and emergency visits for at least 12 months after the intervention[30]. In another controlled trial, intervention in the form of a 30-minute one-to-one session, a 60-minute attendance at an asthma support group, and two brief telephone reinforcement calls increased practical skills as well as compliance, with the benefit extending over a 12-month period[31].

Discerning which component of an intervention (giving information, closer medical care, self-management, or followup and enhanced supervision) has been most effective is not always easy. What is probably most effective is to give information verbally and then by several other routes–with those routes selected on the basis of patient education status and literacy level[32]. Instruction via videos may be more appropriate than leaflets in some instances and has been shown to be useful in teaching good inhaler techniques. (Information about different types of inhalers and their use can be found on the GINA website (http://www.ginasthma.com).

Many patients appear to benefit by being put in touch with patient support groups as a supplement to education by the health care professional. The format of these groups varies from country to country and from area to area, but most provide information materials, and many provide opportunities for group education, mutual support, and exchange of personal tips on managing asthma and coping with the stress a chronic disorder can present to patients and their families. Such patient support groups exist in a number of countries, and some are listed on the GINA website (http://www.ginasthma.com).

Education at Initial Consultation

In early consultation the patient with asthma needs information about the diagnosis and simple information about the types of treatment available and about the rationale for the specific therapeutic interventions being recommended. For example, different inhaler devices should be demonstrated, and patients should take part in a 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.com). Additional devices are becoming available each year. It may be useful to use a criterion-based performance checklist for teaching patients about inhaler techniques. Patients should be advised about secondary prevention measures–for example, to avoid cigarette smoke as well as to avoid allergens, occupational sensitizing agents, and drugs known to cause asthma exacerbations in an individual. The consequences of ongoing exposure to such chronic pollutants and allergens even when the exposure does not always lead to an exacerbation should be explained. Advising patients to avoid such day-to-day triggers as exercise and cold air generally imposes inappropriate restrictions, and it is often preferable to adjust treatment to prevent exacerbations precipitated by exposure to these.

Patients should be given adequate opportunity to express their expectations of both the 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. In many cases, it is up to the health care professional to raise patients' level of expectations. It is reasonable for most patients to expect:

- Freedom from symptoms day and night
- No restriction on activities, including sports
- Best possible lung function (e.g., peak expiratory flow).

At the initial consultation, verbal information should be supplemented by the provision of written (or pictorial, for low-literacy-level patients)[33] information about asthma and its treatment. The patient and the patient's family should be encouraged to make note of any questions that arise from reading this information or as a result of the consultation. Patients should understand that time will be

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set aside for further information and for answering questions during each subsequent consultation.

During this initial visit, or a followup consultation if necessary, the concept of peak expiratory flow (PEF) monitoring should be considered as appropriate to the patient's age, ability, and clinical assessment. Patients, especially those with more than mild disease, should receive training in how to measure and record PEF. The technique of rapid exhalation required for peak flow meter use is very different from the slow breathing required for using metered-dose inhalers; this may be confusing to patients and thus requires careful instruction. When patients are taught how to record and interpret their PEF, it is helpful to explain that in addition to the absolute value of peak expiratory flow, its variability is important. The patient should understand that such monitoring is undertaken to check on the effectiveness of therapy and to give early warning of potential deterioration. It may be helpful to stress that PEF monitoring is not done merely for the health care professional's record, but rather provides critical information for making decisions about treatment, and thus PEF monitoring is a tool for patients to help themselves.

The aim then is for patients to be offered training in self-management techniques. A recent systematic review by the Cochrane Airways group[34] of 22 studies involving patient education compared with usual care showed significant benefits in the intervention groups in terms of reduced morbidity and reduced use of health services. The effects were greatest where the intervention involved the issuing of written self-management action plans (**Evidence A**).

Guided Self-Management and Personal Asthma Action Plans

In guided self-management or asthma self-management, individual asthma patients make changes to their treatment in response to changes in the severity of their asthma, in accordance with predetermined guidelines[22,35]. The process involves the integration of assessment and treatment, and incorporates written guidelines for both long-term treatment of asthma and treatment of exacerbations. Indeed, to be effective, written action plans must be imbedded into a total health care package[54]. Followup and supervision by the health care provider is also an important contributor to the success of this strategy.

The concept of guided self-management arose as clinicians realized that delays in recognizing asthma exacerbations and initiating appropriate therapy are important factors contributing to asthma morbidity and mortality[10,36,37]. Moreover, they knew that the majority of asthma attacks occur in the community and are managed by patients without immediate consultation with a doctor. This situation caused physicians to try to develop ways to teach asthma patients how to recognize and treat asthma attacks in accordance with current medical knowledge.

Figure 6-8. The Basic Principles of Guided Self-Management in Adult Asthma

- Patients are taught to combine objective assessment of asthma severity (peak flow recordings) with educated interpretation of key symptoms.
- Patients are taught which medication to use regularly and which medication to use as needed. This may include as-needed β_2-agonist therapy or, for patients with severe asthma, systemic glucocorticosteroids, high-dose inhaled β_2-agonists, oxygen therapy, and medical review.
- Self-assessment and self-management are integrated with written guidelines for both the long-term treatment of asthma and the treatment of asthma exacerbations.

Guided self-management has been promoted in nearly all national and international asthma guidelines. The basic principles of guided self-management are shown in **Figure 6-8**.

A number of specific systems of guided self-management have been developed and shown to be effective in the management of adult asthma[34,38-45]. Examples of self-management plans that have been recommended can be found on several web sites (UK National Asthma Campaign Plan, http://www.asthma.org.uk; International Asthma Management Plan "Zone System," http://www.nhlbisupport.com/asthma/index.html; New Zealand "Credit Card" System, http://www.asthmanz.co.nz).

Assessment

Fundamental to the success of guided self-management is the ability of the patient to recognize deterioration in asthma control. The patient must be taught to assess asthma severity by interpreting key symptoms and performing measurements of peak flow[46-48]. Simple advice to seek medical attention if there are any nighttime symptoms, especially nocturnal wakening, or if symptoms do not respond to increased use of inhaled β_2-agonist therapy may be the most important message to convey[49,50]. Domiciliary measurements of peak flow, with values

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interpreted as a percentage of normal predicted or previous best achieved recordings, are used as an objective assessment of the degree of airflow obstruction. Objective measurements are important because studies suggest that many patients are unable to reliably detect changes in their lung function–that is, they cannot correlate their subjective perception of asthma with measurements of lung function such as peak expiratory flow[47]. This diminished perception of lung function changes may correlate with the severity of the underlying asthma[51] and is associated with an increased risk of death[52], so peak flow monitoring is particularly important in adults with severe asthma.

Followup and Supervision

There is increasing evidence that self-management and inhaler skills need regular reinforcement by the health care professional. Moreover, a reduction in asthma therapy can only be adopted if the patient is seen regularly for followup.

At the followup consultation, the patient's questions are discussed, and any problems with asthma and its initial treatment are reviewed. Followup consultations at regular intervals should include checking the patient's inhaler technique and adherence to the medication plan and environmental control recommendations. Symptoms (and where appropriate, home peak flow recordings) noted in the patient diary are also reviewed regularly. Review of home PEF and symptom monitoring is necessary to assure that the goals of therapy are met and appropriate adjustments in therapy are made. After a period of initial training, the frequency of home peak flow and symptom monitoring depends in part on the severity of the patient's asthma. Patients with mild to moderate asthma with infrequent attacks can be advised to monitor their control during exacerbations only, whereas patients with more severe or "brittle" asthma should undertake more regular monitoring.

Self-Management in Children

Just like adults, children with asthma (and their parents) need to know how to self-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[53] although conclusions about the relative effectiveness of the various components are limited by the lack of data on direct comparisons[55]. This is especially important because asthma is a common reason for children to be admitted to the hospital, and this can cause considerable disruption to other family members and interfere with education.

Effectiveness and Cost-Effectiveness

Guided self-management plans, based on the above structure and principles, have been shown to lead to significant reductions in morbidity and patients' need for medical services[34,38-42,44] (**Evidence A**). 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 1 hospitalization, and successful completion of such a program by 8 patients prevents 1 emergency department visit[22]. Less detailed or intensive interventions that involve self-management education but not a written plan are less effective.

Self-management plans based on either peak flow or symptoms are of similar efficacy[43] (**Evidence B**), so the method of self-monitoring should be tailored to patient skill levels, preferences, and resources. Similar efficacy results from guided self-management plans in which patients self-adjust their medications according to an individual written plan, and regular review and adjustment of medication by a doctor[32] (**Evidence B**). Thus, patients who are unable to undertake guided self-management can still achieve benefit from a structured program of regular medical review.

Economic evaluation of asthma self-management programs has shown them to be cost effective, largely because they reduce patients' use of health care resources. The cost-benefit ratios in published studies are between 1:2.5 and 1:7[29,44] (**Evidence B**). However, further studies in this area are clearly needed.

Special Situations

Individualization of asthma therapy and the use of written guided self-management plans enable patients to cope with most situations, but trips away from home may require special planning. Particularly helpful may be a preholiday or pretravel check with the health care professional during which patients can get advice about taking along a sufficient quantity of routine and emergency medication, keeping the medication available during travel, remembering to take medication despite the different routine of a holiday, and checking in advance on how to find local medical attention if it should become necessary.

Pregnant patients may be counseled about possibilities for preventing the development of asthma in their babies.

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Although more research is needed, evidence suggests that breast feeding and reducing an infant's exposure to indoor allergens, especially domestic mites, and reducing exposure to maternal smoking could prevent the onset of asthma. This may be particularly relevant for the children of patients with allergies because atopy occurs in families and is the single most important risk factor for the development of asthma.

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 encourages those with asthma to seek medical attention and follow their asthma management program. Greater awareness of the condition is also likely to reduce feelings of stigmatization and to help dispel misconceptions that may exist about the condition.

Specific advice about asthma and its management should be offered to school teachers and physical education instructors, and several organizations produce such materials for this purpose. 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.

SOURCES OF FURTHER EDUCATIONAL MATERIALS

Sources of further educational materials, including links to several asthma websites, can be found at http://www.ginasthma.com.

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CHAPTER

7

A SIX-PART ASTHMA MANAGEMENT PROGRAM

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INTRODUCTION

Asthma is a chronic disorder with significant impact on individuals, their families, and society. Although there is no cure for asthma, appropriate management most often leads to control of the disorder.

The goals for successful management of asthma are to:

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

These goals for therapy reflect an understanding of asthma as a chronic disorder with progressively developing chronic airway inflammation leading to recurrent episodes of such airway responses as airflow limitation, mucus production, and cough. Numerous clinical studies have shown that any asthma more severe than mild, intermittent asthma is more effectively controlled by intervening to suppress and reverse the inflammation rather than by only treating the bronchoconstriction and related symptoms[1-3]. Furthermore, early intervention to stop exposure to the risk factors that sensitized the airway should result in optimal control of the disease[4], although the long-term results of specific avoidance measures are not yet known. It is noteworthy that experience in occupational asthma indicates that longstanding exposure to sensitizing agents may lead to irreversible disease[5].

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. This chapter reviews the different approaches to asthma management; discusses the relative efficacy, applicability, safety, and cost of the approaches; and integrates the approaches into a recommended six-part asthma management program.

The recommendations in this chapter link the rationale for the therapies to the 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, the recommendations are based on the literature review, clinical experience, and expert opinion of project members.

Asthma management has six interrelated parts:

1. Educate patients to develop a partnership in asthma management
2. Assess and monitor asthma severity with both symptom reports and, as much as possible, measurements of lung function
3. Avoid exposure to risk factors
4. Establish individual medication plans for long-term management in children and adults
5. Establish individual plans for managing exacerbations
6. Provide regular followup care.

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PART 1: EDUCATE PATIENTS TO DEVELOP A PARTNERSHIP IN ASTHMA MANAGEMENT

Patient education is a continual process. The patient with asthma and his or her family must be provided with suitable information and training so that the patient can successfully achieve control, adjust medication as needed according to a management plan developed with the health care professional, and maintain a satisfactory quality of life. The emphasis must be on developing a partnership among the health care professional(s), the patient, and the patient's family. The chapter on education and delivery of care explores in depth this important partnership and the essential elements of teaching individual patients about asthma management.

PART 2: ASSESS AND MONITOR ASTHMA SEVERITY WITH MEASUREMENTS OF SYMPTOMS AND MEASUREMENTS OF LUNG FUNCTION

KEY POINTS:

- Asthma severity can be judged by measurements of symptoms, measurements of lung function, and medication requirements.
- Pulmonary function studies are essential for diagnosing and assessing the severity of asthma in patients over 5 years old. Measures of lung function should also be used to monitor the course of asthma and the patient's response to therapy.
- Peak expiratory flow (PEF) monitoring is an important clinical tool in the office, emergency department, and hospital, and is useful in the home.

Asthma severity can be judged by measurements of symptoms, measurements of lung function, and medication requirements as discussed in the chapter on diagnosis and classification.

MEASUREMENTS OF SYMPTOMS

Structured questionnaires to be filled in by the patient or by the health care professional can be used to quantify or score patients' reports of their different asthma symptoms over a period of time. Many such questionnaires have been developed, but few have as yet been validated against other objective measurements of asthma severity. However, carefully administered serial questionnaires can be a sensitive method for detecting a deterioration of asthma[6]. The specific questions about symptoms should depend on the objectives of the questionnaire and the cultural setting. Particularly important questions in monitoring the patient's asthma and the patient's response to therapy are how frequently the patient is using reliever medication, and how frequently the patient has experienced nighttime symptoms such as cough, wheezing, or breathlessness. Questions about how frequently the patient limits normal activities may also be helpful. A visual analog scale to measure dyspnea has been demonstrated to be a reasonable tool for measuring and monitoring asthma severity in individual patients when more objective tests are not available[7].

MEASUREMENTS OF LUNG FUNCTION

Lung function (pulmonary function) studies are essential for diagnosing and assessing the severity of asthma in patients over 5 years old. The measurements provide an indirect assessment of airway hyperresponsiveness, which may correlate with the degree of airway inflammation.

Measurements of lung function should also be used to monitor the course of asthma and the patient's response to therapy. Poor perception of the severity of asthma symptoms on the part of the patient and health care professional may be a major factor causing delay in treatment and thus may contribute to increased morbidity and mortality from asthma exacerbations[8]. Patients who have access to peak expiratory flow (PEF) information may use their medication less frequently and more appropriately. Measurement of lung function for monitoring asthma is analogous to measurement in other chronic diseases. For example, blood pressure measurements with a sphygmomanometer are used for monitoring hypertension, and blood glucose measurements with reagent strips or digital read-out meters are used for monitoring diabetes.

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Spirometry is recommended in the initial assessment of most patients with suspected asthma and periodically in selected patients to confirm home PEF measurements made with a peak flow meter. Subsequent measurement of PEF may be sufficient in most cases as the minimum objective parameter to follow in assessing symptoms and making therapeutic recommendations, when such recommendations depend on the severity of airflow limitation. For individual cases with complex questions related to their pulmonary function, periodic assessment in a specialized pulmonary testing facility should be considered.

PEF monitoring is an important clinical tool in the office, emergency department, and hospital and is useful in the home. It is valuable to assess severity, assess degree of diurnal variation in lung function, monitor response to therapy during an acute exacerbation, detect asymptomatic deterioration of lung function in the home and office and intervene before it becomes more serious, monitor response to chronic therapy, provide objective justification for therapy to the patient, and identify triggers, including occupational sensitizers[9]. Regular measurement of PEF in the health care professional's office is recommended. Monitoring PEF during the assessment of acute exacerbations in the health care professional's office or emergency department is essential.

Daily or twice daily PEF home monitoring by the patient is indicated in the initial assessment of the severity of the asthma and the response to therapy. Regular PEF home monitoring for several months or years may be especially useful to patients over 5 years of age with persistent asthma, but might not be necessary for many patients. When priorities have to be set because of a shortage of PEF meters, continued home monitoring beyond initial assessment is particularly recommended for patients who have been hospitalized and for patients who are poor perceivers of their airflow limitation, i.e., they have difficulty recognizing early symptoms and are thus at increased risk for life-threatening asthma exacerbations. These patients might be identified during the initial monitoring and assessment period and by observing their perception of the severity of an acute exacerbation.

Measurement of PEF

Most adults, as well as children as young as 5 years of age, usually can perform a PEF measurement. The effort required to produce the measurement is a full inspiration to total lung capacity followed by a short maximal exhalation in a standing position. Because PEF measurement is effort dependent, patients need to be coached initially to give their best effort. For both spirometry and PEF measurements, it is essential to use correct techniques and equipment[9-14].

Ideally, PEF measurements should be taken twice daily, immediately upon arising and 10 to 12 hours later, before and after using a bronchodilator if a bronchodilator is needed. If PEF measurements are taken only once daily, they should be done in the morning upon arising and consistently before using a bronchodilator, if a bronchodilator is needed. A few patients will not comply, or their asthma will become extremely stable, and they may prefer to perform PEF measurements intermittently. Although this method loses the benefit of detecting early deterioration in lung function, it still provides important information about variability. If PEF is being measured only 2 or 3 times a week, it is best to do both a morning and an evening reading on the same day and consistently either before or after using a bronchodilator, if a bronchodilator is taken, so that any variation greater than 20 percent (which indicates worsening of asthma) can be detected.

Interpreting PEF measurements. Predicted values of PEF are corrected for height, sex, race, and age, and normal limits of diurnal (or circadian) variability are available in the literature[15-18]. However, in many patients, PEF values are consistently higher or lower than the average predicted values. It is recommended that PEF objectives for therapy be based on each patient's personal best and daily variability rather than on a percent of normal predicted value, particularly for patients with chronically impaired lung function.

Establishing personal best values and minimum diurnal variability when the patient is under effective treatment is important. During a monitoring period of 2 to 3 weeks, the patient should record PEF measurements at least twice a day. On both occasions the patient should measure the PEF three times and note the highest number. If the patient takes a bronchodilator, then PEF should be measured before and after using the bronchodilator. The personal best is the highest PEF measurement achieved when the patient's asthma is under control. If the patient's highest value during the monitoring period is less than 80 percent of predicted value after taking a bronchodilator (if the patient takes a bronchodilator), or daily variability is more than 20 percent again after taking a bronchodilator, more aggressive therapy and continued daily monitoring are indicated. A course of oral steroids in the initial evaluation period may be needed to establish personal best and minimum PEF daily variability.

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The variability of PEF provides a reasonable index of asthma stability and severity. One method of describing diurnal PEF variability is as the amplitude (the difference between the prebronchodilator morning value and the postbronchodilator value from the evening before) expressed as a percentage of the mean daily PEF value[18]. Another method is the minimum morning prebronchodilator PEF over 1 week, expressed as a percent of the recent best (Min%Max)[19] (**Figure 5-3**). This latter method has been suggested to be the best PEF index of airway lability because it requires only a once-daily reading, it correlates better than any other index with airway hyperresponsiveness, and the calculation is simple.

Using PEF measurements to manage asthma. To help patients manage their asthma at home, a system of PEF zones can be used[20]. This system correlates PEF measurements and variability with appropriate levels of medication to control asthma. The specific zones are established as a function of the individual's personal best or predicted value, whichever is highest, and/or daily variability. The emphasis is not on an isolated reading but rather on the variability from the patient's personal best or from one reading to the next.

Supervising home PEF monitoring. Several elements appear to be essential for the successful integration of home peak expiratory flow monitoring into the treatment plan. The following guidelines should be used:

- Educate the patient and family about the purpose and technique of home monitoring. Education should include:
  - How and when to use the peak flow meter
  - How to record PEF measurements in a diary
  - How to interpret the measurements
  - How to respond to change
  - What information to communicate to the health care professional (including emergency department health care professionals).
- Explain how the health care professional uses the home PEF data to choose and evaluate treatment.

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PART 3: AVOID EXPOSURE TO RISK FACTORS

KEY POINTS:

- Although pharmacological intervention to treat established asthma is highly effective in controlling symptoms and improving quality of life, every attention should be given to measures to prevent this chronic, lifelong, and incurable disease.
- Asthma exacerbations may be caused by a variety of risk factors including allergens, pollutants, foods, and drugs. Tertiary prevention aims to reduce the exposure to these risk factors to improve the control of asthma and reduce medication needs.

Although pharmacological intervention to treat established asthma is highly effective in controlling symptoms and improving quality of life, every attention should be given to measures to prevent this chronic, lifelong, and incurable disease. Three levels of prevention have been described and, in relation to asthma, include the following[21]:

Primary prevention is introduced before exposure to risk factors known to be associated with a disease. The goal is to prevent the onset of disease in susceptible (at-risk) individuals. This is not yet possible in asthma. Increasing evidence indicates that allergic sensitization is the most common precursor to the development of asthma. Since sensitization can occur antenatally[22,23], much of the focus of primary prevention will likely be on perinatal interventions.

Secondary prevention is employed after primary sensitization to allergen(s) has occurred, but before there is any evidence of disease. The aim is to prevent the establishment of chronic, persistent disease in people who are susceptible and who have early signs of the disease. This is currently being investigated in asthma. Secondary prevention of asthma is likely to focus very specifically on the first year or two of life.

Tertiary prevention involves avoidance of allergens and nonspecific triggers when asthma is established. The goal is to prevent exacerbations or illness that would otherwise occur with exposure to identified allergens or irritants. It is considered that tertiary prevention should be introduced when the first signs of asthma have occurred. However, increasing evidence would suggest that the histopathology of the disease is fully established by the time asthma symptoms occur[24].

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A prerequisite for establishing any form of preventive strategy is to have reliable markers that predict the progression of a disease, but to date there are no such markers available for asthma. At all levels of prevention, many of the issues remain speculative and have yet to be put to the test in proper long-term controlled clinical studies, though many such studies are in progress.

PRIMARY PREVENTION

It is clear from the development of immune responsiveness that future strategies for primary prevention of asthma will concentrate on the prenatal and perinatal periods. A number of factors have been shown to either increase or decrease the likelihood of fetal sensitization to allergens, but the influence of these factors is complex and varies with gestational age. Primary prevention of asthma is not yet possible, but promising leads are being actively investigated.

Potential Measures to be Applied Prenatally

In the second trimester of pregnancy, when antigen-presenting-cell and T-cell maturity is sufficient for allergen sensitization to occur, the most likely route of fetal sensitization is via the gut, although the concentration of allergen able to penetrate the amnion may be critical. Paradoxically, low-dose allergen exposure may be more likely to result in sensitization than high-dose exposure[25]. Thus, there is considerable concern that there is insufficient information on the critical doses and timing of exposure that might be associated with the development of either sensitization or tolerance. Indeed, there is even limited evidence to suggest that high-dose exposure will induce IgG antibody production in the mother and thereby reduce the possibility of allergy developing in the offspring. High cord blood IgG concentrations of antibodies to cat dander and the major allergen of birch pollen have been associated with fewer allergic symptoms in children during the first 8 years of life[26]. One study has shown reduced allergic sensitization in children of mothers who received specific immunotherapy during pregnancy[27].

Prescription of a food-allergen-avoidance diet to a high-risk woman during pregnancy is unlikely to reduce substantially her risk of giving birth to an atopic child[28]. Moreover, such a diet may have an adverse effect on maternal and/or fetal nutrition.

In summary, there are no measures applied prenatally that can be recommended at this time for primary prevention.

Potential Measures To Be Applied Postnatally

Early efforts at allergen avoidance have focused on infant feeding and, in particular, early avoidance of cow's milk protein and sometimes eggs, fish, and nuts. Most studies have commenced avoidance in the postnatal period, and results have been inconclusive. The two studies[29,30] that have had the longest followup have both identified a transient effect of avoidance on reducing food allergy and atopic dermatitis. Continued followup has shown a diminishing and eventually no effect on allergic manifestations in the respiratory tract. The conclusion from one of these studies was that the effort required for an allergen-avoidance diet was not justified by the outcome[30]. Furthermore, there is at least limited evidence that early dietary manipulation may create a risk of impaired growth. Therefore, great caution is required in employing such approaches[31].

Prescription of an antigen-avoidance diet to a high-risk woman during lactation may substantially reduce her child's risk of developing atopic eczema, but better trials are needed[32] (**Evidence C**).

Aeroallergen avoidance has been promoted in order to avoid sensitization, and a correlation between the level of allergen exposure in infants and sensitization to allergens has been shown in some[33] but not all[34] studies. Moreover, recent studies suggest that, contrary to previously published results, avoidance of early exposure to cats does not prevent allergy[35,36], and that early contact with cats and dogs may in fact prevent allergy more effectively than avoidance of these animals[37,38].

These controversial results have led to the suggestion that, in the future, primary prevention strategies will be designed to redirect the newborn infant's immune response toward a Th1, nonallergic response. Efforts to establish a proper Th1/Th2 balance might be achieved by high-dose exposure to relevant allergens (as distinct from the normal low-dose exposure) and by the utilization of fusion proteins combining allergen and cytokines such as IL-12[39]. These approaches have gained considerable credibility in relation to the "hygiene hypothesis," which has identified associations between early microbial experience and subsequent reduced allergic disease[40].

Young children with older siblings and those who attend day care are at increased risk for infections, which in turn may protect against the development of allergic diseases, including asthma[41]. Repeated viral infections other than lower respiratory tract infections early in life may reduce the risk of developing asthma up to school age[42]. There are some specific infections that may have an asthma-

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promoting role. Respiratory syncytial virus (RSV) bronchiolitis has been clearly associated with a higher prevalence of recurrent wheezing disorders, although it is controversial whether this is associated with a greater risk of allergic sensitization[43]. Thus, one unresolved issue is whether RSV actually predisposes to allergic diseases or whether atopic individuals are more likely to get severe RSV bronchiolitis.

Rather than focusing on active infection to modify outcomes, it is perhaps more appropriate to consider the infant's gut colonization by microbial flora[44]. It has been shown that in countries with a low prevalence of atopy (e.g., Estonia), there are very different intestinal bacteria than in countries with a higher atopic disease prevalence (e.g., Sweden)[45]. A study on probiotics administered perinatally showed that, although the occurrence of atopic dermatitis was halved in the group of subjects receiving probiotics, there was no change in overall allergic sensitization[46].

In summary, the most promising opportunities for primary prevention to be applied postnatally will be immunomodulation using Th1 immunoadjuvants, DNA vaccines, antigen in association with IL-12 or IFN-γ, or oral administration of relevant gut microorganisms. However, all of these strategies currently remain in the realm of hypothesis and require appropriate investigation.

Environmental Tobacco Smoke

No discussion of the primary prevention of asthma would be complete without considering the impact of environmental tobacco smoke. The health effects of passive smoking have been extensively reviewed[47,48]. The data related to parental smoking and lower respiratory illness in exposed children up to 3 years of age indicate a direct causal relationship between these factors. However, it is impossible to distinguish the independent contributions of prenatal and postnatal maternal smoking[49]. In-depth studies of lung function immediately after birth have shown that maternal smoking during pregnancy has an influence on lung development[50]. Further, infants of smoking mothers are 4 times more likely to develop wheezing illnesses in the first year of life[51]. In contrast, there is little evidence (based on meta-analysis) that maternal smoking during pregnancy has an effect on allergic sensitization[48]. Thus, smoking during pregnancy has an impact on lung development, which increases the frequency of nonallergic wheezing illnesses in infancy, but has less impact on later allergic asthma. Overall, these observations are sufficient to make the very firm conclusion that environmental tobacco smoke exposure both prenatally and postnatally has an adverse influence on wheezing illnesses (**Evidence A**).

SECONDARY PREVENTION

Once allergic sensitization has occurred, there are additional opportunities to prevent the actual development of asthma. Two studies have suggested that pharmacologic intervention with H1 antihistamines may reduce the onset of wheezing in young children who present initially with atopic dermatitis[52,53]. However, these studies need confirmation before it can be proposed that this class of compounds can prevent the onset of asthma. An older study found that allergen-specific immunotherapy may reduce the onset of asthma[54]. The Preventive Allergy Treatment (PAT) Study results indicate that immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis[620].

Observations of occupational allergy suggest that early cessation of exposure to an offending allergen, after there is evidence of sensitization and symptoms, is more likely to lead to a total resolution of symptoms than if the exposure continues.

TERTIARY PREVENTION

Asthma exacerbations may be caused by a variety of triggers including allergens, pollutants, foods, and drugs. Tertiary prevention aims to reduce the exposure to these triggers to improve the control of asthma and reduce medication needs.

Avoidance of Indoor Allergens

The occurrence and severity of asthma symptoms are related to environmental allergens[55]. Thus, indoor environmental control measures to reduce exposure to allergens might be important, although it is difficult to achieve complete control, and there is conflicting evidence about whether such control measures are effective at reducing asthma symptoms[56,57]. The majority of single interventions have failed to achieve a sufficient reduction in allergen load to lead to a clinical improvement. It is likely that no single intervention will achieve sufficient benefits to be cost effective. However, properly powered and designed studies of combined allergen-reduction strategies in large groups of patients are urgently required[58].

The effectiveness of allergen reduction in the treatment of asthma was first suggested by studies in which patients were removed from their homes to a low-allergen environment at high altitude[59,60]. However, the real challenge is to create a low-allergen environment in patients' homes. Effective control strategies should be

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Figure 7-1. Measures that Have Been Used to Reduce Exposure to Domestic Dust Mite Allergens

- Encase mattress, pillow, and quilt in impermeable covers[63,64].
- Wash all bedding in the hot cycle (55-60°C) weekly[73].
- Replace carpets with linoleum or wood flooring.
- Treat carpets with acaricides and/or tannic acid[74].
- Minimize upholstered furniture/replace with leather furniture.
- Keep dust-accumulating objects in closed cupboards.
- Use a vacuum cleaner with integral HEPA filter and double-thickness bags[75].
- Replace curtains with blinds or easily washable (hot cycle) curtains.
- Hot wash/freeze soft toys[76,77].

tailored to individual allergens, flexible to suit individual needs, and cost effective.

Among the wide variety of allergens that occur within human dwellings are domestic mites, animal allergens (furred animals), cockroach allergen, and fungi.

Domestic mites. Domestic mite allergy is a universal health problem[61]. Since mites live and thrive in many sites throughout the house, they are impossible to eradicate and difficult to reduce. No single measure is likely to reduce exposure to mite antigen but an integrated approach including barrier methods, dust removal, and reduction of microhabitats favorable to mites is recommended (**Evidence C**) (**Figure 7-1**).

Little is known about the influence of different types housing on mite populations. The introduction of blankets increases the number of mites in homes dramatically, and has been shown to be associated with the occurrence of asthma in adults, but not in children[62]. Carpets are also an important microhabitat, and a possible source of reinfestation of bedding. High levels of humidity are essential for mite population growth, and reducing humidity has been shown to be effective control method in some[65] but not all[66,67] studies. Some investigations have shown that use of mattress, pillow and duvet covers that are impermeable to mite allergens are effective[63,64] (**Evidence B**), but others have shown no effect of these measures in reducing symptoms in adults with asthma[663] or allergic rhinitis[664]. Other mite avoidance methods have been advocated (**Figure 7-1**), but for most their effect on symptoms has not been adequately tested. Due to the aerodynamic characteristics of mite allergens, air filtration units and ionizers are ineffective at reducing exposure.

Animal allergens. Furred, warm-blooded animals, including small rodents, produce dander, urine, and saliva that can cause allergic sensitization and subsequent

Figure 7-2. Measures for Reducing Exposure to Animal Allergens

- Keep the pet out of the main living areas and bedrooms[78].
- Install HEPA air cleaners in the main living areas and bedrooms.
- Have the pet washed twice a week[79], although some studies report this to be ineffective[80].
- Thoroughly clean upholstered furniture/replace with leather furniture.
- Replace carpets with linoleum or wood flooring.
- Use a vacuum cleaner with integral HEPA filter and double-thickness bags[81].

reactions. Complete avoidance of pet allergens is impossible, as the allergens are ubiquitous and can be found in many environments outside the home[69], including schools[70], public transportation, and even cat-free buildings[71]. Removal of such animals from the home is important, but even after permanent removal of the animal it can be many months before reservoir allergen levels decrease[72]. In patients who are allergic to cats or dogs and persist in keeping their pet, exposure-reduction measures listed in **Figure 7-2** may be considered. However, the clinical effectiveness of these measures remains unproven and there are many conflicting data on this subject.

Cockroach allergen. Cockroach infestation is an important cause of allergic sensitization, particularly in inner-city homes[82]. Avoidance measures for cockroaches include eliminating suitable environments (restricting havens by caulking and sealing cracks in the plaster work and flooring, controlling dampness, and reducing the availability of food), restricting access (sealing entry sources such as around paperwork and doors), chemical control (abamectin), and traps. However, these measures are only partially effective[83].

Fungi. The number of fungal spores can best be reduced by removing or cleaning mold-laden objects. Maintaining a low humidity (less than 50 percent) is important. Air conditioners and dehumidifiers reduce humidity and filter large fungal spores, lowering the mold and yeast count indoors, although their benefit in terms of reducing asthma symptoms is controversial. 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.

Avoidance of 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

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conditioning if possible. Some countries use radio, television, and the Internet to provide information on outdoor allergen levels. Knowledge of a patient's sensitivity to specific allergens may be useful for giving advice about the timing and location of the patient's travel.

Avoidance of Indoor Air Pollutants

The most important measure is to avoid passive and active smoking. Passive smoking increases the risk of allergic sensitization in children[48,84]. It also increases the frequency and severity of symptoms in children with asthma. Parents of children with asthma should be advised not to smoke and not to allow smoking in rooms their children use. Active cigarette smoking reduces treatment efficacy of inhaled and systemic glucocorticosteroids[621,665] (**Evidence B**) and smoking cessation needs to be vigorously encouraged.

The major indoor air pollutants are respirable particles, nitric oxide, nitrogen oxides, carbon monoxide, carbon dioxide, sulfur dioxide, formaldehyde, and biologicals such as endotoxin[31]. Preventing and controlling indoor air quality problems–except by cigarette smoke avoidance–can be expensive and time consuming, and the effectiveness of most control methods has not been adequately evaluated. The principal steps known to reduce exposure to respirable particles are avoiding cigarette and other tobacco smoke, venting all furnaces to the outdoors, and maintaining heating systems adequately. To reduce exposure to nitric oxide, nitrogen oxides, and carbon monoxide, all gas appliances should have sufficient flues or ducts. Adequate ventilation will decrease carbon dioxide concentration. Avoiding wood smoke, household sprays, and volatile organic compounds (e.g., polishes and cooking oils) is also important (**Evidence D**).

Avoidance of Outdoor Air Pollutants

Several studies have implicated various pollutants as aggravating asthma, mainly in controlled chamber exposure experiments. 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, weather and atmospheric conditions create a period of intense air pollution in a defined geographic area. Useful steps to consider for patients with asthma during such air pollution episodes include:

- Avoid unnecessary physical activity. Cold temperature and low humidity are additionally stressful to the patient with asthma who exercises under conditions of high air pollution.
- Avoid smoking and smoke-filled rooms.
- Avoid exposure to dust and other irritants such as hair spray, paint, exhaust fumes, or smoke from any fire.
- Avoid exposure to persons with respiratory infections.
- Try to stay indoors in a clean environment. Air conditioning and other filters may be helpful. When it is necessary to go outdoors, it is recommended to take a rapid-acting inhaled bronchodilator beforehand in order to prevent acute symptoms.
- If it appears that the air pollution episode will persist or worsen, it may be a good idea to leave the polluted area temporarily.
- The health care professional and patient should formulate special plans to be followed with regard to medication use.

Avoidance of Occupational Exposure

A large number of substances have been identified as occupational allergens and as risk factors that can cause asthma. Levels above which sensitization frequently occurs have been proposed for many chemicals. However, once a patient has been sensitized, the level of exposure necessary to induce symptoms may be extremely low, and resulting exacerbations may 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 or sensitizing substances. Prevention of latex allergy has been made possible by the production of hypoallergenic gloves, which are powder-free and have a lower allergen content[85,86]. Although more expensive than untreated gloves, they are cost effective. 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**).

Food Avoidance

Food allergy as an exacerbating factor for asthma is uncommon and occurs primarily in young children. Food avoidance should preferably not be recommended before a double-blind food challenge has been made. When the outcome of such a challenge is positive, food allergen avoidance can reduce asthma exacerbations.

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 and occasional deaths. They should

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be avoided by sensitive patients. Proof for the involvement of other dietary substances, including the yellow dye tartrazine, benzoate, and monosodium glutamate, is difficult to ascertain, and their role in exacerbating asthma is probably minimal. Confirmation of their relevance requires double-blind challenge before making specific dietary restrictions.

Avoidance of Certain Drugs

Some medications can exacerbate asthma. Aspirin and other nonsteroidal anti-inflammatory agents can cause severe exacerbations and should be avoided in patients with a history of reacting to these agents. Beta-blocker drugs administered orally or by eye drops may exacerbate bronchospasm and in general, should not be used by patients with asthma. If they are used, close medical supervision is essential. Avoidance of these drugs prevents exacerbations in susceptible patients.

Vaccination

Patients with moderate to severe asthma might be advised to receive an influenza vaccination every year[87,88]. The purification of the vaccine preparations has made adverse reactions to the vaccine less frequent. Inactivated influenza vaccine is safe to administer to adults and children with asthma, including those with severe asthma[622].

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PART 4A. ESTABLISH MEDICATION PLANS FOR LONG-TERM ASTHMA MANAGEMENT IN ADULTS

KEY POINTS:

- Preferred treatment recommendations in this report are based on efficacy and safety outcomes in populations. The response of individual patients may, of course, differ significantly from the mean response of the population. Decisions about treatment are often a compromise between what the physician recommends and what the patient is prepared to take.
- Medications for asthma can be administered in different ways, including inhaled, oral (ingested), and parenteral (subcutaneous, intramuscular, or intravenous). The major advantage of delivering drugs directly into the airways via inhalation is that high concentrations can be delivered more effectively to the airways, and systemic side effects are avoided or minimized.
- Although no cure for asthma has yet been found, it is reasonable to expect that in most patients with asthma, control of the disease can and should be achieved and maintained.
- Control of asthma can be achieved in many patients and can be defined as:
  - Minimal (ideally no) chronic symptoms, including nocturnal symptoms
  - Minimal (infrequent) exacerbations
  - No emergency visits
  - Minimal (ideally no) need for p.r.n. (as-needed) ß$_2$-agonist
  - No limitations on activities, including exercise
  - PEF circadian variation of less than 20 percent
  - (Near) normal PEF
  - Minimal (or no) adverse effects from medicine.
- Therapy should be selected on the basis of the severity of a patient's asthma, availability of anti-asthma medications, conditions of the health care system, and individual patient circumstances.
- For **intermittent asthma**, no daily medication is recommended for the vast majority of patients. Treatment of exacerbations should depend on the severity of the exacerbation. A rapid-acting inhaled β_2-agonist may be taken as needed to relieve asthma symptoms. The occasional patient with intermittent asthma, but severe exacerbations, should be treated as having moderate persistent asthma.
- Patients with **mild persistent asthma** require controller medication every day to achieve and maintain control of their asthma. Treatment with an inhaled glucocorticosteroid is preferred. Sustained-release theophylline, cromones, or a leukotriene modifier are other options.
- The preferred therapy for **moderate persistent asthma** is regular treatment with a combination of inhaled glucocorticosteroid and a long-acting inhaled β_2-agonist twice daily. Sustained-release theophylline or a leukotriene modifier are alternatives to the β_2-agonist in this combination therapy. An alternative to combination therapy is a higher dose of inhaled glucocorticosteroid.

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- The primary therapy for **severe persistent asthma** includes inhaled glucocorticosteroid at higher doses plus a long-acting inhaled β_2-agonist twice daily. Alternatives to the long-acting inhaled β_2-agonist for add-on treatment are an oral sustained-release theophylline, leukotriene modifier, or oral β_2-agonist. These drugs may also be added to the combination of high-dose inhaled glucocorticosteroid and long-acting inhaled β_2-agonist if necessary.

- Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.

This section focuses on general aspects of the pharmacological treatment of asthma and on the long-term management of asthma in adults. A separate section discusses the management of asthma in children.

THE MEDICATIONS

Medications for asthma are used to reverse and prevent symptoms and airflow limitation and include controllers and relievers.

Controllers are medications taken daily on a long-term basis that are useful in getting and keeping persistent asthma under control. Controllers have been variably labeled as prophylactic, preventive, or maintenance medications and include anti-inflammatory agents and long-acting bronchodilators. Of all single medications, inhaled glucocorticosteroids are at present the most effective controllers. The so-called "antiallergic" agents may also be controllers, although there are insufficient data about their efficacy in the long-term management of asthma. It must be stressed that few clinical studies have addressed the question of how effective any of the anti-asthma medications are in getting asthma under complete control and in preventing symptoms and exacerbations.

Most studies have examined the effect of medications on one or more of the parameters of asthma control, for example, on reduction in the frequency of exacerbations, reduction in chronic symptoms, improvement in lung function, decreases in airway hyperresponsiveness, and improvement in the patient's quality of life[623]. Inhaled glucocorticosteroids suppress airway inflammation, reduce airway hyperresponsiveness, and control and prevent asthma symptoms[1,89-91]. Bronchodilators act principally to dilate the airways by relaxing airway smooth muscle. They reverse and/or inhibit bronchoconstriction and related symptoms of acute asthma, but do not reverse airway inflammation or reduce airway hyperresponsiveness[92,93]. Several long-term clinical studies have shown that treatment with anti-inflammatory agents is more effective than treatment with bronchodilators for long-term control of symptoms, improvement of lung function, and decrease of airway responsiveness[1,2,93-97].

Relievers include rapid-acting bronchodilators that act to relieve bronchoconstriction and its accompanying acute symptoms such as wheezing, chest tightness, and cough. Relievers have been variably labeled as quick-relief medicine or rescue medicine.

This section presents an overview of the characteristics of different controller and reliever medications. Some clinical studies have shown a substantial heterogeneity in individual patient responses to antiasthma medications[98]. However, the concepts of "responder" and "non-responder" developed in these studies are very often based on a single outcome measure such as morning PEF or FEV_1. Future developments in pharmacogenomics may result in asthma therapy that is more tailored to each patient's response to specific medications[99]. Further studies are needed before the current, empirical approach can be replaced by treatment selected on the basis of specific genotypes. Thus, the preferred treatment recommendations in this section are based on efficacy and safety outcomes in populations. The response of an individual patient to a given treatment may, of course, differ significantly from the population mean. Decisions about treatment are often a compromise between what the physician recommends and what the patient is prepared to take.

Route of Administration

Medications for asthma can be administered via different ways, including inhaled, oral (ingested), and parenteral (subcutaneous, intramuscular, or intravenous). The major advantage of delivering drugs directly into the airways via inhalation is that high concentrations can be delivered more effectively to the airways, and systemic side effects are avoided or minimized. Some of the drugs that are effective in asthma can only be used via inhalation because they are not absorbed when given orally (e.g., anticholinergics and cromones). The onset of action of bronchodilators is substantially quicker when they are given via inhalation than when these drugs are administered orally[100,101].

Aerosolized medications that are used to treat asthma are available as pressurized metered-dose inhalers (MDIs), breath-actuated MDIs, dry powder inhalers (DPIs), and

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nebulized or "wet" aerosols. Patients should be instructed in the use of the inhaler device, and their technique should be checked regularly. Inhaled asthma medications can be given either singly or in combination inhalers, the latter of which most often contain a glucocorticosteroid and a bronchodilator.

The disadvantage of pressurized MDI therapy is that training and skill are required to coordinate activation of the inhaler and the inhalation. The use of a spacer (holding chamber) improves drug delivery from an MDI (**Evidence A**)[102]. The spacer device allows discharge of the drug into a chamber where particles of medications are held in suspension for 10 to 30 seconds[103]. During this time, the patient can inhale the drug. Spacers also reduce deposition in the mouth and oropharynx, decreasing cough as well as the possibility of oral candidiasis when used to deliver glucocorticosteroids (**Evidence A**). Further, the use of spacers for the delivery of inhaled glucocorticosteroids decreases their systemic bioavailability and the risk of systemic side effects[104] (**Evidence B**). Some studies suggest that high doses of rapid-acting inhaled β_2-agonists administered from MDIs using spacer devices achieve bronchodilatation equivalent to that effected by nebulization in treating severe exacerbations[105,106]. A systematic review comparing MDI-plus-spacer versus wet-nebulizer delivery of high-dose rapid-acting inhaled β_2-agonists in patients with severe acute exacerbations of asthma showed these two delivery systems lead to equivalent clinical outcomes in adults but the MDI-plus-spacer system yields better clinical outcomes in children[102] (**Evidence B**). Breath-actuated aerosols may be helpful for patients who have difficulty using the pressurized MDI[107].

DPIs do not utilize freon propellants. They require an inhalation technique that is different from the MDI technique, and are generally easier to use. A minimal inspiratory flow rate is necessary to inhale from a DPI, and thus the DPI may be difficult for some patients to use during an exacerbation. The dosage should be adjusted to ensure adequate drug delivery at the inspiratory flow rate that patients can achieve. Some DPIs deliver pure drug, while others deliver the drug mixed with a filler (such as lactose), and thus the dosage should also take into account the fact that different DPIs yield different drug delivery to the lung. The dose of therapy may need to be adjusted when switching from an MDI to a DPI[108]. DPIs are more ecological than MDIs because they do not utilize chlorofluorocarbons (CFCs), but storage of some dry powder formulations may be more difficult in humid climates.

The CFCs in MDIs are now being replaced by hydrofluoroalkanes (HFAs)and the medication insert for dosage of the HFA preparations should be carefully reviewed by the clinician[109]. For bronchodilators the doses from CFC and HFA inhalers appear to be equivalent[109]. However, for some glucocorticosteroids the HFA formulations, which deliver a greater fraction of smaller particles to the lung, may result in both greater efficacy and greater systemic effects[110,111,624,666].

The therapeutic ratio is the relationship between the clinical and systemic effects of a given drug. This ratio is the only meaningful parameter to use for comparisons of different drugs or inhalers; for example increased lung deposition of an inhaled drug is normally associated with an increase in clinical effect until a plateau of the dose-response curve is reached so an inhaler that delivers 50% of the delivered dose to the intrapulmonary airways will normally have a greater clinical effect than an inhaler that delivers 10% to the lungs. On the other hand the drug has to be absorbed from the airway lumen to produce a clinical effect and all drug that is absorbed from the airway lumen subsequently goes into the systemic circulation. Therefore, a higher lung deposition of drug is often also associated with greater systemic effects, which often parallel the increase in clinical effect. So, a higher lung deposition normally allows the use of lower doses, but often does not change the relationship between clinical and systemic effects (the therapeutic ratio) for a given drug. The same considerations are normally true for increases in drug potency and receptor affinity.

- *Improved therapeutic ratio*: Increase in clinical effect is greater than the increase in systemic effects.
- *Reduced therapeutic ratio*: Increase in systemic effects is greater than the increase in clinical effects
- *Unchanged therapeutic ratio*: Increase in clinical effect is paralleled by an increase in systemic effects.

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Controller Medications

Controller medications–medications used daily on a long-term basis to achieve and maintain control of persistent asthma–include inhaled glucocorticosteroids, systemic glucocorticosteroids, sodium cromoglycate (cromolyn sodium), nedocromil sodium, sustained-release theophylline, long-acting inhaled β_2-agonists, long-acting oral β_2-agonists, leukotriene modifiers, and systemic steroid-sparing therapies. Inhaled glucocorticosteroids are at present the most effective controller medications.

Inhaled glucocorticosteroids.

• *Mode of administration*–Inhaled.

• *Mechanisms of action*–Several studies have demonstrated that treatment with inhaled glucocorticosteroids for 1 month or more significantly reduces the pathological signs of airway inflammation in

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Figure 7-3. Estimated Comparative Daily Dosage for Inhaled Glucocorticosteroids

Drug	Low Daily Dose (μg)		Medium Daily Dose (μg)		High Daily Dose (μg)	
	Adult	Child	Adult	Child	Adult	Child
Beclomethasone-CFC	200-500	100-250	500-1000	250-500	>1000	>500
Beclomethasone-HFA	100-250	50-200	250-500	200-400	>500	>400
Budesonide-DPI	200-600	100-200	600-1000	200-600	>1000	>600
Budesonide-Neb Inhalation suspension	200-500	100-250	250-500	250-500		>1000
Flunisolde	500-1000	500-750	1000-2000	750-1250	>2000	>1250
Fluticasone	100-250	100-200	250-500	200-400	>500	>400
Mometasone furoate	200-400		400-800		>800	
Triamcinolone acetonide	400-1000	400-800	1000-2000	800-1200	>2000	>1200

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 several clinical parameters and adjust the dose accordingly. The stepwise approach to therapy emphasizes that 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.
- As CFC preparations are taken from the market, medication inserts for HFA preparations should be carefully reviewed by the clinician for the correct dosage level.

asthma[90-93,112]. Airway hyperresponsiveness continues to improve with prolonged treatment[2].

- *Role in therapy*–Glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of asthma. Studies have demonstrated their efficacy in improving lung function, decreasing airway hyperresponsiveness[113], reducing symptoms, reducing frequency and severity of exacerbations, and improving quality of life[1,89-91,114] (**Evidence A**). Inhaled glucocorticosteroids are the preferred treatment for patients with persistent asthma at all levels of severity[667].

  Glucocorticosteroids differ in potency and bioavailability after inhalation, but relatively few studies have examined these differences. Dose comparison of glucocorticosteroids is difficult due to their long time course of action and the relative flatness of their dose-response curves. **Figure 7-3** lists approximately equipotent doses of different inhaled glucocorticosteroids administered via different inhalation devices[20]. A dose of 500 μg beclomethasone dipropionate (BDP) or equivalent daily controls asthma in the majority of patients. Because the dose-response curve of inhaled glucocorticosteroids is relatively flat for a number of outcome measures in asthma (e.g., symptoms, lung function measurements, airway responsiveness), going to a high dose of inhaled glucocorticosteroid provides little further benefit in terms of asthma control but increases the risk of side effects[115,625,668]. Add-on therapy with another class of controller is preferred over increasing the dose of inhaled glucocorticosteroids (**Evidence A**). There is, however, a clear relationship between the dose of inhaled glucocorticosteroids and the prevention of severe acute exacerbations of asthma[116]. Therefore, some patients with severe asthma may benefit from long-term treatment with higher doses of inhaled glucocorticosteroids, which allow the decrease or withdrawal of oral glucocorticosteroids in these patients. The safety profile of higher doses of inhaled glucocorticosteroids is clearly better than that of oral glucocorticosteroids[117,118].

- *Side effects*–Local adverse effects from inhaled glucocorticosteroids include oropharyngeal candidiasis, dysphonia, and occasional coughing from upper airway irritation. These effects may be prevented by use of spacer devices[119], gargling (and spitting out) with water, or gargling with a 1:50 dilution of amphotericin B[669].

  All inhaled glucocorticosteroids currently available are absorbed from the lung, so there is inevitably some systemic absorption. The risk of systemic adverse effects from inhaled glucocorticosteroids depends on the dose and the potency of the glucocorticosteroid as well as its bioavailability, absorption in the gut, first-pass metabolism in the liver, and the half-life of its systemically absorbed (from lung and possibly gut) fraction[120]. The systemic effects will therefore differ among the various in-

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haled glucocorticosteroids. Several comparative studies have demonstrated that budesonide and fluticasone propionate (FP) have less systemic effect than BDP and triamcinolone[89,120,121]. The risk of systemic effects also depends on the delivery system; use of spacers decreases the systemic bioavailability and the risk of systemic side effects for most glucocorticosteroids[122].

Controlled clinical trials have demonstrated that long-term treatment with high doses of inhaled glucocorticosteroids may be associated with systemic effects, including skin thinning and easy bruising[123,124], adrenal suppression[104,120], and decreased bone mineral density[125,126,626,627]. Inhaled glucocorticosteroids have also been associated with cataracts and glaucoma in cross-sectional studies[127,128], but there is no evidence of post-capsular cataracts in prospective studies[129-131]. The clinical significance of the adrenal suppression or the decrease in osteoblast activity during treatment with high doses of inhaled glucocorticosteroids is not yet known. One difficulty in establishing this clinical significance 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 supports the use of prophylactic treatment for osteoporosis in patients on inhaled glucocortiocosteroids. There are no data in malnourished populations on the possible effects of inhaled glucocorticosteroids on pulmonary tuberculosis or on calcium metabolism and bone density. The influence of inhaled glucocorticosteroids on growth is discussed in Chapter 7.4B, Establish Medication Plans for Long-Term Asthma Management in Infants and Children.

Current evidence suggests that in adults systemic effects of inhaled glucocorticosteroids are not a problem at doses of 500 μg or less BDP or equivalent daily, but some patients may be susceptible to systemic effects at lower doses. Inhaled glucocorticosteroids are effective controllers, and their use in the treatment of persistent asthma should be balanced against the possible risk of systemic effects. The risks of uncontrolled asthma should be weighed against the (probably limited) risk of this form of treatment.

Systemic glucocorticosteroids.

- *Mode of administration*–Oral (ingested) or parenteral.

- *Mechanisms of action*–The proposed mechanisms of action are the same as for inhaled glucocorticosteroids. However, systemic glucocorticosteroids may reach different target cells than inhaled glucocorticosteroids.

- *Role in therapy*–Long-term oral glucocorticosteroid therapy (daily or alternate-day) may be required to control severe persistent asthma, but its use is limited by the risk of significant adverse effects. Note that the therapeutic index (effect/side effect) of long-term inhaled glucocorticosteroids is always better than any form of long-term oral or parenteral glucocorticosteroid therapy in asthma[117,118]. Inhaled glucocorticosteroids are more effective than alternate-day oral glucocorticosteroids[117].

  If oral glucocorticosteroids have to be administered on a long-term basis, then attention should be paid to measures that minimize the systemic side effects. Oral preparations are preferred over parenteral for long-term therapy. Oral glucocorticosteroids such as prednisone, prednisolone, or methylprednisolone are preferred because of their minimal mineralocorticoid effect, their relatively short half-life, and their limited effects on striated muscle. The short half-life allows their use on an alternate-day schedule. Whenever possible, long-term therapy with oral glucocorticosteroids should be given once in the morning every day or every other day[117,132]. This generally allows sufficient control of the asthma and minimizes the systemic side effects. Some patients with very severe asthma may need daily and even twice-daily therapy with oral glucocorticosteroids.

- *Side effects*–The systemic side effects of long-term oral or parenteral glucocorticosteroid treatment include osteoporosis, arterial hypertension, diabetes, hypothalamic-pituitary-adrenal axis suppression, cataracts, glaucoma, obesity, 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[133,134].

  Although it is rare, adrenal failure may occur when a patient is withdrawn from long-term suppressive doses of oral glucocorticosteroids. Any such withdrawal should thus be observed for clinical and laboratory evidence of adrenal insufficiency. Withdrawal of oral glucocorticosteroids can also unmask underlying disease, such as Churg-Strauss Syndrome[135].

  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. If radiological signs of healed pulmonary tuberculosis are present in a patient who is taking long-term oral glucocorticosteroid therapy for asthma, and the patient has never been treated with

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effective antituberculosis drugs, then the patient should also be given chemoprophylaxis with isoniazid.

Fatal herpes virus infections have been reported among patients who are exposed to these viruses while taking systemic glucocorticosteroids, even short bursts. If a patient is exposed to varicella, the following actions should be considered: discontinue the systemic glucocorticosteroids, give the patient anti-zoster immunoglobulin, and consider acyclovir therapy if the patient develops progressive varicella[136,137]. Oral glucocorticosteroids also make patients more susceptible to herpes zoster infections, and the same steps should be taken as for the generalized varicella if the patient develops the infection.

Cromones: sodium cromoglycate and nedocromil sodium.

• Mode of administration–*Inhaled.*

• *Mechanisms of action*–The exact mechanisms of action of sodium cromoglycate and the related cromone nedocromil sodium are not fully understood, although these nonsteroidal anti-inflammatory medications partly inhibit the IgE-mediated mediator release from human mast cells in a dose-dependent way, and they have a cell-selective and mediator-selective suppressive effect on other inflammatory cells (macrophages, eosinophils, monocytes). There is some evidence that these medications inhibit a chloride channel on target cells[138]. The long-term effects of sodium cromoglycate on the chronic inflammatory changes in patients with asthma have not been directly demonstrated, except for one study in which prolonged treatment with sodium cromoglycate was associated with a significant decrease in the percentage of bronchial lavage eosinophils[139]. No long-term effect of nedocromil sodium on the chronic inflammatory changes in asthma has yet been demonstrated[140].

• *Role in therapy*–Sodium cromoglycate or nedocromil sodium may be used as controller therapy in mild persistent asthma. Administered prophylactically, these medications inhibit early- and late-phase allergen-induced airflow limitation and acute airflow limitation after exposure to exercise, cold dry air, and sulfur dioxide. Sodium cromoglycate reduces symptoms and the frequency of exacerbations[141], but studies have only inconsistently shown a benefit on nonspecific airway hyperresponsiveness. In adult patients with asthma, clinical trials show that nedocromil sodium improves symptoms and lung function, and reduces nonspecific airway responsiveness[142], although it is less effective than inhaled glucocorticosteroids[143] (**Evidence B**).

There is insufficient knowledge about the mechanisms of action to predict which patients will benefit from cromones; a 4- to 6-week therapeutic trial may be required to determine efficacy in individual patients.

• *Side effects*–Sodium cromoglycate and nedocromil sodium produce only minimal side effects, such as occasional coughing upon inhalation of the powder formulation. Some patients find the taste of nedocromil sodium unpleasant.

Methylxanthines.

• *Mode of administration*–Oral (ingested).

• *Mechanisms of action*–Theophylline is a bronchodilator that may have extrapulmonary effects, including anti-inflammatory effects[144]. The bronchodilator effect of theophylline may be related to phosphodiesterase inhibition and is seen at high concentrations (>10 mg/l), whereas the anti-inflammatory effect is due to an unknown mechanism and may occur at lower concentrations (5-10 mg/l). At low doses theophylline has some minor influence on chronic airway inflammation in asthma[145,146]. Most studies show little or no effect on airway hyperresponsiveness.

• *Role in therapy*–Sustained-release theophylline and aminophylline can be used as controller medications in asthma. Many clinical studies have shown that long-term treatment with sustained-release theophylline is effective in controlling asthma symptoms and improving lung function. When given as a sustained-release preparation, it has a long duration of action and is thus useful in the control of nocturnal symptoms that persist despite the regular treatment with anti-inflammatory therapy[147]. Theophylline is also useful as an additional bronchodilator in patients with severe asthma[148]. Now that theophylline at low doses has been shown to be effective in asthma control in both adults and children, it may be used in patients with milder disease and as an add-on therapy to low or high doses of inhaled glucocorticosteroids when further asthma control is needed[149-153] (**Evidence B**). As add-on therapy, theophylline is less effective than long-acting inhaled β_2-agonists[154,155] (**Evidence A**). It is, however, a less expensive option.

Due to the risk of adverse effects, and the difficulty of monitoring therapy (see discussion of side effects below), theophylline is regarded in some countries as a therapy that should be reserved for use after inhaled glucocorticosteroids and inhaled β_2-agonists fail to

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Figure 7-4. Onset and Duration of Action of Inhaled β_2-Agonists

Onset of Action	Duration of Action	
	Short	Long
Rapid	Fenoterol Pirbuterol Procaterol Salbutamol (Albuterol) Terbutaline	Formoterol
Slow		Salmeterol

achieve therapeutic goals. In other countries, theophylline is recommended earlier in the course of daily long-term therapy because it is a bronchodilator useful for the control of asthma, especially of nocturnal asthma symptoms, and it is inexpensive.

- *Side effects*–At higher doses (10 mg/kg body weight/day or more), theophylline has the potential for significant adverse effects, although these can generally be avoided by appropriate dosing and monitoring. The signs and symptoms of theophylline intoxication involve many different organ systems. Gastrointestinal symptoms, nausea, and vomiting are the most common early events. However, theophylline intoxication in children and adults can result in seizures and even death, and these events may not be preceded by evidence of central nervous system stimulation. Cardiopulmonary effects include tachycardia, arrhythmias, and, occasionally, stimulation of the respiratory center.

  Generally, serious toxic effects do not occur at serum concentrations below 15 µg per ml. Individual patient needs will vary, but a general approach to dosing and monitoring is to aim for a steady-state serum concentration for theophylline of between 5 and 15 µg per ml (28 to 85 µM) during long-term theophylline treatment. Monitoring of serum concentrations is advised when high-dose theophylline therapy (10 mg/kg body weight/day or more) is started and at occasional intervals thereafter. Monitoring is also advised when a patient develops an adverse effect on the usual dose, when expected therapeutic aims are not achieved, and when conditions or concomitant medications known to alter theophylline metabolism exist. For example, febrile illness, pregnancy, and anti-tuberculosis medications[670] reduce blood levels while liver disease, congestive heart failure and use of certain drugs including cimetidine, certain quinolones and certain macrolides increase the risk of toxicity. Lower doses of theophylline are associated with less frequent side effects, and there is less need for measurement of plasma levels in patients on low-dose therapy (unless there are problems of side effects or lack of therapeutic effect).

Long-acting inhaled β_2-agonists.

Long-acting inhaled β_2-agonists, including formoterol and salmeterol, have a duration of action lasting more than 12 hours. (Most rapid-acting inhaled β_2-agonists have a 4- to 6-hour duration of action). **Figure 7-4** compares the onset and duration of action of various inhaled β_2-agonists.

- *Mode of administration*–Inhaled.

- *Mechanisms of action*–Long-acting inhaled β_2-agonists are bronchodilator medications with activity that persists for at least 12 hours. Like other β_2-agonists, they relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability, and may modulate mediator release from mast cells and basophils[156,157]. Biopsy studies show that the chronic airway inflammation in asthma is not increased by treatment with long-acting inhaled β_2-agonists[92,158]; in fact, a small anti-inflammatory effect has been reported with long-term use[159,160]. Therapy with long-acting inhaled β_2-agonists produces bronchodilation comparable to, or better than, oral therapy. Long-acting inhaled β_2-agonists also provide long-term (>12 hours) protection against bronchoconstrictor stimuli[161]. Clinical pharmacology studies have shown that the duration of the bronchoprotective effect provided by long-acting inhaled β_2-agonists decreases when these medications are used on a regular basis[162,163]. The clinical significance of these findings is still unclear however, as long-term clinical studies do not indicate any decrease in efficacy over time[182]. Formoterol is a full agonist at the β_2-receptor, while salmeterol is a partial agonist[164], but the clinical significance of this difference is unclear[628].

- *Role in therapy*–Long-acting inhaled β_2-agonists should be considered when standard introductory doses of inhaled glucocorticosteroids fail to achieve control of asthma before raising the dose of inhaled glucocorticosteroids (**Evidence A**). Because long-term treatment with long-acting inhaled β_2-agonists does not appear to influence the persistent inflammatory changes in asthma, this therapy should *always* be combined with inhaled glucocorticosteroids[96,97] (**Evidence A**). Addition of long-acting inhaled β_2-agonists to a daily regimen of inhaled glucocorticosteroids improves symptom scores, decreases nocturnal asthma, improves lung function, decreases the use of rapid-acting inhaled β_2-agonists[165-167], and reduces the number of exacerbations[165-167,116,168] (**Evidence A**).

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Several studies have now shown that adding a long-acting inhaled β_2-agonist (salmeterol or formoterol) in patients whose asthma is not controlled on either low or high doses of inhaled glucocorticosteroids results in better control of asthma (in terms of lung function and symptoms) than increasing the dose of inhaled glucocorticosteroids 2-fold or more[116,169,170,629] (**Evidence A**).

The greater efficacy of adding an inhaled long-acting β_2-agonist to an inhaled glucocorticosteroid than increasing the dose of inhaled glucocorticosteroids has led to the development of fixed combination inhalers (fluticasone propionate plus salmeterol, budesonide plus formoterol). Controlled studies have shown that delivering glucocorticosteroids and long-acting β_2-agonists together in a combination inhaler is as effective as giving each drug separately[182-184,671] (**Evidence B**). Use of this combination does not appear to be associated with masking or exacerbating airway inflammation[672] (**Evidence B**). Fixed combination inhalers are more convenient for patients, may increase compliance, ensure that the long-acting β_2-agonist is always accompanied by a glucocorticosteroid, and are usually less expensive than giving the two drugs separately.

Long-acting inhaled β_2-agonists may also be used to prevent exercise-induced bronchospasm and may provide longer protection than rapid-acting inhaled β_2-agonists[162]. 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[171,172], which may make formoterol suitable for symptom relief as well as symptom prevention, although its effectiveness and safety as rescue medication needs further study.

- *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. There is no evidence that long-acting inhaled β_2-agonists worsen exacerbations of asthma or the chronic airway inflammation in asthma[116,173,174].

Long-acting oral β_2-agonists.

Long acting oral β_2-agonists include slow-release formulations of salbutamol or terbutaline and bambuterol, a prodrug that is converted to terbutaline in the body.

- *Mode of administration*–Oral (ingested).

- *Mechanisms of action*–Long-acting oral β_2-agonists (sympathomimetics) are bronchodilators. Like other β_2-agonists, they relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability, and may modulate mediator release from mast cells and basophils.

- *Role in therapy*–Long-acting oral β_2-agonists may be helpful in controlling nocturnal symptoms of asthma. They may be used as an addition to inhaled glucocorticosteroids when standard doses do not sufficiently control nocturnal symptoms. Bambuterol appears to be as effective as salmeterol in controlling asthma in patients not controlled on low doses of inhaled glucocorticosteroids alone, although it may be associated with more frequent side effects[175,176].

- *Side effects*–Possible side effects include cardiovascular stimulation, anxiety, and skeletal muscle tremor. Adverse cardiovascular reactions may also occur with the combination of oral β_2-agonists and theophylline.

Leukotriene modifiers.

Leukotriene modifiers are a new class of antiasthma drugs that include cysteinyl leukotriene 1 (CysLT1) receptor antagonists (montelukast, pranlukast, zafirlukast) and a 5-lipoxygenase inhibitor (zileuton).

- *Mode of administration*–Oral (ingested).

- *Mechanisms of action*–5-lipoxygenase inhibitors block the synthesis of all leukotrienes. Leukotriene receptor antagonists block the CysLT1 receptors on airway smooth muscle and other cells and thus inhibit the effects of cysteinyl leukotrienes that are released from mast cells and eosinophils. These mechanisms result in a small bronchodilator effect and reductions in allergen-, exercise-, and sulfur-dioxide-induced bronchoconstriction[177,178]. There is also evidence for some anti-inflammatory effect[179,180,630].

- *Role in therapy*–The role of leukotriene modifiers in asthma management remains under investigation. Clinical studies have demonstrated that leukotriene modifiers have a small and variable bronchodilator effect, reduce symptoms including cough[631], improve lung function, and reduce asthma exacerbations[177,178,181]. The effect of leukotriene modifiers is less than that of low doses of inhaled glucocorticosteroids[673], and, in patients already on inhaled glucocorticosteroids, leukotriene modifiers cannot substitute for this treatment without risking the loss of asthma control[182,183]. There is evidence that leukotriene modifiers used as add-on therapy reduce the dose of inhaled

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glucocorticosteroids required by patients with moderate to severe asthma[184], and may improve asthma control in patients whose asthma is not controlled with low or high doses of inhaled glucocorticosteroids[183,185,674,675] (**Evidence A**). Several short-term studies have demonstrated that leukotriene modifiers are less effective than long-acting inhaled B2-agonists as add on therapy[196,632,633,676] (**Evidence A**). However, a single one year study demonstrated equivalent effects of long-acting inhaled B2-agonists and leukotriene modifiers as add-on therapy on asthma exacerbations[677]. An advantage of leukotriene modifiers is their administration as a tablet. Some patients with aspirin-sensitive asthma may respond well to leukotriene modifiers[187].

- *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, and monitoring of liver tests is recommended during treatment with this medication. There are several reports of Churg-Strauss syndrome in association with leukotriene modifier therapy[135]. In most but not all of these cases, the appearance of the Churg-Strauss syndrome was associated with a reduction in the dose of systemic glucocorticosteroids[188,189]. The causal relationship between leukotriene modifier therapy and Churg-Strauss syndrome is still unclear.

Anti-IgE

- *Mode of administration*–subcutaneous

- *Mechanism of action*–Antigen-specific IgE binds to high-affinity receptors on mast cells and basophils. Interaction with specific allergens cross-link cell-bond IgE to signal these cells to release preformed mediators (histamine) and initiate synthesis of other potential proinflammatory molecules (leukotrienes, cytokines, and chemokines)[634]. Thus, an antibody directed against IgE was considered a reasonable therapeutic target for allergic diseases, including asthma.

- *Role in therapy*–Anti-IgE allows for the reduction of glucocorticosteroids, and improves asthma control as indicated by fewer exacerbations, symptoms, and need for rescue medications[635,636]. A principal indication for anti-IgE, at present, is patients with severe, allergic asthma[637,678,679]. (**Evidence B**). Further investigation will help to provide additional clarification of the role of Anti-IgE therapy for asthma, although use of this treatment might be limited by the cost.

- *Side effects*–Based on several studies in asthma patients age 11-50 years, already receiving treatment with inhaled and/or oral glucocorticosteroids, anti-IgE appears safe[634-637].

Second generation antihistamines (H_1-antiantagonists)

- *Mode of administration*–Oral (ingested).

- *Mechanisms of action*–The mechanism of action of anti-allergic H_1-antagonists (acrivastine, astemizole, azelastine, cetirizine, ebastine, fexofenadine, ketotifen, loratidine, mizolastine, and terfenadine) in asthma has not been clearly established, but they are recognized to have some inhibitory effects on the allergic response.

- *Role in therapy*–Current evidence does not suggest a primary role for these agents in the treatment of asthma. They may have a small beneficial effect on asthma in subjects with concurrent rhinitis[190-192] (**Evidence B**).

- *Side effects*–The most frequent side effect of some second-generation antihistamines is still sedation, especially in the initial treatment period. Astemizole and terfenadine have been associated with severe cardiac side effects (torsade de point) and are therefore best avoided. Ketotifen may also cause weight gain.

Other oral antiallergic compounds.

Among oral antiallergic compounds introduced in some countries for the treatment of mild to moderate allergic asthma are tranilast, repirinast, tazanolast, pemirolast, ozagrel, celatrodast, amlexanox, and ibudilast.

- *Mode of administration*–Oral (ingested).

- *Mechanisms of action*–These compounds inhibit mast cell activation, interfere with the synthesis of allergic inflammatory mediators, or act as mediator antagonists.

- *Role in therapy*–Further studies on the relative efficacy of these compounds are needed before recommendations can be made about the inclusion of these oral anti-allergic compounds in the long-term treatment of asthma. Their antiasthma effect appears to be limited[193].

- *Side effects*–Sedation is potentially a side effect; other serious side effects have not yet been reported for this very heterogeneous class of drugs.

Systemic steroid-sparing therapies.

Several types of treatment have been tested to reduce the requirement for oral glucocorticosteroids in patients with severe asthma who experience significant side effects from glucocorticosteroids[194]. These steroid-sparing therapies include immunomodulators and some macrolides.

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- *Mode of administration*–Oral (ingested).

- *Role in therapy*–Therapeutic regimens to reduce the dose of oral glucocorticosteroids required by patients with severe asthma may include such medications as troleandromycin, methotrexate[195-197], cyclosporin[198], and gold[199,200]. These medications should be used only in selected patients under the supervision of an asthma specialist, as their potential steroid-sparing effect may not outweigh the risk of serious side effects. Two meta-analyses that considered the steroid-sparing effect of low-dose methotrexate showed a small overall benefit, but a relatively high frequency of adverse effects[201,202] (**Evidence B**). Intravenous immunoglobulin has been shown to have some steroid-sparing effect in some controlled trials, but has been found ineffective in others[203-205]. This treatment is also very expensive and has a high frequency of adverse effects, so it cannot be recommended. Some macrolides have a small steroid-sparing effect when used with methylprednisolone, decreasing metabolism of the glucocorticosteroid[206,207].

- *Side effects*–Side effects vary with the medication but commonly include nausea, vomiting, and abdominal pain. Less frequent but potentially severe adverse effects include hepatitis and hematological, teratogenic, and pulmonary effects.

Allergen-specific immunotherapy.

Specific immunotherapy (SIT) using allergen extracts has been administered in many countries for the treatment of allergic diseases, including asthma. The greatest benefit from this therapy has been obtained in the treatment of allergic rhinitis.

- *Mode of administration*–Subcutaneous injection. Sublingual administration currently under assessment.

- *Mechanisms of action*–Although the mechanisms of action of SIT have not been fully defined, some studies suggest that SIT may shift the immune system's balance from Th2 to Th1 cells, with increased production of interleukin (IL)-12 and interferon-γ[208,209]. SIT also increases the anti-inflammatory cytokine IL-10[210]. Precisely how and under what circumstances these changes affect immune regulation of allergic inflammation is not fully ascertained.

- *Role in therapy*–The greatest benefit of SIT has occurred when administered to patients with allergic rhinitis that has been unresponsive to conventional pharmacotherapy or specific environmental control or in circumstances in which patients do not wish to use medications for prolonged periods of time. Several studies have demonstrated that SIT using extracts of common aeroallergens may have some benefit in patients with allergic asthma[211,212], but several large, well-conducted studies have not demonstrated such a benefit[142,213]. A Cochrane review[214] that examined 54 randomized controlled trials of SIT in asthma confirmed the efficacy of this therapy in asthma (**Evidence A**). In particular, it emphasized the clinically useful outcomes of decreased symptom scores and medication requirements, as well as improved allergen-specific and nonspecific airway hyperresponsiveness. Importantly, the results of the Cochrane review were consistent and the number of patients studied was greater than 1,000, making interpretation of the meta-analysis valid. Despite this evidence, a number of questions remain to be addressed regarding the role of SIT in asthma therapy. First, which individuals are most likely to benefit? Second, is SIT directed at some aeroallergens more likely to be effective than that directed at other aeroallergens? Third, what is the long-term effectiveness of SIT compared to other forms of anti-inflammatory therapy? Finally, which clinical outcomes are most likely to be affected by SIT?

  Because of these questions, and the relatively modest effect of SIT in asthma especially compared to inhaled glucocorticosteroids, the possible benefits of this therapy must be measured in relation to the risk of adverse (occasionally fatal) effects and the inconvenience of the prolonged course of injection therapy, including a half-hour wait after each injection. Given the current state of information, SIT should be considered only after strict environmental avoidance and pharmacologic intervention, including inhaled glucocorticosteroids, have failed to control a patient's asthma[215]. There are no studies that compare SIT with pharmacologic therapy for asthma.

- *Side effects*–Local and systemic side effects may occur in conjunction with SIT 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. These systemic reactions are best treated with subcutaneously administered epinephrine and other pharmacologic therapies[214]. Deaths from SIT have occurred in patients with severe asthma. Therefore, every patient with severe persistent asthma receiving SIT should undergo pulmonary function assessment prior to each SIT administration.

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Reliever Medications

Reliever medications–medications that act quickly to relieve bronchoconstriction and its accompanying acute symptoms–include rapid-acting inhaled β_2-agonists, systemic glucocorticosteroids, inhaled anticholinergics, short-acting theophylline, and short-acting oral β_2-agonists.

Rapid-acting inhaled β_2-agonists.

Rapid-acting inhaled β_2-agonists provide rapid relief of symptoms and include salbutamol (albuterol), terbutaline, fenoterol, reproterol, and pirbuterol. Formoterol has both a rapid onset and a long duration of action.

- *Mode of administration*–Inhaled.

- *Mechanisms of action*–Rapid-acting inhaled β_2-agonists (sympathomimetics) are bronchodilators. Like other β_2-agonists, they relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability, and may modulate mediator release from mast cells[156]. Therapy with rapid-acting inhaled β_2-agonists is comparable to or better than oral therapy in producing bronchodilatation and avoiding side effects. The clinical significance of β_2-receptor polymorphisms requires further examination[216]. There is no evidence of a difference in therapeutic ratio between R-albuterol compared to the normally used racemic (RS)-albuterol in terms of bronchodilator response or side effects[638].

- *Role in therapy*–Rapid-acting inhaled β_2-agonists are the medication of choice for treatment of acute exacerbations of asthma and are useful for the pretreatment of exercise-induced asthma[217] (**Evidence A**). Rapid-acting inhaled β_2-agonists are used to control episodic bronchoconstriction. Use of rapid-acting inhaled β_2-agonists as required for symptom control is recommended and provides a good indication of the need for further therapy. However, frequent or regularly scheduled use of rapid-acting inhaled β_2-agonists for long-term management of asthma does not adequately control asthma symptoms, peak flow variability, or airway hyperresponsiveness. In one study, regularly scheduled (as opposed to as-needed) therapy with the β_2-agonist fenoterol was associated with diminished control of asthma[218], but subsequent studies have shown no adverse effect of regular compared to as needed treatment with salbutamol in patients with mild to severe asthma[109-111]. In any case, regular treatment with rapid-acting inhaled β_2-agonists four times daily has largely been superseded by the use of long-acting inhaled β_2-agonists.

Increased use–or even daily use–of rapid-acting inhaled β_2-agonists is a warning of deterioration of asthma and indicates the need to institute or to intensify the regular anti-inflammatory therapy. 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.
As-needed use of formoterol, a β_2-agonist with both a rapid onset and a long duration of effect, improves asthma control compared to as-needed use of the rapid- and short-acting β_2-agonist terbutaline in patients with moderate asthma who are taking inhaled glucocortocosteroids[219]. Formoterol has a well-documented role as controller therapy in asthma, and further studies are needed to identify its role as a reliever therapy.

- *Side effects*–Therapy with rapid-acting inhaled β_2-agonists causes fewer adverse systemic effects–such as cardiovascular stimulation, skeletal muscle tremor, and hypokalemia–than oral therapy.

Systemic glucocorticosteroids.

- *Mode of administration*–Oral (ingested) or parenteral.

- *Mechanisms of action*–See the section on systemic glucocorticosteroids in "Controller Medications" above.

- *Role in therapy*–Although onset of action of these medications is 4 to 6 hours, they are important in the treatment of severe acute exacerbations because they prevent progression of the asthma exacerbation, decrease the need for emergency department visits or hospitalizations, prevent early relapse after emergency treatment, and reduce the morbidity of the illness. Oral therapy is preferred and is as effective as intravenous hydro-cortisone[220,221] (**Evidence B**). Prednisone, prednisolone, and methyprednisolone are generally continued for 3 to 10 days following initial treatment of the exacerbation. A typical short course of oral glucocorticosteroids for an exacerbation is 30 mg prednisolone given daily for 5 to 10 days depending on the severity of the exacerbation. When the symptoms have subsided and the lung function has approached the personal best value, the oral glucocorticosteroids can be stopped or tapered, provided that treatment with inhaled glucocorticosteroids continues.

- *Side effects*–Potential adverse effects of high-dose short-term systemic therapy include reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, rounding of the face, mood alteration, hypertension, peptic ulcer, and aseptic necrosis

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of the femur. These side effects are generally not observed during a short course of oral or parenteral therapy.

Anticholinergics.

- *Mode of administration*–Inhaled.

- *Mechanisms of action*–Inhaled anticholinergic agents (ipratropium bromide, oxitropium bromide) are bronchodilators that block the effect of acetylcholine released from cholinergic nerves in the airways. When inhaled, these agents produce bronchodilation by reducing intrinsic vagal cholinergic tone to the airways. They also block reflex bronchoconstriction caused by inhaled irritants. They do not diminish the early and late allergic reactions and have no effect on airway inflammation. In asthma, inhaled anticholinergics are less potent bronchodilators than inhaled β_2-agonists, and in general, they have a slower onset of action (30 to 60 minutes to maximum effect).

- *Role in therapy*–Some reports show that ipratropium bromide has an additive effect when nebulized together with a rapid-acting β_2-agonist for exacerbations of asthma[222,223]. A meta-analysis of trials in which nebulized ipratropium bromide was added to a nebulized β_2-agonist showed the anticholinergic produced a statistically significant, albeit modest, improvement in pulmonary function, and significantly reduced the risk of hospital admission[224] (**Evidence B**). 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[225].

Methylxanthines.

- *Mode of administration*–Oral (ingested) or parenteral.

- *Mechanisms of action*–Theophylline is a bronchodilator that is, in general, less effective than an inhaled β_2-agonist.

- *Role in therapy*–Short-acting theophylline may be considered for relief of symptoms (although its onset of action is considerably longer than that of a rapid-acting β_2-agonist)[147] (**Evidence A**). The role of theophylline/aminophylline 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 or respiratory muscle function and prolong or sustain the response to rapid-acting β_2-agonist between doses.

- *Side effects*–As already noted, 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.

Short-acting oral β_2-agonists.

- *Mode of administration*–Oral (ingested).

- *Mechanisms of action*–Short-acting oral β_2-agonists are bronchodilators that relax airway smooth muscle.
- *Role in therapy*–Short-acting oral β_2-agonists are appropriate for use in the few patients who are unable to use inhaled medication.

- *Side effects*–The potential for adverse side effects such as cardiovascular stimulation, skeletal muscle tremor, hypokalemia, and irritability is more significant with oral therapy.

Alternative and Complementary Methods of Healing

Although alternative and complementary medicines may be popular with some patients, they have as yet been insufficiently researched, and their effectiveness is largely unproven. However, their use merits consideration[226,227]. The use of unconventional therapy is widespread, and it is associated with considerable individual health care expenditure[228]. In some countries traditional methods of healing are a primary way of treatment; in many countries, there has been a move toward using various traditional methods of healing. The scientific basis of these modes of therapy needs to be studied in detail, especially for countries in which these forms of therapy are frequently used. These traditional therapies are not validated by conventional standards, and it is difficult to evaluate traditional healing methods in randomized controlled trials. Furthermore, the psychotherapeutic benefit of a holistic approach, a characteristic of many traditional and alternative systems of medicine, cannot be excluded.

Although alternative and complementary healing methods cannot be recommended for asthma therapy until they have been studied more rigorously, the most widely known methods are described here.

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Acupuncture. The use of acupuncture originated over 2,000 years ago, and the technique was written up in detail soon thereafter. Traditional Chinese medicine is essentially holistic: The upset balance in disease is seen to be restored by diet, lifestyle, acupuncture, and herbs. Acupuncture is rarely used in this holistic way for the treatment of asthma in the West and in urban parts of China, where it is used as a complementary medicine. This holistic approach is very complex for investigation, and the available evidence points out that acupuncture *per se* is not indicated for the management of asthma[229]. In a review of 13 trials on the efficacy of acupuncture in the treatment of patients with asthma, a score was established based on 18 predefined methodological criteria. The results showed that the quality of even the eight better studies was mediocre, and the authors concluded that claims that acupuncture is effective in the treatment of asthma are not based on the results of well-performed clinical trials[230]. Another systematic review found only seven acceptable trials, and even in these the placebo was often inappropriate. In the acceptable trials, acupuncture did not produce a significant improvement in asthma[229]. Acupuncture is not entirely innocuous– acupuncture-associated hepatitis B, bilateral pneumothorax, and burns have all been described.

Homeopathy. There is no evidence that homeopathy is effective in asthma. A systematic review, which found only three relevant trials of homeopathy in asthma, did not reach any conclusions about efficacy and homoeopathic immunotherapy has been shown to be ineffective in the treatment of patients with asthma[231,639]. Nevertheless, homeopathy is widely used, and in some countries is the only alternative medicine accepted as part of government care. More rigorous trials are necessary to assess the efficacy of homeopathy.

Herbal medicine. Several modern treatments have their origins in the folk medicine tradition, including β_2-agonists, anticholinergics, methylxanthines, and sodium cromoglycate, the last of which was developed from analogs of the naturally occurring cromone khellin found in the West Asian plant *Amni visnaga*.

In different countries, several herbs are used in the treatment of asthma, and herbal remedies are quite popular for asthma and many other conditions. Since the beginning of time, humans have been using plants for healing. However, up to now, no controlled clinical trials of herbal folk remedies have been reported.

A public perception seems to be that because herbal remedies are "natural" they are safe. There are, however, no requirements on efficacy and safety for herbal treatments. Some of these popular remedies could be potentially 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 pyrrolizidine alkaloids.

Dietary supplements. Although vitamin supplements are commonly taken by patients with asthma, regular dietary supplementation with vitamin C or magnesium adds no clinical benefit to current standard asthma therapy[680].

Ayurvedic medicine. "Ayurveda" is a Sanskrit word meaning knowledge of life. Ayurvedic medicine is a complex system of health care that has been practiced on the Indian subcontinent for thousands of years[232]. It consists of 20 separate components that include transcendental meditation, rasayanas (herbal preparations), pulse diagnosis, and yoga. The evidence that transcendental meditation may help in asthma is as yet poor and uncontrolled. The effect of one aspect of yoga breathing exercises, called pranayama, was well studied in a double-blind controlled trial that used a training and a placebo device. After two weeks there was no difference between the two groups regarding lung function, symptom score, and inhaler use[233]. However, there was a small but significant reduction in histamine reactivity in the group treated with pranayama breathing. The reason for this improvement is not clear. Ayurvedic medicine deserves attention in well-conducted clinical trials.

Ionizers. Ionizers impart a negative charge to particles dispersed in room air, which are attracted to walls and floors that carry a positive charge. Controlled trials failed to show a significant benefit in patients with asthma from the use of ionizers[234,681]. The negative ion generator in a room has several disadvantages, including production of ozone (a respiratory irritant). This therapy is not recommended for asthma.

Osteopathy and chiropractic manipulation. A controlled trial of chiropractic spinal manipulation showed no significant benefit of this therapy in asthma[235]. Other manual therapies, including osteopathy and physiotherapy, have so far not been shown to be helpful in asthma management[236]. The Alexander technique, consisting of a series of postural exercises, has been claimed to be beneficial in asthma management, but controlled trials have not been conducted[237].

Speleotherapy. Treatment of asthma with periods in underground environments, including salt mines, has been popular in some regions, such as Eastern Europe. However, there are few controlled studies of this therapy, and no conclusions can be made about its benefits until adequate controlled trials are conducted[238].

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Buteyko. Buteyko, a breathing technique consisting of a series of exercises in which subjects reduce the depth and the frequency of respiration, does not modify asthma, but may improve symptoms in some people, although the mechanism for this is not known[682]. A randomized controlled trial[239] concluded that patients with asthma who practiced the Buteyko breathing technique reduced their alveolar ventilation (this finding was especially prominent in patients who tended to hyperventilate) and their use of β_2-agonists. No objective change in measures of airway calibre or end-tidal $PaCO_2$ values were found. The results suggest that benefits, if any, may be in patients who tend to hyperventilate and use excessive amounts of β_2-agonist.

Other methods. Reports of the effects of hypnosis and suggestion, naturopathy, behavioral therapy, and biofeedback on asthma are either scarce or contradictory. Clearly, more rigorous studies are warranted. It is strongly recommended that conventional treatment be continued if these treatments –or other traditional healing methods–are tried.

A STEPWISE APPROACH TO PHARMACOLOGIC THERAPY

Although no cure for asthma has yet been found, it is reasonable to expect that in most patients with asthma control of the disease can and should be achieved and maintained. Control of asthma is defined as:

- Minimal (ideally no) chronic symptoms, including nocturnal symptoms
- Minimal (infrequent) exacerbations
- No emergency visits
- Minimal (ideally no) use of p.r.n. (as-needed) β_2-agonist
- No limitations on activities, including exercise
- PEF circadian variation of less than 20 percent
- (Near) normal PEF
- Minimal (or no) adverse effects from medicine.

Choice of Therapy

The selection of pharmacologic treatment options is made on the basis of asthma severity, the patient's current treatment, the pharmacological properties and availability of antiasthma treatment, and economic considerations. Because asthma is a dynamic as well as chronic condition, medication plans need to accommodate variability among patients as well as within individual patients over time. An essential aspect of any treatment plan is the need for monitoring the effect of the treatment (including use of measurements of lung function and symptoms) and adapting the treatment to the variability of the asthma. An approach to pharmacologic therapy that correlates with asthma severity permits this flexibility. As discussed previously, the classification of asthma severity should include symptom and medical history evaluation, current treatment, clinical examination, and measurements of lung function where possible.

An appropriate approach to therapy recommends that the number (type), dose, and eventually the frequency of medications are increased with increasing asthma severity. The aim is to accomplish the goals of therapy with the least possible medication. Thus in developing an asthma management plan, the health care professional must judge whether to give maximum treatment at the onset, which may include a burst or cycle of oral glucocorticosteroids and/or full doses of inhaled glucocorticosteroids plus long-acting β_2-agonists (**Evidence D**) in order to achieve control of the patient's asthma as quickly as possible, and then decrease the medication, or to start with treatment judged appropriate for the severity of the patient's asthma and increase treatment gradually if necessary. Once control is sustained for about 3 months, a reduction in therapy to a lower step can be carefully considered. This reduction in therapy is needed to identify the minimum therapy required to maintain control.

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Few studies have as yet investigated the efficacy of various comprehensive therapeutic programs in accomplishing a broad set of therapeutic goals for controlling asthma. The recommendations that follow are thus based on an understanding of the pathology of asthma and an extrapolation from controlled clinical therapeutic trials that have evaluated the effects of particular antiasthma therapies on separate outcomes such as asthma symptoms, lung function, and the use of bronchodilators on an as-needed basis to relieve symptoms.

Figure 7-5 presents the stepwise approach to therapy to achieve and maintain control of asthma. The step system for classifying asthma severity takes into account the treatment that the patient is currently receiving (**Figure 5-7**). **Figure 7-5** presents all therapies that can be recommended for treating each step of asthma severity. Guidance for selecting among these available modalities is provided in the text. The cost of the medication is an obvious factor in determining the choice of treatment. Cost of treatment varies from country to country and is only one of the factors that contribute to the total cost of a disorder such as asthma.

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Figure 7-5. Recommended Medications by Level of Severity: Adults and Children Older Than 5 Years of Age

All Levels: In addition to regular daily controller therapy, rapid-acting inhaled β_2-agonist* should be taken as needed to relieve symptoms, but should not be taken more than 3 to 4 times a day. Patient education is essential at every level.

Level of Severity**	Daily Controller Medications	Other Treatment Options***
Step 1 Intermittent Asthma****	• None necessary	
Step 2 Mild Persistent Asthma	• Low-dose inhaled glucocorticosteroid	• Sustained-release theophylline, *or* • Cromone, *or* • Leukotriene modifier
Step 3 Moderate Persistent Asthma	• Low-to-medium inhaled glucocorticosteroid *plus* long-acting inhaled β_2-agonist	• Medium-dose Inhaled glucocorticosteroid *plus* sustained-release theophylline, *or* • Medium-dose Inhaled glucocorticosteroid *plus* long-acting oral β_2-agonist, *or* • High-dose inhaled glucocorticosteroid *or* • Medium-dose Inhaled glucocorticosteroid *plus* leukotriene modifier
Step 4 Severe Persistent Asthma	• High-dose Inhaled glucocorticosteroid *plus* long-acting inhaled β_2-agonist, *plus* one or more of the following, if needed: • Sustained-release theophylline • Leukotriene modifier • Long-acting oral β_2-agonist • Oral glucocorticosteroid	

All Levels: Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.

** Other options for reliever medication are (in increasing order of cost) inhaled anticholinergic, short-acting oral β_2-agonist, and short-acting theophylline.*
*** See **Figure 5-6** and **Figure 5-7** for classification of severity.*
**** Other treatment options listed in order of increasing cost. Relative medication costs may vary from country to country.*
***** Patients with intermittent asthma but severe exacerbations should be treated as having moderate persistent asthma (**Evidence D**).*

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How To Achieve and Maintain Control of Asthma

This section describes the therapy appropriate for different steps of asthma severity. The presence of one or more features of clinical severity places a patient at the respective step (**Figure 5-6**). The current treatment should be included in the assessment of severity (**Figure 5-7**).

In the stepwise approach to therapy, progression to the next step is indicated when control is not achieved or is lost with the current treatment, and there is assurance the patient is using medication correctly. The frequent (e.g., more than 3 times a week) presence of such symptoms as cough, wheezing, and dyspnea, and the increased use of rapid-acting bronchodilators may indicate inadequate control of asthma. The presence of symptoms at night or early in the morning is an especially useful indicator. Measurement of PEF and its variability is helpful in the initial assessment of asthma severity and in monitoring the initial treatment, assessing changes in severity, and preparing for a reduction in therapy.

The treatments suggested for each step below are guidelines only; evidence levels assigned are based on references provided in the previous text. Specific medication plans should be tailored by the health care

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professional depending on the availability of antiasthma medication, the conditions of the health care system, and individual patient circumstances. Repeated use of reliever medication more than 4 times a day indicates that the patient's asthma is not well controlled, and the intensity of treatment should be increased.

Step 1–Intermittent Asthma. A patient has intermittent asthma if the patient experiences symptoms (episodes of cough, wheezing, or dyspnea) less than once a week over a period of at least 3 months, and the episodes are brief, generally lasting only a few hours to a few days. Nocturnal asthma symptoms do not occur more than 2 times a month. In between exacerbations, the patient is asymptomatic and has completely normal lung function, i.e., a pretreatment baseline FEV_1 greater than 80 percent of predicted or PEF greater than 80 percent of personal best, and PEF variability of less than 20 percent.

Intermittent asthma includes the patient with allergy who is occasionally exposed to the allergen (e.g., cat or dog) that is responsible for causing his or her asthma symptoms, but who is completely symptom-free and has normal lung function when not exposed to the allergen. Intermittent asthma also includes the patient who has occasional exercise-induced asthma (e.g., under bad weather circumstances).

Intermittent asthma is not trivial. The severity of the asthma exacerbation may vary from patient to patient and from time to time. Severe exacerbations are rare in patients with intermittent asthma but can occur.

The low frequency of the symptomatic episodes and the fact that in between exacerbations the patient has completely normal lung function support the recommendations that no long-term treatment with a controller medication should be started. Further, patient compliance with long-term therapy could be low when the patient only experiences occasional symptoms. Rather, the exacerbations should be treated as such, depending on their severity.

Rapid-acting inhaled β_2-agonist as needed is recommended for the majority of patients with mild intermittent asthma (Evidence A). People with intermittent asthma with severe exacerbations should be treated as having moderate persistent asthma (Evidence D).

Treatment includes medication prior to exercise as needed (rapid-acting inhaled β_2-agonist is the preferred treatment; a cromone or a leukotriene modifier are alternative choices) (**Evidence B**) or upon allergen exposure (a cromone is the preferred treatment) (**Evidence B**). A rapid-acting inhaled β_2-agonist may be taken as needed to relieve asthma symptoms (**Evidence A**). An inhaled anticholinergic, short-acting oral β_2-agonist, or short-acting theophylline may be considered as alternatives to rapid-acting inhaled β_2-agonists, although these alternatives have a slower onset of action and/or a higher risk for side effects (**Evidence A**). Occasionally, more severe or prolonged exacerbations may require a short course of oral glucocorticosteroids.

If medication is required more than once a week over a 3-month period, the patient should be considered to have mild persistent asthma. The same applies if the lung function between exacerbations becomes abnormal.

Step 2–Mild Persistent Asthma. A patient has mild persistent asthma if he or she experiences symptoms and/or declines in lung function with sufficient frequency to warrant daily long-term therapy with controller medication. Mild persistent asthma is present if the patient experiences symptoms at least once a week but less than once a day over a 3-month period and some of the symptomatic episodes affect sleep and activity levels; and/or if the patient has chronic symptoms that require symptomatic treatment almost daily and experiences nocturnal asthma symptoms more than twice a month. The patient with mild persistent asthma has a pretreatment baseline PEF of more than 80 percent of predicted or personal best and PEF variability of 20 to 30 percent. Furthermore, cough variant asthma should be treated as mild persistent asthma.

Patients with mild persistent asthma require controller medication every day to achieve and maintain control of their asthma. The primary therapy for mild persistent asthma is regular use of anti-inflammatory medication taken on a daily basis. Treatment with an inhaled glucocorticosteroid is preferred (Evidence A). The suggested introductory dose of inhaled glucocorticosteroids is 200 to 500 μg per day of BDP or budesonide, 100 to 250 μg per day of fluticasone propionate (FP), or equivalent (Figure 7-3), divided over 1 or 2 dosings (Evidence B). Alternative controller medications (listed in order of increasing cost) are sustained-release theophylline, cromones, and leukotriene modifiers, but these are less effective than inhaled glucocorticosteroids or are effective in only a portion of patients, who cannot be identified without a treatment trial (**Evidence A**). Long-term treatment with sustained-release theophylline may be considered, but the need for monitoring of serum theophylline levels may make this treatment less feasible. Long-term trials that compare the effectiveness of these alternative controller medications in patients with mild persistent asthma are needed.

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In addition to regular controller therapy, a rapid-acting inhaled β_2-agonist should be available to take as needed to relieve symptoms, but should not be taken more than 3 to 4 times a day. Other bronchodilator choices include an inhaled anticholinergic, short-acting oral β_2-agonist, or sustained-release theophylline, although these have a slower onset of action and/or a greater risk of side effects. Because of the risk of serious side effects, short-acting theophylline should not be used as a reliever medication if the patient is already on long-term controller therapy with sustained-release theophylline. Use of reliever medication more than 4 times a day indicates that the patient's asthma is not well controlled at the current treatment level, and the patient should be considered to have a higher step of asthma severity.

If the patient's long-term therapy was initiated with sustained-release theophylline, a cromone, or a leukotriene modifier, and symptoms persist after 4 weeks of this initial treatment, then inhaled glucocorticosteroids should be introduced. The inhaled glucocorticosteroids may be initiated instead of the other medication, or together with it to allow an overlap period.

Step 3–Moderate Persistent Asthma. Moderate persistent asthma is characterized by daily symptoms over a prolonged time or nocturnal asthma more than once a week. A patient with a pretreatment baseline PEF of more than 60 percent but less than 80 percent of predicted or personal best and PEF variability of 20 to 30 percent has moderate persistent asthma. If the patient's asthma is not controlled on a low dose of inhaled glucocorticosteroids (Step 2), then the asthma should also be considered moderate persistent.

Patients with moderate persistent asthma require controller medication every day to achieve and maintain control of their asthma. The preferred controller treatment for moderate persistent asthma is a combination of an inhaled glucocorticosteroid (200 to 1000 µg of BDP, 400 to 1000 µg of budesonide, 250 to 500 µg of fluticasone, or equivalent, divided over 2 dosings per day), and a long-acting inhaled β_2-agonist twice daily (Evidence A). If a patient's asthma is not controlled on a low dose of inhaled glucocorticosteroid (up to 500 µg of beclomethasone or equivalent), then regular treatment with a long-acting inhaled β_2-agonist should be added. If this is still not sufficient then the dose of inhaled glucocorticosteroid should be increased. A fixed combination inhaler containing a glucocorticosteroid and a long-acting β_2-agonist is a convenient way to deliver this medication. Use of a spacer device to deliver the inhaled glucocorticosteroid is recommended to reduce oropharyngeal side effects and systemic absorption.

Although combination therapy of glucocorticosteroid and a long-acting inhaled β_2-agonist is most effective and is the preferred option (**Evidence A**), alternative add-on therapies include the following (in increasing order of cost):

- Sustained-release theophylline. This is a less expensive option, but is also less effective than a long-acting inhaled β_2-agonist. Serum theophylline concentrations should be monitored, with a general therapeutic range of 5 to 15 µg per ml.

- Long-acting oral β_2-agonist. This option may be as effective as a long-acting inhaled β_2-agonist, although the risk of side effects is greater.

- Leukotriene modifier. This option is less effective than a long-acting inhaled β_2-agonist.

An alternative to this combination therapy is a higher dose of inhaled glucocorticosteroid, but adding another class of controller drug is preferable to increasing the inhaled glucocorticosteroid dose.

In addition to regular controller therapy, rapid-acting inhaled β_2-agonists should be available to take as needed to relieve symptoms, but should not be taken more than 3 to 4 times a day. An inhaled anticholinergic, short-acting oral β_2-agonist, or short-acting theophylline may be considered instead of the rapid-acting inhaled β_2-agonist, although these alternatives have a slower onset of action and/or a greater risk of side effects. Because of the risk of serious side effects, short-acting theophylline should not be used as a reliever medication if the patient is already on long-term controller therapy with sustained-release theophylline.

Step 4–Severe Persistent Asthma. Patients who have severe persistent asthma experience highly variable, continuous symptoms, and frequent nocturnal symptoms; have limited activities; and experience severe exacerbations in spite of medication. A patient with a pretreatment baseline PEF of less than 60 percent of predicted or personal best and PEF variability greater than 30 percent has severe persistent asthma. Control of asthma as defined earlier may not be possible.

In severe persistent asthma, the goal of therapy is to achieve the best possible results - the least symptoms, the least need for rapid-acting inhaled β_2-agonist, the best PEF, the least circadian (night to day) variation, and the least side effects from medication. Therapy usually requires multiple daily controller medications. Primary therapy includes inhaled glucocorticosteroids at higher doses (> 1000 µg per

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day of BDP or equivalent) plus a long-acting inhaled β_2-agonist twice daily (Evidence A). Better control may sometimes be achieved with 4-times-daily rather than twice-daily inhaled glucocorticosteroids[240,241] (**Evidence A**).

A long-acting inhaled β_2-agonist is preferred as add-on treatment, but alternatives are sustained-release theophylline, leukotriene modifier, or long-acting oral β_2-agonist (**Evidence B**). These medications may also be added to the combination therapy (high-dose inhaled glucocorticosteroid plus long-acting inhaled β_2-agonist). A rapid-acting inhaled β_2-agonist should also be available for use as needed. If needed, long-term oral glucocorticosteroids should be used in the lowest possible dose, and are best given as a single morning dose in order to minimize systemic side effects. When patients are switched from oral glucocorticosteroids to high-dose inhaled glucocorticosteroids, they should be monitored closely for evidence of adrenal insufficiency.

A nebulizer can deliver a higher dose of inhaled glucocorticosteroid (budesonide or FP), but there is little evidence that this results in fewer systemic effects than an equivalent dose of oral glucocorticosteroid[242,243]. In addition, this treatment is relatively expensive and may produce local side effects, such as soreness of the mouth. There is no evidence yet from controlled trials to recommend the use of nebulized glucocorticosteroids in stable asthma in adults.

Steroid-sparing therapies may be considered in patients with severe persistent asthma who have asthma that is controlled with oral glucocorticosteroids but who experience systemic side effects from this treatment (**Evidence B**). Such steroid-sparing therapies include methotrexate, cyclosporin A, and oral gold. These treatments are poorly effective and have side effects that are often more troublesome than those of steroids. They should therefore only be used if there is clear evidence of benefit, and patients on these therapies must be monitored carefully. All patients who require such therapy should be under the care of a specialist. Note that difficult-to-manage asthma may herald a life-threatening underlying disorder such as Churg-Strauss syndrome or other forms of systemic vasculitis[181].

The complexity of a multiple daily medication regimen is often a factor in patient nonadherence, and this in turn complicates control of asthma. Patients with severe persistent asthma may require particularly intensive patient education and referral to appropriate sources of support.

Reduction of Maintenance (Controller) Therapy

Asthma is a variable disorder, and spontaneous and therapy-induced variations in severity occur. Inhaled glucocorticosteroids reduce asthma severity over the long term. Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control. This will help reduce the risk of side effects and enhance patient adherence to the treatment plan. The therapy reduction should be done by gradually reducing the dose of inhaled glucocorticosteroids by approximately 25 percent every 3 months or withdrawing the bronchodilator in subjects on low doses of inhaled glucocorticosteroids. That is, reduction of therapy should follow the reverse order of what has just been described, with close monitoring of symptoms, clinical signs, and, as much as possible, lung function. Reduction of therapy in patients on combination therapy should begin with a reduction in the dose of inhaled glucocortiocosteroid. Once the dose of the glucocortiocosteroid is at 500 μg BDP or equivalent, then withdrawal of the add-on therapy may be considered (**Evidence D**). It is recommended that patients be reviewed at least every 3 months during the reduction phase.

Seasonal Asthma

A patient has seasonal asthma when he or she has asthma symptoms due to seasonal exposure to allergen. This may be intermittent in patients who are otherwise entirely asymptomatic with normal PEF values between seasons, or it may occur as a seasonal worsening of persistent asthma. The severity varies from patient to patient and from season to season. Treatment will vary accordingly but should follow the recommendations for the treatment of persistent asthma. Ideally, treatment should start just before the expected season or upon the first symptoms, and can be stopped at the end of the season when symptoms or lung function abnormalities are no longer present (**Evidence D**).

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PART 4B: ESTABLISH MEDICATION PLANS FOR LONG-TERM ASTHMA MANAGEMENT IN INFANTS AND CHILDREN

KEY POINTS:

- Childhood and adult asthma share the same underlying pathophysiological mechanisms. However, because of the processes of physical and cognitive growth and development, the effects, and adverse effects, of asthma and asthma treatments in children differ from those in adults.
- Many asthma medications (e.g., glucocorticosteroids, β_2-agonists, theophylline) are metabolized faster in children than in adults, and young children tend to metabolize drugs faster than older children.
- Therapy should be selected on the basis of the severity of asthma in the individual patient, the availability of antiasthma medications, the characteristics of the health care system, and the individual patient's social, family, and economic circumstances.
- Inhaled glucocorticosteroids are at present the most effective controller medications and are therefore recommended for persistent asthma at any step of severity. Long-term treatment with inhaled glucocorticosteroids markedly reduces the frequency and severity of exacerbations.
- Long-term treatment with inhaled glucocorticosteroids has not been shown to be associated with any increase in osteoporosis or bone fracture. Studies including a total of over 3,500 children treated for mean periods of 1 to 13 years have found no sustained adverse effect of inhaled glucocorticosteroids on growth.
- Rapid-acting inhaled β_2-agonists are the most effective reliever therapy in asthma, and this class of drugs has been the mainstay of asthma treatment in children for many years. These drugs are the most effective bronchodilators available and are therefore the treatment of choice for acute asthma symptoms.
- Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.

Childhood and adult asthma share the same underlying pathophysiological mechanisms. However, because of the processes of physical and cognitive growth and development, the effects, and adverse effects, of asthma and asthma treatments in children differ from those in adults. There are important age-related differences in anatomy, physiology, pathology, and drug metabolism, as well as effects from the unique social, emotional, and developmental characteristics of childhood. Therefore, the diagnosis and management of asthma in children must be considered in its own right, and not merely extrapolated from experience with adults. Because growth and development is a dynamic process, adverse effects may not become evident immediately, but only at a later stage of maturation. Thus, long-term outcome studies are particularly important to determine the possible effects of asthma and its treatments during childhood on skeletal, behavioral, cognitive, sexual, and immune growth, development, and maturation.

Children with asthma normally continue to grow until the age of 18. Within this childhood population it is convenient to make a distinction between *adolescents (puberty-18 years), school children (6 years-puberty), preschool children (1-6 years), and infants (< 1 year)*, as there are clinically important differences between these age groups in patterns of asthma symptoms, medication effects and side effects, and behavioral, cognitive, and social development. However, it may sometimes be more appropriate to collect data over broad age ranges and examine the effect of age as a covariant. In this section, the role in therapy of various drugs is discussed separately for each age group where such information is available. In developing a treatment plan, factors such as the severity of the individual patient's asthma, the benefits, risks, and availability of each treatment, cultural preferences, and the characteristics of the health care system need to be considered. The final choice of treatment should integrate the individual clinician's expertise with the patient's preferences and the best available evidence from systematic, clinically relevant research in children.

THE MEDICATIONS

Medications for the management of pediatric asthma include both controllers and relievers. Controllers are medications taken daily on a long-term basis to achieve and maintain control of asthma. Relievers act quickly to relieve bronchoconstriction and its accompanying acute symptoms such as wheezing, chest tightness, and cough.

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Figure 7-6. Choice of Inhaler Device for Children*

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 face mask
Older than 6 years	Dry powder inhaler, or Breath-actuated pressurized metered-dose inhaler, or pressurized metered-dose inhaler with spacer	Nebulizer with mouthpiece

**Based on efficacy of drug delivery, cost effectiveness, safety, and convenience. Additional information about available inhaler devices can be found on www.ginasthma.com.*

Many asthma medications (e.g., glucocorticosteroids, β_2-agonists, theophylline) are metabolized faster in children than in adults, and young children tend to metabolize drugs faster than older children. Although this rapid metabolism to inactive drug is advantageous from a safety perspective, it also means that when medication is administered orally, higher doses should be given to young children than to adults or older children. In this section, a summary of pharmacokinetic information is provided where such information is available.

Route of Administration

Medications for asthma can be administered via different ways, including inhaled, oral (ingested), and parenteral (subcutaneous, intramuscular, or intravenous). The major advantage of delivering drugs directly into the airways via inhalation is that high concentrations can be delivered more effectively to the airways, and systemic side effects are avoided or minimized. Some of the drugs that are effective in asthma can only be used via inhalation because they are not absorbed when given orally (e.g., anticholinergics and cromones). The onset of action of bronchodilators is substantially quicker when they are given via inhalation than when these drugs are administered orally[100,101]. The choice of inhaler device should emphasize the efficacy of drug delivery, cost effectiveness, safety, and convenience[244].

Information about lung dose for a particular drug formulation is seldom available for children. Differences between devices do not alter the potential maximum effect of a given drug, but they do result in different potencies for the same nominal dose of the drug given by different inhalers. If these differences are disregarded, clinically important over- or undertreatment may be seen. Dose recommendations need to be evaluated depending on the device to be used.

The choice of device for maintenance treatment should be related to the class of drug. The actual dose of β_2-agonist administered by inhaler is often greater than necessary, but the potential side effects are minimal. Due to the greater potential for side effects, however, inhaled glucocorticosteroids merit a more careful choice of device to ensure an optimal therapeutic effect with minimal side effects. The differences in first-pass metabolism of different inhaled glucocorticosteroids should also influence the choice of device. A spacer is advised when administering beclomethasone, flunisolide, triamcinolone, or budesonide by pressurized metered-dose inhaler (MDI). A spacer is not required for budesonide delivered from a turbohaler.

For maximum convenience, an inhaler device should be freely portable with no power requirement, and technically simple to operate with minimal maintenance requirements. Simplicity of operation is especially important in the treatment of infants and preschool children, who are often cared for by different people at different times of day (and night). Cooperation and coordination required to use a device should be minimal. Passive cooperation, such as the acceptance of a face mask, can be expected from most preschool children and even infants. Active cooperation, such as performing specific inhalation maneuvers and priming or activating a device, can only be expected in older children.

**"In this chapter recommendations for doses of inhaled glucocorticosteroids are given as "µg/day budesonide or equivalent," because a majority of the scientific literature on the use of these medications in children uses this comparison.*

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For infants and preschool children, in whom active cooperation cannot be expected, a pressurized MDI used with a spacer and face mask is the device of choice for maintenance treatment. As cooperation improves, often around the age of 4 to 6 years, the child should be encouraged to use a mouthpiece rather than a face mask to inhale from the spacer. From the age of 6, a dry powder inhaler (DPI) or breath-activated MDI is the device of choice (**Figure 7-6**)[244,245].

Nebulizers are not preferred for maintenance treatment. Current nebulizers are expensive, bulky, time-consuming to use and care for, and require maintenance. Furthermore, a nebulizer provides imprecise drug delivery unless equipped with a dosimeter. In infants and young children when even passive cooperation cannot be achieved, the loose face mask of a jet nebulizer is often more acceptable than the close-fitting face mask of a spacer. However, parents should be advised of the advantages of the MDI with spacer and encouraged to persevere with attempts at its use.

During severe acute asthma, nebulizer treatment is preferred for all infants and most children. Often the child may have a fever, or may be physically exhausted by respiratory distress. This is not the ideal time to expect compliance with treatment requiring active cooperation, nor to promote the advantages of a closely fitted face mask with spacer. For these children, high doses of drugs are used, and the imprecise drug delivery from a nebulizer is of little concern in the short-term.

Controller Medications

Controller medications include inhaled glucocorticosteroids, systemic glucocorticosteroids, leukotriene modifiers, sodium cromoglycate (cromolyn sodium), nedocromil sodium, methylxanthines, long-acting inhaled β_2-agonists, and long-acting oral β_2-agonists. Inhaled glucocorticosteroids are at present the most effective controller medications. The evidence on the effects of ketotifen in children is insufficient to warrant its use.

Inhaled glucocorticosteroids.*

• *Mode of administration*–Inhaled.

• *Pharmacokinetics*–Most of the inhaled glucocorticosteroid deposited in the intrapulmonary airways is absorbed systemically; that deposited in the oropharynx is swallowed and absorbed from the gastrointestinal tract. A much higher proportion of the inhaled dose is deposited in the oropharynx, and a lower proportion in the intrapulmonary airways, in children compared to adults[246]. Children metabolize budesonide about 40 percent faster than adults[247,248]. The pharmacokinetics of other inhaled glucocorticosteroids have not been studied in children.

• *Role in therapy*–Inhaled glucocorticosteroids are the most effective controller therapy, and are therefore recommended treatment for persistent asthma at any step of severity (**Evidence A**). Dose-response studies and dose titration studies in children[249-252] demonstrate marked and rapid clinical improvements in symptoms and lung function at low doses of inhaled glucocorticosteroids (e.g., 100 μg budesonide daily)[250,253,254].

However, the dose of inhaled glucocorticosteroid required to produce the maximum clinical effect depends on several factors: the outcome measure studied, the duration of administration of the inhaled glucocorticosteroid, the severity of the individual patient's asthma, the drug/inhaler combination used, the age of the patient, and the duration of asthma when treatment is initiated. For example, in patients with mild disease, low doses of inhaled glucocorticosteroids offer full protection against exercise-induced asthma[251], but children with more severe asthma may require four weeks' treatment with 400 μg/day budesonide to achieve a maximum protection against exercise-induced asthma. As a consequence of all these factors, each patient may have her/his own individual dose-response curve. This emphasizes the importance of regular, individual tailoring of the dose. If this is done, the majority of patients with mild to moderate asthma will be optimally controlled on 400 μg or less of budesonide or equivalent daily. As CFCs in MDIs are being replaced by hydrofluoroalkanes (HFAs), the medication insert for dosage of the HFA preparations should be carefully reviewed by the clinician[640].

<u>School children</u>. 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 in school-age children[2,113,149,255,256] (**Evidence A**).

Symptom control and improvements in peak expiratory flow rate occur rapidly (after 1 to 2 weeks) at low doses (e.g., 100 μg/day), even in children with moderate to severe asthma[249-251,257], although longer treatment (1 to 3 months) with somewhat higher doses (e.g., 400 μg/day) is required to achieve maximum improvement in airway hyperresponsiveness as assessed by an exercise challenge test[258-260]. When inhaled glucocorticosteroid treatment is discontinued, there is usually a deterioration

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of asthma control and airway hyperresponsiveness to pretreatment levels within weeks to months, though in some patients the effect of the glucocorticosteroid is maintained for much longer[261].

When a child has already developed an exacerbation, a 4-fold increase in the daily dose of inhaled glucocorticosteroid or the introduction of oral glucocorticosteroid treatment have both been found to reduce the severity and duration of the exacerbation[262] However, in one study a doubling of the inhaled glucocorticosteroid dose did not significantly modify exacerbations that had already developed[263].

Infants and preschool children. Randomized double-blind controlled trials of inhaled glucocorticosteroids in preschool children with asthma have generally shown significant and clinically relevant improvements in health outcomes, including day- and nighttime symptom scores for cough, wheeze, and dyspnea, physical activity, use of rescue treatment, and use of health care resources[264-269] (**Evidence A**). Lung function and airway hyperresponsiveness in wheezy children are also improved[270].

Although inhaled glucocorticosteroids typically reduce the number of asthma exacerbations in infants and preschool children[266,268], they may not completely control the disease in some children. Whether this is due to insufficient patient adherence, poor delivery of medication, insufficient dose of glucocorticosteroid, pharmacogenetic heterogeneity, or a distinct pathology in childhood asthma or in subgroups of wheezy young children needs to be studied.

The clinical benefits of systemic or inhaled glucocorticosteroids for viral-induced wheeze remain controversial. Some randomized double-blind controlled trials found no short- or long-term clinical benefits from the administration of systemic[271-274] or inhaled[275-279] glucocortiosteroids during the acute phase of viral-induced wheeze in previously healthy infants, though some short-term improvements have been reported in other studies[280,281]. A Cochrane review concluded that episodic high-dose inhaled glucocorticosteroids provide a partially effective strategy for the treatment of mild episodic viral-induced wheeze in children, but there is no current evidence to support maintenance low-dose inhaled glucocorticosteroids for the prevention and management of mild viral-induced wheeze[282].

- *Side effects*–The vast majority of studies evaluating the risk of systemic effects of inhaled glucocorticosteroids have been undertaken in children older than 5. Clinically relevant adverse effects should be studied in controlled, long-term clinical trials, using clinically relevant doses in groups of patients with a disease severity and age similar to the groups in which the drugs would normally be prescribed.

Figure 7-7. Summary: Growth and Asthma

- No controlled studies have reported any statistically or clinically significant adverse effect on growth of 100 to 200 μg per day of inhaled glucocorticosteroid[342,343].
- Growth retardation may be seen with all inhaled glucocorticosteroids when a sufficiently high dose is administered without any dose adjustment for disease severity[113,331].
- Growth retardation in both short- and medium-term studies is dose dependent[337].
- Important differences seem to exist between the growth-retarding effects of various inhaled glucocorticosteroids and inhalers[334-337].
- Different age groups seem to differ in susceptibility to the growth-retarding effects of inhaled glucocorticosteroids; children aged 4 to 10 are more susceptible than adolescents[308,338].
- Children with asthma treated with inhaled glucocorticosteroids have consistently been found to attain normal final adult height[308-310].
- Uncontrolled or severe asthma itself seems to adversely affect growth and final adult height[308,310,315,356].
- Glucocorticosteroid-induced changes in growth rate during the first year of treatment appear to be temporary and do not predict adult height[95,113,308].

Bones. The only potential clinically relevant adverse effects of inhaled glucocorticosteroids on bones are osteoporosis and fracture. Biochemical markers of bone metabolism (bone formation and degradation) and bone mineral density are the most commonly used surrogate markers for osteoporosis and risk of fracture in clinical trials. There have been no reports or studies showing an increased incidence of fractures in children treated with inhaled glucocorticosteroids. Several cross-sectional and longitudinal studies including a total of more than 700 patients found no adverse effects of long-term inhaled glucocorticosteroid treatment (mean daily dose about 450 μg) on bone mineral density[113,283-290] (**Evidence A**). Several short-term studies involving patients with mild asthma have reported that daily glucocorticosteroid doses of 400 μg or less have no effect on bone metabolism, but high doses (800 μg daily) lead to a reduction in both bone formation and degradation[283,291-295] (**Evidence A**).

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In adults the skeletal mass is decreasing over time, while in children it is increasing, with peak bone mass and density reached in early adulthood. Thus, maximal peak bone mass or density is probably the most clinically relevant outcome measure for assessing the influence of glucocorticosteroids on bones in children. Several confounding factors must be considered when the effects of glucocorticosteroids on bone metabolism in children are assessed. In children, the rate of bone modeling or turnover is much higher than in adults. Some chronic diseases have been reported to be associated with reduced peak bone mass in children[283]. Delayed puberty is also associated with a significantly lower peak bone mass/density[296,297], and delayed puberty is seen in many children with asthma and atopy, regardless of treatment. Other factors such as nutrition (including calcium intake), heredity (both parents), poor asthma control, and level of physical activity appear to have profound effects on peak bone mass formation[298-306]. Finally, children show a remarkable ability to repair glucocorticosteroid-induced bone loss. In one study, children under 3 years old with synacten-induced compression fractures of the spine had normal spinal x rays 5 to 10 years later[307]. Such repair is not seen in adults.

Growth. Important findings of studies on inhaled glucocorticosteroids and growth are summarized in **Figure 7-7**. Children with asthma treated with inhaled glucocorticosteroids have consistently been found to attain normal final adult height[308-310]. Studies including a total of more than 3,500 children treated for mean periods of 1 to 13 years found no sustained adverse effect of inhaled glucocorticosteroid treatment on growth[149,308,311-332]. A meta-analysis of 21 studies including a total of 810 patients compared attained height with expected height of children with asthma treated with inhaled or oral glucocorticosteroids[333]. Children treated with inhaled glucocorticosteroids attained normal height, while a significant–though weak–retardation of growth was found in children receiving oral glucocorticosteroids. Furthermore, there was no statistical retardation evidence that inhaled glucocorticosteroid therapy was associated with growth retardation, even at high doses or with long-term therapy.

However, inhaled glucocorticosteroid therapy can affect the growth rate of children with asthma, producing a retardation of growth when high doses are administered[113,331]. This growth retardation occurs with all inhaled glucocorticosteroids, although important differences seem to exist between the growth-retarding effects of various inhaled glucocorticosteroids and inhaler devices[334-337]. Children's susceptibility to the growth-retarding effects of inhaled glucocorticosteroids also depends on their age; children 4 to 10 years old are more susceptible than adolescents[308,338]. In addition, several studies have suggested that the systemic bioavailability and systemic effects of an inhaled drug are more pronounced in patients with mild asthma than in patients with more severe disease[339-341], probably due to differences in deposition pattern caused by a smaller airway diameter in more severe disease. This means that a given dose of inhaled glucocorticosteroid may be more likely to adversely affect the growth of a child with mild asthma than that of a child with more severe disease.

Growth retardation in both short- and medium-term studies of inhaled glucocorticosteroid treatment is dose dependent[337]. No controlled studies have reported any statistically or clinically significant adverse effect on growth of inhaled glucocorticosteroid doses of 100 to 200 μg per day[342,343]. In addition, glucocorticosteroid-induced changes in growth rate during the first year of treatment appear to be temporary and do not predict adult height[95,113,308].

Knemometry, a method that captures short-term changes in linear growth of the lower leg, may be a valuable adjunct or alternative to traditional growth studies because it facilitates controlled designs. Importantly, knemometry is not a measure of statural growth, but it is a very sensitive marker of systemic glucocorticosteroid activity. Thus far, all placebo-controlled, double-blind knemometry studies assessing the effects of inhaled glucocorticosteroids on lower leg growth have been undertaken in children with mild asthma who have not required continuous treatment[344-349]. These studies show that, in both school children and preschool children, the effect of inhaled glucocorticosteroids on lower leg growth rate is dose dependent. Low doses of inhaled glucocorticosteroid (200 μg per day or less) are not associated with any detectable effects. As in statural growth studies, growth inhibition dose-response curves in knemometry studies seem to differ between the various inhaled glucocorticosteroids.

When assessing the effects of inhaled glucocorticosteroids on growth in children with asthma, it is important to account for potential confounding factors. For example, many children with asthma experience a reduction in growth rate, most often toward the end of the first decade of life[313,314,350-355]. 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 rate 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. Ultimately, adult height is not decreased, although it is reached at a later than normal

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age[313,314,350-355]. Studies also suggest that poorly controlled asthma may itself adversely affect growth[308,312,315]. In one study, a daily inhaled glucocorticosteroid dose of 400 μg produced growth impairment, but this effect was smaller than the effect of low socioeconomic status on growth of children with severe asthma[356].

Although the influence of inhaled glucocorticosteroids on the growth of children with asthma has been studied extensively in school children, more research is necessary. Many studies conducted to date have had design flaws, and several have been retrospective or uncontrolled. Others have been conducted under conditions that are very different from the day-to-day treatment situation. Moreover, few data are available on the effect of inhaled glucocorticosteroid treatment on growth in infants and young children. These groups' rapid growth rates and somewhat different metabolism distinguish them from older children and may make these younger children more vulnerable to the adverse effects of drugs and/or disease. Therefore, the findings on the safety of inhaled glucocorticosteroids in school children or adults cannot be uncritically extrapolated to infants and preschool children. Studies should be undertaken to specifically address the effect of inhaled glucocorticosteroids on the rapid growth rates during the first 2 to 3 years of life, which is mainly influenced by factors similar to those controlling fetal growth, as well as growth from age 3 onward, which is mainly controlled by the endocrine system, particularly growth hormone[357].

Hypothalamic-pituitary-adrenal (HPA) axis. Adrenal suppression is the most extensively studied systemic effect of inhaled glucocorticosteroids, and its occurrence and magnitude have been examined in detail. Though differences exist between the various inhaled glucocorticosteroids and inhaler devices, treatment with inhaled glucocorticosteroid doses less than 400 μg daily is normally not associated with any significant suppression of the HPA axis in children[113,358,359]. At higher doses, small changes in HPA-axis function can be detected with sensitive methods. The clinical relevance of these findings needs further study.

Lung development. The observation that systemic glucocorticosteroids given during the first 2 weeks after birth (but not after this time) adversely affect alveolar development in rats[360] has raised fears that inhaled glucocorticosteroids may impair normal alveolar development. However, there are no human data on this subject. Thus, in situations where inhaled glucocorticosteroids have a definite positive clinical effect, concerns about their possible adverse effects on lung growth should not be a reason to withhold this treatment[361]. More studies of inhaled glucocorticosteroids and lung development are needed in infants.

Cataracts. Studies evaluating the risk of posterior subcapsular cataracts in more than 800 children receiving long-term (1 to 15 years) treatment with inhaled glucocorticosteroids have found that this treatment is not associated with an increased occurrence of cataract development[113,129,131,362].

Central nervous system effects. Published evidence of effects of inhaled glucocorticosteroids on the central nervous system is limited to isolated case reports in a total of 9 patients (3 adults and 6 children)[363-366] who exhibited hyperactive behavior, aggressiveness, insomnia, uninhibited behavior, and impaired concentration with this treatment. All patients returned to normal after the inhaled glucocorticosteroid was discontinued.

Oral candidiasis. Clinical thrush is seldom a problem in children treated with inhaled or systemic glucocorticosteroids. The occurrence of this side effect seems to be related to concomitant use of antibiotics, dose, dose frequency, and inhaler device. Spacers seem to reduce the incidence of oral candidiasis[367-370]. Mouth rinsing has not been reported to be beneficial. In any case, oral candidiasis is easily treated and rarely necessitates withdrawal of inhaled glucocorticosteroid treatment.

Dental side effects. There is no evidence that inhaled glucocorticosteroid treatment is associated with increased incidence of caries. However, an increased level of dental erosion has been reported in children with asthma[371-373]. This may be associated with a reduction in oral pH, which is mainly seen after inhalation of β_2-agonists[374].

Bruising and hoarseness. Although bruising and hoarseness have been reported to occur at increased frequency in adults treated with high doses of inhaled glucocorticosteroids, few studies have assessed the occurrence of these side effects in children. One study found that 178 children treated with inhaled budesonide at an average daily dose of about 500 μg for 3 to 6 years did not have an increased occurrence of bruising, tendency to bruise, hoarseness, or other noticeable voice change[129]. Hoarseness is reversible after withdrawal of inhaled glucocorticosteroid treatment, but unlike thrush it tends to recur when the treatment is reintroduced. Spacers do not appear to protect against dysphonia.

Other local side effects. There is no evidence of an increased incidence of lower respiratory tract infections, including tuberculosis, with chronic use of inhaled

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glucocorticosteroids. Although local skin changes around the mouth may occur in children treated with nebulized glucocorticosteroids inhaled through a face mask, there is no evidence that a similar process occurs in the airways when glucocorticosteroids are inhaled.

Systemic glucocorticosteroids.

- *Mode of administration*–Oral (ingested) or parenteral.

- *Role in therapy*–The use of oral glucocorticosteroids in the treatment of children with asthma is limited to acute exacerbations, whether viral-induced[280,375] or otherwise[376,377]. However, some studies have been unable to detect any effect of systemic glucocorticosteroids on exacerbations of asthma in children[378,379]. There is no evidence that systemic glucocorticosteroids cause reactivation of tuberculosis in children who have a strongly positive tuberculin reaction[380].

Leukotriene modifiers.

Leukotriene modifiers are a new class of anti-asthma drugs that include, for the treatment of asthma in children, the cysteinyl leukotriene 1 (CysLT1) receptor antagonists montelukast, pranlukast, and zafirlukast. The 5-lipoxygenase inhibitor zileuton has been approved in some countries for use in adults, but is not available for children.

- *Mode of administration*–Oral.

- *Role in therapy*–Leukotriene receptor antagonists may be used as add-on treatment for moderate persistent and severe persistent asthma in children whose asthma is insufficiently controlled by a low dose of inhaled glucocorticosteroids. Leukotriene receptor antagonists have not been studied as monotherapy in children with mild persistent asthma so there are no data to support their use. However, moderate improvements in lung function (in children 6 and older) and in asthma control (in children 2 and older) have been demonstrated with leukotriene receptor antagonist monotherapy in patients with severe disease[381-383] and in patients with moderate disease [384] (**Evidence B**). By extrapolation, this class of drug may be an alternative for monotherapy in some patients with mild persistent disease (**Evidence D**).

  Because the clinical effect of leukotriene modifiers begins a few hours to days after they are first administered, they are considered controller, not reliever, medications. Dose recommendations for children are based on pharmacokinetic studies; the optimal dosing is therefore uncertain.

Montelukast, approved for the treatment of asthma in children 2 years and older in some countries, is administered once daily[385]. The dosage (5 mg) yields a pharmacokinetic profile (single-dose area under the plasma concentration-time curve) in children comparable to that achieved with the 10-mg tablet in adults[386]. There is no difference in bioavailability in children compared to adults, and food does not appear to have a clinically important influence on the bioavailability of this medication.

Zafirlukast, approved for treatment of asthma in children 7 years and older in some countries, is administered twice daily. One study supports the use of a 10-mg BID (twice-daily) dose for long-term treatment of mild to moderate asthma in children[381]. The bioavailability of zafirlukast is reduced by up to 40 percent when the drug is taken with food. Zafirlukast is metabolized by the liver, and therapeutic concentrations of the drug inhibit the hepatic cytochrome P450. This effect creates a risk of drug interactions. Transient elevations of liver enzymes have also been reported[387,388].

Pranlukast is approved for treatment in children 2 years or older in some countries.

School children. Zafirlukast appears to be modestly effective in improving lung function and asthma control in children 12 years and older with moderate to severe asthma[389-391](**Evidence A**). Studies so far have failed to find a plateau of effects at the highest dose used, which suggests that higher doses may be more effective, although such doses are prohibited by the risk of side effects. In double-blind randomized controlled trials of children aged 6 to 14 with asthma[381,392], treatment with zafirlukast reduced nocturnal awakenings and provided 20 to 30 percent protection against exercise-induced bronchoconstriction 4 hours after the medication was taken.

Montelukast was compared to placebo in 336 children aged 6 to 14 with moderate to severe asthma[383]. Approximately one-third of the children in both groups received maintenance therapy with a constant dose of inhaled glucocorticosteroids during the study. The primary outcome measure, FEV_1, increased significantly, and the daily use of inhaled β_2-agonists decreased significantly, in the children who took montelukast compared to those who received the placebo. Montelukast appears to provide less protection against exercise-induced asthma than 400 μg budesonide per day[393].

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Preschool children. Montelukast, compared to placebo, provides significant therapeutic benefit, i.e. improvement in asthma signs and symptoms, for children, ages 2-5, with asthma[641] (**Evidence B**).

Cromones: sodium cromoglycate and nedocromil sodium.

• *Mode of administration*–Inhaled.

• *Role in therapy*–The role of sodium cromoglycate or nedocromil sodium in the long-term treatment of pediatric asthma is limited, particularly in preschool children. A clinical trial in children indicated that nedocromil sodium was associated with less prednisone use and fewer urgent care visits, but by all other measures was no different from placebo[113].

School children. Sodium cromoglycate is less effective than inhaled glucocorticosteroids[255,285,395-400] with respect to symptoms, lung function, exercise-induced asthma, and airway hyperresponsiveness. Although some early placebo-controlled clinical trials found that sodium cromoglycate reduced symptoms, improved lung function, and a decreased the need for rescue bronchodilators[401-403], a meta-analysis of 22 controlled clinical trials concluded that long-term treatment with sodium cromoglycate is not significantly better than placebo for management of asthma in children[404] (**Evidence A**).

A Cochrane review concluded that nedocromil sodium used before exercise appears to reduce the severity and duration of exercise-induced bronchoconstriction[405]. A long-term placebo-controlled trial found a significant, albeit marginal, effect of nedocromil sodium (8 mg per day) on exacerbations, but all other outcome parameters were unaffected[113].

Preschool children and infants. The clinical documentation on the use of sodium cromoglycate in preschool children is sparse, and there are no reports on infants. The available randomized double-blind controlled trials have yielded conflicting results. Several studies have been unable to demonstrate any effect of 20 mg nebulized sodium cromoglycate given 3 to 4 times daily on health outcomes[406-408] or lung function[409], while other studies have indicated that sodium cromoglycate has a significant effect[410-412]–of the same magnitude as theophylline[413,414]–on these parameters.

• *Side effects*–Cough, throat irritation, and bronchoconstriction are problems that occur in a small proportion of patients treated with sodium cromoglycate, and the hypotonicity of the nebulized solution may cause bronchoconstriction[415]. A bad taste, headache, and nausea are the most common side effects of nedocromil[350].

Methylxanthines.

The role of theophylline in the long-term treatment of children with asthma is limited, but the low cost of this treatment may justify more frequent use in some countries.

• *Mode of administration*–Oral.

• *Pharmacokinetics*–Because children metabolize theophylline very rapidly, frequent dosing (4 to 6 times a day) is required when plain tablets are used for long-term treatment. Therefore, sustained-release products are preferable for maintenance therapy, and they enable twice-daily dosing in most children.

It is important to note that concomitant intake of food may change the absorption characteristics of many sustained-release theophylline products in an unpredictable way. Reduced absorption, dose dumping, and marked variations in absorption profiles may be seen[416], complicating the task of ensuring safe, effective treatment. Because the effect of concomitant food intake is quite unpredictable, only sustained-release products that have been shown to be well absorbed in combination with food should be used for maintenance treatment. In this respect, it is important to evaluate both mean and individual absorption profiles; the variation in absorption with food seems to be more pronounced in children than in adults[416]. Sustained-release theophylline products with reliable absorption profiles and complete bioavailability with food have been developed[417].

Dose-response studies with theophylline in a limited number of children with asthma have mainly assessed bronchodilation[418,419] and protection against exercise-induced asthma[420,421]. Dose recommendations have been based on lean body weight and aim at plasma theophylline levels between 55 and 110 μmol/l, which may be required to achieve maximum bronchodilatory effect in children with acute wheeze. However, there is still considerable difference in opinion regarding the optimum plasma levels that should be obtained. Studies in adults and some studies in children suggest that lower levels may be sufficient to achieve a measurable effect on other outcomes in day-to-day management. For example, theophylline's anti-inflammatory effects may be seen at about one-half of the plasma levels required for maximum bronchodilatory effect[20]. Therefore, it seems rational to individualize the dose on the basis of the clinical effect rather than aiming at specific plasma levels, which are more useful in preventing intoxication. At

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present, good studies of therapy with low-dose theophylline in children are lacking.

Within each age group in children, interindividual variations in theophylline half-life may be up to 10-fold. Other drugs may affect theophylline metabolism, such as β_2-agonists (which increase clearance so that higher doses are required), as may viral infections (which reduce clearance). Therefore, the theophylline dose must always be individualized, and if high doses are used plasma theophylline levels must be measured two hours before administration of the next dose. When dose adjustments are made on the basis of serum theophylline concentrations, theophylline often shows dose-dependent kinetics so that, on average, the percent change in serum concentration is about 50 percent greater than the percent change in dose[422].

- *Role in therapy*–Sustained-release theophylline may be used as an alternative to inhaled glucocorticosteroids for maintenance therapy in mild persistent asthma and as add-on therapy with a low dose of inhaled glucocorticosteroids.

  School children. Theophylline is significantly more effective than placebo at controlling symptoms and improving lung function, even at doses below the normally recommended therapeutic range[423-425] (**Evidence A**). Furthermore, a single dose of 15 mg/kg of sustained-release theophylline taken before bedtime is effective at preventing nocturnal asthma symptoms[425]. Long-term maintenance treatment offers a marginal protective effect against exercise-induced asthma[420,426]. Theophylline and oral β_2-agonists seem to have an additive effect on control of asthma[427,428], although it remains unclear whether the combination has any clear clinical advantage compared to either drug used alone.

  Preschool children. There are indications that theophylline treatment has some beneficial clinical effects, such as bronchodilation, in this age group[429,430] (**Evidence C**). However, further double-blind studies are needed to assess the optimal dose and preference of theophylline relative to other treatments in young children.

  Infants. The effect of long-term theophylline treatment has not been assessed in double-blind controlled studies in infants with wheeze.

- *Side effects*–Theophylline has a narrow therapeutic window and potentially lethal side effects when overdosed[431-433]. The most common side effects are anorexia, nausea, vomiting, and headache[431,432,434]. Mild central nervous stimulation, palpitations, tachycardia, arrhythmias, abdominal pain, diarrhea, and, rarely, gastric bleeding may also occur. When maintenance therapy with theophylline is begun, the initial dosage should be low because side effects seem to occur much more frequently if the initial dose is high. Some patients do not tolerate theophylline, regardless of what precautions are taken.

  Theophylline has been reported to induce changes in mood and personality and to impair school performance in children[435,436], although these findings were not reproduced in another study[437].

Long-acting inhaled β_2-agonists.

- *Mode of administration*–Inhaled.

- *Role in therapy*–In children with asthma long-acting inhaled β_2-agonists are primarily used as add-on therapy in combination with inhaled glucocorticosteroids, either as maintenance treatment or as single-dose therapy before vigorous exercise. Inhaled formoterol has a rapid onset of action (3 minutes) and a maximum effect at 30 to 60 minutes after inhalation, much like the short-acting β_2-agonist salbutamol[438,439]. Inhaled salmeterol has a relatively slow onset of action, with a significant effect reported 10 to 20 minutes after inhalation of a single 50-μg dose[440], and an effect comparable to that of salbutamol after 30 minutes[441]. Because of its slow onset of action, salmeterol should not be used to treat acute asthma symptoms, including exercise-induced bronchoconstriction, or to treat patients with rapidly deteriorating asthma. Patients who take salmeterol should also have a short-acting β_2-agonist available at all times for the treatment of breakthrough symptoms.

  Although long-acting inhaled β_2-agonists may be useful in some children with asthma, in contrast to the situation with adults there is insufficient documentation of the effectiveness of these drugs to support a general recommendation for their use in children. Randomized double-blind controlled trials of long-acting inhaled β_2-agonists as add-on treatment in children with poorly controlled asthma have so far yielded conflicting results[442-444]. Most of these trials have shown a statistically significant, albeit small, improvement in lung function[642], but for other outcomes, such as symptoms and exacerbations, the effect of these drugs is marginal and less than that seen in adults.

  The recommended dose of formoterol for children (older than 6 years) is 4.5 μg twice daily, although individual patient responses to the medication can vary considerably and some patients may benefit from doses above the

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usual recommended level. The recommended dose of salmeterol for children (older than 4 years) is 50 μg twice daily. Some children achieve full bronchoprotection for more than 12 hours after a single dose of inhaled salmeterol or formoterol, although a considerable heterogeneity in the duration and magnitude of the response may be seen in different individuals[445].

- *Side effects*–Long-acting inhaled β_2-agonists are well tolerated in children, even after long-term use, with a side-effect profile comparable to that of short-acting β_2-agonists.

Long-acting oral β_2-agonists.

Long acting oral β_2-agonists include slow-release formulations of salbutamol or terbutaline and bambuterol, a prodrug that is converted to terbutaline in the body.

- *Mode of administration*–Oral (ingested).

- *Mechanisms of action*–Long-acting oral β_2-agonists (sympathomimetics) are bronchodilators. Like other β_2-agonists, they relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability, and may modulate mediator release from mast cells and basophils.

- *Role in therapy*–Long-acting oral β_2-agonists may be helpful in controlling nocturnal symptoms of asthma. They may be used as an addition to inhaled glucocorticosteroids when standard doses do not sufficiently control nocturnal symptoms[446,447].

- *Side effects*–Possible side effects include cardiovascular stimulation, anxiety, and skeletal muscle tremor. Adverse cardiovascular reactions may also occur with the combination of oral β_2-agonists and theophylline.

Reliever Medications

β_2-agonists.

Rapid-acting inhaled β_2-agonists have been the mainstay of asthma treatment in children for many years. These drugs are by far the most effective bronchodilators available and therefore the preferred treatment for acute asthma (**Evidence A**).

- *Mode of administration*–Inhaled, oral, and intravenous.

- *Role in therapy*–Rapid-acting β_2-agonists should preferably be given by inhalation since this allows bronchodilation to be achieved more rapidly, at a lower dose, and with fewer side effects than occurs with either oral or intravenous administration[447,448]. Furthermore, inhalation offers significant protection against exercise-induced asthma[449], which is not seen after systemic administration[450]. Generally quite low doses (25 percent of the normal dose in the inhaler) produce marked bronchodilation, while higher doses are required to protect effectively against various challenges[258].

Short-acting oral β_2-agonists have low systemic absorption and a high first-pass metabolism in the wall of the gastrointestinal tract and in the liver. Thus, the systemic bioavailability of these drugs after oral dosing is only about 10 to 15 percent when plain tablets are used. This figure is around 30 percent lower after administration of a slow-release product. Therefore, somewhat higher doses should be used when β_2-agonist therapy is changed from plain to slow-release tablets. Concomitant intake of food further reduces gastrointestinal bioavailability by about one-third[451]. Clearance of β_2-agonists is higher in children than in adults[452,453].

There is a significant correlation between plasma drug levels and bronchodilatory effect after systemic administration of β_2-agonists in children, although considerable inter-individual variations in this relationship exist[454,455]. Therefore, effective therapy cannot be assured by standardized dosing. Rather, dosing should be individualized, with monitoring of the therapeutic response and the occurrence of side effects to determine the proper dose[453]. A rational approach is to start oral treatment at around 0.15 mg/kg/day and then gradually increase the dose until a sufficient clinical effect or systemic side effects are seen. Oral doses of about 0.5 mg/kg/day are often required to produce optimal clinical effects[450,455].

School children. Rapid-acting inhaled β_2-agonists have repeatedly proven superior to other drugs in the treatment of acute episodes of wheeze[456,457] (**Evidence A**). Furthermore, premedication with a single dose of these drugs effectively inhibits exercise-induced asthma[449,458]. The normal duration of bronchodilation produced by a single dose of rapid-acting inhaled β_2-agonist in children is 1 to 5 hours[459], although the duration of action of these drugs depends upon the outcome measure assessed. For example, the duration of protection against exercise-induced asthma is markedly shorter than the duration of bronchodilation[449].

Maintenance treatment with a short-acting oral β_2-agonist does not protect effectively against exercise-induced asthma[450], though it improves symptoms and peak expiratory flow rates and protects against nocturnal

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asthma, particularly when a slow-release product is used[427,450]. A combination of theophylline and short-acting oral β_2-agonist has been found to be more effective than either drug used alone[427], though it is not known whether the combination is preferable to single-drug therapy when the single drug is used in optimal doses.

Preschool children and infants. Bronchodilation[460-470] and bronchoprotection[471,472] with rapid-acting inhaled β_2-agonists have been demonstrated by objective measurements in preschool children. In infants, early studies failed to find any bronchodilator response to nebulized short-acting β_2-agonist[376,473-475], which led to the belief that short-acting β_2-agonists are ineffective in this age group. In these early studies, a fall in transcutaneous oxygen was interpreted as a lack of bronchodilator response[476], although alternative explanations for this effect have since been presented, including acidity of the nebulizer solution[477] and ventilation-perfusion mismatch. Other studies have reported an increase in transcutaneous oxygen[478]. Moreover, more recent double-blind placebo-controlled studies have demonstrated significant bronchodilation[460-465], protection against broncoconstrictor agents[471,472], and clinical improvement in infants treated with rapid-acting inhaled β_2-agonist either alone or in combination with glucocorticosteroids[280]. The reason for these inconsistent results is not clear, although the various studies have differed with respect to dose, inhaler device (spacer, nebulizer), baseline lung function, duration of symptoms, and method of lung function measurement, and the inconsistencies are only seen in bronchodilator effects. All studies find that short-acting β_2-agonists provide significant protection against bronchoconstriction induced by various challenges. Thus, it seems that infants have functional beta-adrenergic receptors from birth, and that stimulation of these receptors can produce the same effects as in older children.

- *Side effects*–As in adults, skeletal muscle tremor, headache, palpitations, and some agitation are the most common complaints in children when high doses of β_2-agonists are used. After systemic administration of these drugs, these complaints seem to occur when the top of the bronchodilatory dose-response curve is reached[454]. Side effects seem to disappear with continued use of the medication[479,480].

Anticholinergic agents.

- *Mode of administration*–Inhaled.

- *Pharmacokinetics*–Virtually all pharmacokinetic data in children concern ipratropium bromide delivered with a nebulizer, although it would be expected that the optimal dose from an MDI would be lower[481]. Various studies have found that increasing the dose above 250 μg provides no extra bronchodilation[482] or protection against exercise-induced asthma[483] or cold air hyperventilation. No formal dose-response studies have been performed in infants, but a dose of 25 μg/kg has produced beneficial effects in one study[461]. The optimal frequency of dosing remains unknown.

- *Role in therapy*–Anticholinergics have a limited role in the management of asthma in children.

  School children. The bronchodilator response to ipratropium bromide seems to be quite variable in school children, but is always less than the response to an inhaled β_2-agonist[484]. Furthermore, there is no benefit from adding the drug to regular β_2-agonist treatment for maintenance therapy[485,486].

  Preschool children. As in school children, bronchodilation is seen in preschool children after inhalation of a single dose of ipratropium bromide[487,488]. However, in one study regular treatment with ipratropium bromide (250 μg 3 times a day) was no better than placebo in the control of asthma in preschool children, and a recent meta-analysis concluded that the effect in children was marginal[488].

  Infants. A Cochrane review concluded that there is not enough evidence to support the uncritical use of anti-cholinergic agents for treatment of wheezing in infants, although patients using it at home were able to identify some benefits[489].

- *Side effects*–Paradoxical bronchoconstriction after inhalation and dryness of the mouth may be a problem in some patients[490,491]. Some of these problems reported in the past seemed to be due to benzalkonium chloride, which has now been removed from the nebulizer solution. No other important side effects are associated with anticholinergic treatment.

Alternative and Complementary Methods of Healing

See the section on management of asthma in adults.

A STEPWISE APPROACH TO PHARMACOLOGIC THERAPY

The stepwise treatment paradigm emphasizes that asthma at any age, even from early childhood, is a disease in which chronic airway inflammation underlies recurrent symptoms. Evidence suggests that any asthma more severe than intermittent is more effectively controlled by interventions

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that suppress and reverse this inflammation than by those that only treat the episodic bronchoconstriction and related symptoms.

The selection of pharmacologic treatment options is made on the basis of an individual patient's asthma severity, the patient's current treatment, the pharmacological properties and availability of various antiasthma treatments, and economic considerations. Because asthma is a dynamic as well as a chronic condition, medication plans must accommodate variability among patients as well as the variability of an individual patient's disease over time. An essential aspect of any treatment plan is monitoring of the effect of the treatment (including measurements of lung function and symptoms) and adaptation of the treatment to the variability of the asthma.

An approach to pharmacologic therapy in which treatment is correlated with asthma severity permits this flexibility. The classification of asthma severity should be made by means of evaluating the patient's symptoms, medical history, and current treatment, a clinical examination, and measurements of lung function where possible (**Figure 5-6** and **Figure 5-7**).

An appropriate approach to asthma therapy recommends that the number (type), dose, and eventually frequency of medications be increased with increasing asthma severity. The aim is to accomplish the goals of therapy with the least possible medication. In developing an asthma management plan, the health care professional must judge whether to give maximum treatment initially–which may involve a burst or cycle of oral glucocorticosteroids in order to achieve control of the patient's asthma as quickly as possible–and then decrease the medication, or to start with treatment judged appropriate for the severity of the patient's asthma and increase the treatment gradually if necessary. Once control of asthma is sustained for 3 months, a reduction in therapy can be carefully considered. This reduction in therapy is needed to identify the minimum therapy required to maintain control.

Figure 7-8 presents the stepwise approach to therapy to achieve and maintain control of asthma in children. The step system for classifying asthma severity takes into account the treatment that the patient is currently receiving (**Figure 5-7**). **Figure 7-8** presents all therapies that can be recommended for treating each step of asthma severity. Guidance for selecting among these available modalities is provided in the text. The cost of the medication is an obvious factor in determining the choice of treatment. Cost of treatment varies from country to country and is only one of the factors that contribute to the total cost of a disorder such as asthma.

How To Achieve and Maintain Control of Asthma

This section describes the therapy appropriate for different steps of asthma severity. The presence of one or more features of clinical severity places a patient at the respective step (**Figure 5-6**). The current treatment should be included in the assessment of severity (**Figure 5-7**).

In the stepwise approach to therapy, progression to the next step is indicated when control is not achieved or is lost with the current treatment, and there is assurance the patient is using medication correctly. The frequent (e.g., more than 3 times a week) presence of such symptoms as cough, wheezing, and dyspnea, and the increased use of rapid-acting bronchodilators, may indicate inadequate control of asthma. The presence of symptoms at night or early in the morning is an especially useful indicator. Measurement of PEF and its variability is helpful in the initial assessment of asthma severity and in monitoring the initial treatment, assessing changes in severity, and preparing for a reduction in therapy.

The treatments suggested for each step below are guidelines only; evidence levels assigned are based on references provided in the previous text. Specific medication plans should be tailored by the health care professional depending on the availability of antiasthma medication, the conditions of the health care system, and individual patient circumstances. Repeated use of reliever medication more than 4 times a day indicates that the patient's asthma is not well controlled, and the intensity of treatment should be increased.

School children.

Step 1–Intermittent Asthma. **Rapid-acting inhaled β_2-agonists may be used as reliever medications (Evidence A).** However, in some cases "as-needed" treatment may be insufficient, such as in physically active children who do not normally exercise on a planned schedule. Regular controller treatment (particularly inhaled glucocorticosteroids) may be considered in such children (**Evidence D**).

Step 2–Mild Persistent Asthma. **Inhaled glucocorticosteroids (< 100-400 μg budesonide or equivalent per day) are recommended for maintenance treatment (Evidence A).** Alternative controller medications (listed according to increasing cost of the medication) are sustained-release theophylline (**Evidence C**) and cromones (**Evidence C**). Monotherapy with drugs other than glucocorticosteroids leaves the underlying inflammatory process in asthma less controlled. Studies of monotherapy

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Figure 7-8. Recommended Medications by Level of Severity for Children Younger Than 5 Years of Age

All Levels: In addition to regular daily controller therapy, rapid-acting inhaled β_2-agonist* should be taken as needed to relieve symptoms, but should not be taken more than 3 to 4 times a day. Patient education is essential at every level.

Level of Severity**	Daily Controller Medications	Other Treatment Options***
Step 1 Intermittent Asthma****	• None necessary	
Step 2 Mild Persistent Asthma	• Low-dose inhaled glucocorticosteroid	• Sustained-release theophylline, *or* • Cromone, *or* • Leukotriene modifier
Step 3 Moderate Persistent Asthma	• Medium-dose inhaled glucocorticosteroid	• Medium-dose Inhaled glucocorticosteroid *plus* sustained-release theophylline, *or* • Medium-dose Inhaled glucocorticosteroid *plus* long-acting oral β_2-agonist, *or* • High-dose inhaled glucocorticosteroid *or* • Medium-dose Inhaled glucocorticosteroid *plus* leukotriene modifier
Step 4 Severe Persistent Asthma	• High-dose Inhaled glucocorticosteroid *plus* long-acting inhaled β_2-agonist, *plus* one or more of the following, if needed: • Sustained-release theophylline • Leukotriene modifier • Long-acting oral β_2-agonist • Oral glucocorticosteroid	

All Levels: Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.

* *Other options for reliever medication are (in increasing order of cost) inhaled anticholinergic, short-acting oral β_2-agonist, and short-acting theophylline.*
** *See **Figure 5-6** and **Figure 5-7** for classification of severity.*
*** *Other treatment options listed in order of increasing cost. Relative medication costs may vary from country to country.*
**** *Patients with intermittent asthma but severe exacerbations should be treated as having moderate persistent asthma (**Evidence D**).*

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with long-acting β_2-agonists in children show some benefit but the results are inconsistent. Leukotriene modifiers have not been studied in children with mild persistent asthma; thus, there are no data to support their use. However, moderate effects have been demonstrated with leukotriene modifiers in patients with more severe disease, and by extrapolation this class of drug may also be considered an alternative controller therapy in some patients (**Evidence D**). Long-term trials that compare the effectiveness of the various alternative controller medications in children with mild persistent asthma are needed.

Step 3–Moderate Persistent Asthma. **A higher dose (400-800 μg budesonide or equivalent per day) of inhaled glucocorticosteroid should be used as controller medication (Evidence A)**. For children who have frequent asthma symptoms despite regular treatment with less than 800 μg inhaled glucocorticosteroid daily, a higher dose of inhaled glucocorticosteroid should be considered (**Evidence D**), but adding another class of controller drug is preferable to increasing the inhaled glucocorticosteroid dose. Long-acting inhaled β_2-agonists are the most studied add-on medications (**Evidence B**). Alternative add-on therapies include sustained-release theophylline (**Evidence B**) and leukotriene modifiers (**Evidence B**). The response to these various medications differs from patient to patient, and the choice of add-on therapy should be individually tailored. Long-term trials that compare the effectiveness of the various alternative add-on therapies in children with moderate persistent asthma are needed.

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Step 4–Severe Persistent Asthma. **A higher dose (> 800 μg budesonide or equivalent per day) of inhaled glucocorticosteroid should be used as controller treatment (Evidence B)**. If the patient's asthma remains uncontrolled, adding another class of controller drug should be considered. Although a long-acting inhaled β_2-agonist is the best-studied and preferred option for add-on therapy (**Evidence B**), alternatives include sustained-release theophylline (**Evidence C**) and leukotriene modifiers (**Evidence B**). If long-term therapy with oral glucocorticosteroids is needed, these drugs should be used in the lowest possible dose (**Evidence C**), and are best given as a single morning dose in order to minimize systemic side effects. When patients are transferred from oral glucocorticosteroids to high-dose inhaled glucocorticosteroids, they should be monitored for evidence of adrenal insufficiency. Again, the patient's response to the various treatment options should be observed, and the choice of treatment should be individually tailored.

Preschool children and infants. Although there are no well-conducted clinical trials to provide scientific evidence for the proper treatment of asthma at each step of severity in these age groups, a treatment algorithm similar to that used in school children is recommended for preschool children and infants. Some adjustments must be made to account for the fact that in these younger children it is difficult to predict the need for reliever medications. At this age, children rarely communicate a need for reliever treatment, and caregivers are often unaware of the signals to observe and are unfamiliar with the drug treatment. These considerations argue for early introduction of controller treatment rather than reliance on "as-needed" rescue treatment. Preschool children and infants with wheeze represent a more heterogeneous group than school children. Thus, the specificity of the asthma diagnosis in children under 3 is poor, and aerosol treatment may present an obstacle to regular treatment.

Young children with asthma may be hospitalized with severe symptoms related to an upper airway infection. Courses of inhaled or oral glucocorticosteroids during such infections may reduce duration and severity of exacerbations, but there is no current evidence to support low-dose maintenance therapy with inhaled glucocorticosteroids in children younger than 3.

Reduction of Maintenance (Controller) Therapy

Asthma is a variable disorder, and spontaneous and therapy-induced variations in its severity occur. Inhaled glucocorticosteroids reduce asthma severity over the long term. **Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.** This will help reduce the risk of side effects and enhance patient adherence to the treatment plan. Reduction of therapy should include close monitoring of symptoms, clinical signs, and, as much as possible, lung function, and should follow the reverse order of what has just been described. In patients on combination therapy the reduction in therapy should begin with a reduction in the dose of inhaled glucocorticosteroid by 25 percent every 3 months. Once the dose of the glucocorticosteroid is at less than 800 μg budesonide per day or equivalent, then the add-on therapy should be stopped (**Evidence D**). It is recommended that patients be reviewed at least every 3 months during the reduction phase.

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PART 5: ESTABLISH PLANS FOR MANAGING EXACERBATIONS

KEY POINTS:

- Treatment of exacerbations depends on the patient, experience of the health care professional, therapies that are most effective for the particular patient, availability of medications, and emergency facilities.
- Primary therapies for exacerbations are the repetitive administration of rapid-acting inhaled β_2-agonist, the early introduction of systemic glucocorticosteroids, and oxygen supplementation.
- Crucial to successful treatment of exacerbations is close monitoring of the patient's condition and response to treatment with serial measurements of lung function.
- Severe exacerbations of asthma are life-threatening medical emergencies. Care must be expeditious, and treatment is often most safely undertaken in a hospital or a hospital-based emergency department.

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Exacerbations of asthma (asthma attacks) are episodes of rapidly progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms. 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)[492]. 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[6]. Still, a minority of patients perceive symptoms poorly[3], and may have a significant decline in lung function without a significant change in symptoms. This situation especially affects patients with near-fatal asthma and also appears to be more likely in males[4].

Figure 7-9. 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 < 2hrs	
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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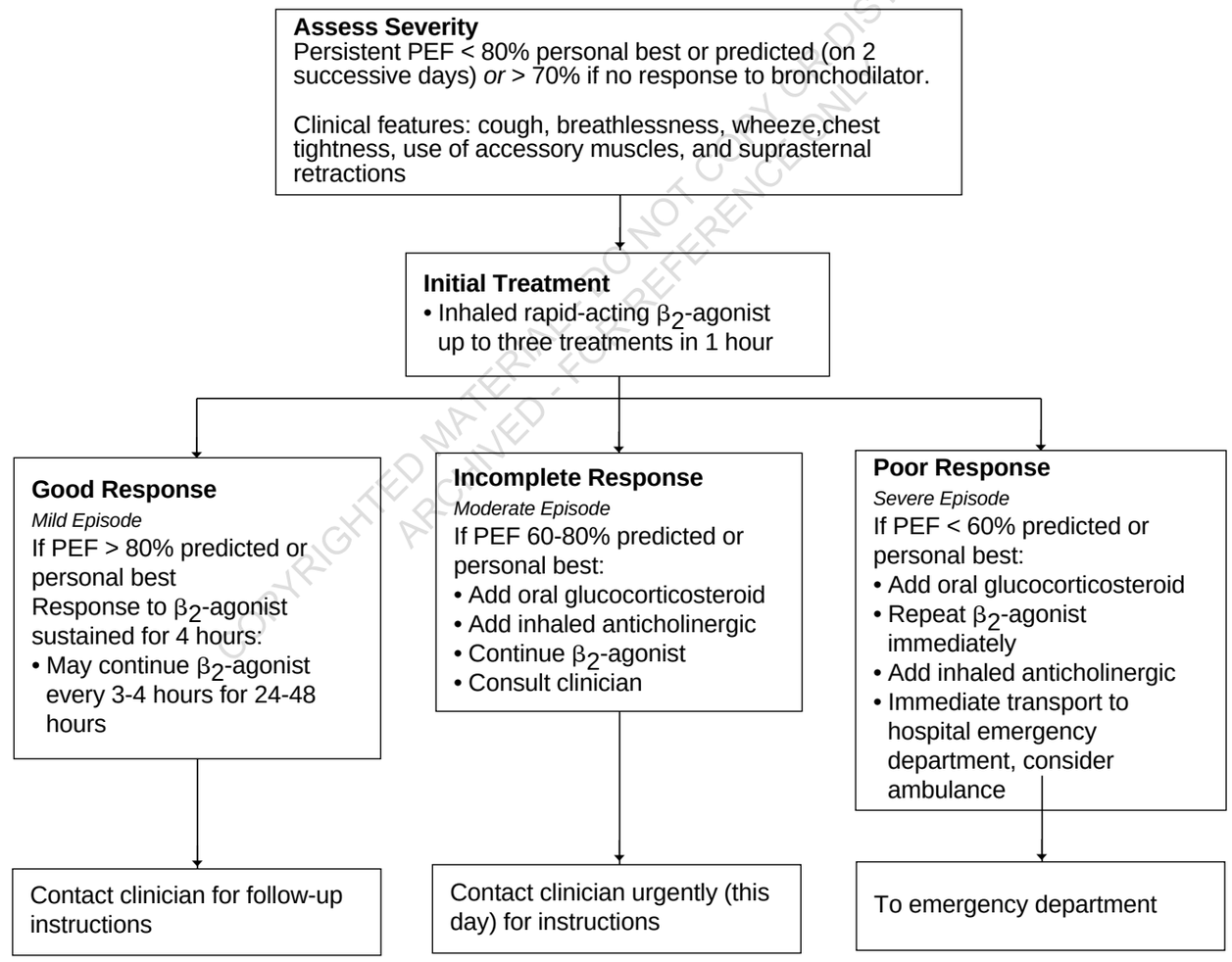
The severity of asthma exacerbations may range from mild to life threatening. Deterioration usually progresses over hours or days, but may occasionally occur precipitously over some minutes. Acute exacerbations usually reflect exposure to a trigger, most often a viral infection or an allergen, but an exacerbation with a more gradual pattern of deterioration may reflect failure of long-term management. Morbidity and mortality are most often associated with failure to recognize the severity of the exacerbation, inadequate action at its onset, and undertreatment of it. Treatment of exacerbations depends on the patient, experience of the health care professional, therapies that are most effective for the particular patient, availability of medications, and emergency facilities. The strategy outlined below is best adapted and implemented at a local level[493] so that its components have the maximal potential for successful utilization[494].

Many patients with moderate persistent to severe persistent asthma will have equipment and medications at home necessary for treating and monitoring an acute asthma exacerbation. Local health care offices or dispensaries often have therapies available to provide temporary relief or amelioration of moderately severe exacerbations. Patients who live in rural settings may, by necessity, have to manage an acute asthma exacerbation at home.

Figure 7-10. Management of Asthma Exacerbations*



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* Patients at high risk of asthma-related death (see text) should contact clinician promptly after initial treatment. Additional therapy may be required.

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Severe exacerbations are potentially life threatening, and their treatment requires close supervision. Thus, although logistical limitations may exist, patients with severe exacerbations should be encouraged to see their usual physician promptly or, if access is not immediately available, should proceed to the nearest hospital. In all settings there should be close objective (PEF) monitoring of the response to therapy to ensure that the patient is not deteriorating and does not require augmented treatment.

The primary therapies for exacerbations are the repetitive administration of rapid-acting inhaled β_2-agonist, the early introduction of systemic glucocorticosteroids, and oxygen supplementation[492]. The aims of treatment are to relieve airflow obstruction and hypoxemia as quickly as possible, and to plan the prevention of future relapses. Crucial to successful treatment is close monitoring of the patient's condition and response to treatment with serial measurements of lung function. Assessment of the patient's pulse, respiratory rate, and current symptoms also guides treatment decisions, but measurements of lung function and oximetry are critical.

Patients at high risk of asthma-related death require prompt care, particularly close monitoring, and intensive patient education. These patients include those:

- With a history of near-fatal asthma requiring intubation and mechanical ventilation, which puts patients at a 19-fold increased risk of needing intubation during subsequent exacerbations[495]
- 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, which appear to offer a protective effect against death or near-fatal asthma[496]
- Who are over-dependent on rapid-acting inhaled β_2-agonists, especially those who use more than one canister of salbutamol (or equivalent) monthly[497]
- With a history of psychiatric disease or psychosocial problems, including the use of sedatives[498]
- With a history of noncompliance with an asthma medication plan.

Full recovery from asthma exacerbations is usually gradual. It may take many days for lung function to return to normal and weeks for airway hyperresponsiveness to decrease. Symptoms and physical signs are not accurate indicators of airflow limitation. The increased treatment should continue until measurements of lung function (PEF or FEV_1) return close to normal, or the patient's personal best.

ASSESSMENT OF SEVERITY OF THE EXACERBATION

The severity of the exacerbation determines the treatment administered. **Figure 7-9** provides a guide to the severity of an exacerbation of asthma at the time the examination is made. Because these are guidelines only, all features in a category need not be present. A more severe grading should be given if the patient has a lack of response to initial treatment, if the exacerbation has progressed quickly, or if the patient is at high risk for asthma-related death.

Indices of severity–particularly peak expiratory flow (PEF) (in patients over 5 years old), pulse, respiratory rate, and pulse oximetry (in children)[499]–should be monitored during treatment. Any deterioration may require prompt intervention. Pulse oximetry has been shown to be particularly useful in pediatric acute asthma. Data also suggest that there are important differences in PEF patterns between periods of poor asthma control and exacerbations; in one study PEF fell during exacerbations, but there was less diurnal variation during exacerbations than during periods of poor asthma control[500].

HOME MANAGEMENT OF EXACERBATIONS

Initiation of appropriate therapy at the earliest possible signs of deteriorating control of asthma is important in the successful management of asthma exacerbations. When patients are able to begin treatment at home, they not only avoid delays in treatment but also add to their sense of control over their asthma. The degree of care provided in the home depends on the health care professional's and patient's (or parents') experience and the availability of medications and emergency care. **Figure 7-10** illustrates the approach to home treatment that is discussed here.

Home PEF measurements ideally should be an integral part of home management strategies, although the degree of symptoms is a more sensitive detector of the early stages of an asthma attack than is PEF[501]. Ideally, all patients should have a written action plan with both a symptom and a peak flow component[501] that outlines how and when to:

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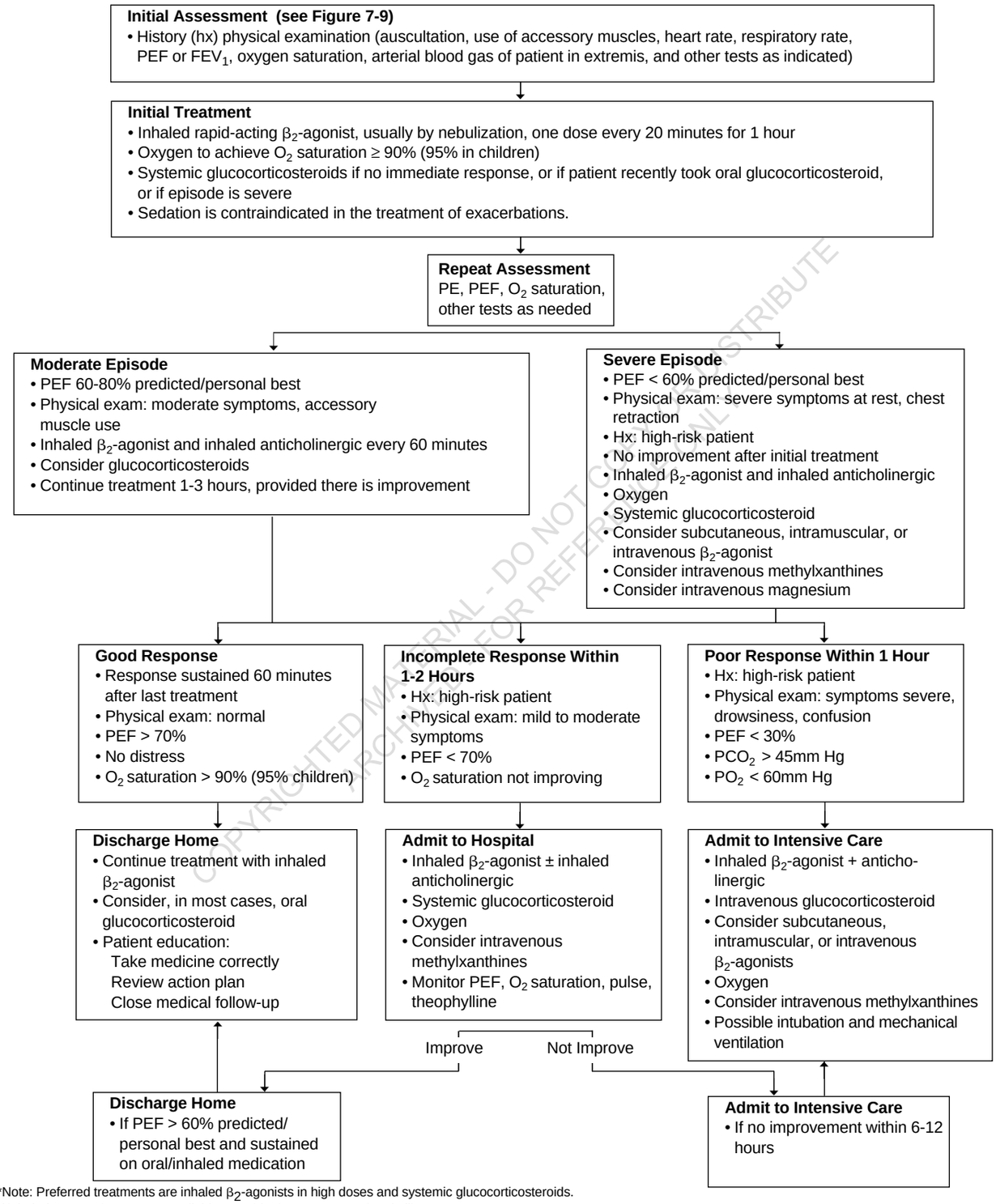
Figure 7-11. Hospital-Based Management of Asthma Exacerbations*



*Note: Preferred treatments are inhaled β_2-agonists in high doses and systemic glucocorticosteroids. If inhaled β_2-agonists are not available, consider intravenous aminophylline; see text.

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- Recognize signs of deterioration
- Modify or augment treatment
- Assess the severity of the attack
- Obtain more specialized care if appropriate.

Treatment

Bronchodilators. For moderate exacerbations, repeated administration of rapid-acting inhaled β_2-agonists (2 to 4 puffs every 20 minutes for the first hour) is usually the best and most cost-effective method to achieve rapid reversal of airflow limitation. After the first hour, the dose of β_2-agonist required will depend on the severity of the exacerbation. Mild exacerbations respond 2 to 4 puffs every 3 to 4 hours; moderate exacerbations will require 6 to 10 puffs every 1 or 2 hours; for more severe exacerbations, up to 10 puffs (preferably given with a spacer), or full doses given via nebulizer, may be required at less than hourly intervals. 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 delivered via nebulizer[102,106]. Depending upon the proportion of patients able to use an MDI, this route of delivery is also likely to be more cost effective[502]. No additional medication is necessary if the rapid-acting inhaled β_2-agonist produces a complete response (PEF returns to greater than 80 percent of predicted or personal best) and the response lasts at least 3 to 4 hours.

Glucocorticosteroids. A number of studies indicate a benefit from action plans that integrate an increase in inhaled glucocorticosteroids early in an asthma exacerbation[501]. The data to support the utility of this strategy are limited[503].

Oral glucocorticosteroids (0.5 to 1 mg/kg prednisolone or equivalent during a 24-hour period) should be used to speed resolution of all but the mildest exacerbations. A useful rough guide is to use oral glucocorticosteroids if the response to the rapid-acting inhaled β_2-agonist alone is not prompt or sustained (e.g., PEF greater than 80 percent of predicted or personal best) after 1 hour.

Additional Care

If there is sustained improvement in PEF and symptoms, care may be continued at home under supervision. Full recovery from the exacerbation is often gradual, and medications for the exacerbation may need to be continued for several days to sustain relief of symptoms and improvement in PEF.

There should be no delay in seeking medical help if:

- The patient is at a high risk for asthma-related death
- The exacerbation is severe (e.g., PEF remains less than 60 percent of predicted or personal best after β_2-agonist therapy)
- The response to the bronchodilator is not prompt and sustained for at least 3 hours
- There is no improvement within 2 to 6 hours after glucocorticosteroid treatment is started
- There is further deterioration.

HOSPITAL-BASED MANAGEMENT OF EXACERBATIONS

Severe exacerbations of asthma are life-threatening medical emergencies. Care must be expeditious, and treatment is often most safely undertaken in a hospital or a hospital-based emergency department. **Figure 7-11** illustrates the approach to hospital-based management of exacerbations that is discussed here.

Assessment

A brief history and physical examination pertinent to the exacerbation should be conducted concurrently with the prompt initiation of therapy. Laboratory studies should not be permitted to delay initiation of treatment.

The brief history should include: severity of symptoms, including exercise limitation and sleep disturbance; all current medication, 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 (see above), especially prior hospitalizations, intensive care admission, and emergency department visits for asthma.

The physical examination should assess the severity of the exacerbation (by evaluating the patient's ability to complete a sentence, pulse rate, respiratory rate, pulsus paradoxicus–though this is a very imprecise sign in children–use of accessory muscles, and other signs detailed in **Figure 7-11**) and identify complications (e.g., pneumonia, atelectasis, pneumothorax, or pneumomediastinum).

Functional assessments include PEF or FEV_1 and arterial oxygen saturation measurements. A baseline PEF or FEV_1 measurement should be made before treatment is initiated, if possible, without unduly delaying treatment.

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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 and an oxygen saturation less than 92 percent is a good predictor of the need for hospitalization[499] (**Evidence C**).

After initial treatment, a chest x ray and arterial blood gas measurements may be helpful in some patients. 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[504]. Similarly, in children routine chest x rays are not recommended unless there are physical signs suggestive of parenchymal disease[505] (**Evidence C**).

Arterial blood gas measurements are not routinely required[506], but should be completed in patients with a PEF of 30 to 50 percent predicted and those who do not respond to initial treatment. The patient should continue on supplemental oxygen while the measurement is made. A PaO_2 less than 60 mm Hg (8 kPa) and a normal or increased $PaCO_2$ (especially greater than 45 mm Hg, 6 kPa) indicates the potential for or presence of respiratory failure. In these circumstances stabilization of the patient in a monitored area, and in the absence of improvement admission to an intensive care unit for ongoing care, is recommended (**Evidence D**).

Special considerations for infants and young children. Several differences in lung anatomy and physiology place infants at theoretically greater risk than older children for respiratory failure. Despite this, respiratory failure is rare in infancy. Close monitoring, using a combination of the parameters listed in **Figure 7-9** other than PEF, will permit a fairly accurate assessment. Breathlessness sufficiently severe to prevent feeding is an important symptom of impending respiratory failure.

Oxygen saturation, which should be measured in infants by pulse oximetry, is normally greater than 95 percent. Arterial or arterialized capillary blood gas measurement should be considered in infants with oxygen saturation less than 90 percent on high-flow oxygen whose condition is deteriorating.

Treatment

The following treatments are usually administered concurrently to achieve the most rapid resolution of the exacerbation[507].

Oxygen. To achieve arterial oxygen saturation of greater than or equal to 90 percent (95 percent in children), oxygen should be administered by nasal cannulae, by mask, or rarely by head box in some infants. Supplemental oxygen should be administered to patients when arterial oxygen monitoring is not available. One study suggests that $PaCO_2$ may worsen in some patients on 100 percent oxygen, especially those with more severe airflow obstruction[508]. Oxygen therapy should be titrated against pulse oximetry to maintain a satisfactory oxygen saturation (> 92%)[683].

Rapid-acting inhaled β_2-agonists. Although rapid-acting inhaled β_2-agonists are generally administered by nebulization, equivalent bronchodilatation with a more rapid onset, fewer side effects, and less time in the emergency department can be achieved using an MDI with a spacer[102,106] (**Evidence A**). However, for some children, administration by nebulizer may be easier. If a jet nebulizer is used, it should be driven by oxygen instead of air. Preliminary results indicate that if salbutamol is used, it may provide greater benefit if it is administered in isotonic magnesium sulfate than in normal saline[509] (**Evidence B**), although isotonic magnesium sulfate cannot be routinely recommended until further studies are complete. Although therapy should ideally be given by the inhaled route, if inhaled medications are not available then oral bronchodilators may be considered. Although short-acting β_2-agonists are the recommended treatment in acute asthma, the long-acting bronchodilator, formoterol, which has rapid onset of action, was shown to be equivalent without increasing side effects, but is considerably more expensive[684].

Compared to racemic albuterol, a modest additional bronchodilator effect has been shown with levabuterol[685-687]. However, there is a substantially higher cost to this therapy which does not support its use in stable asthma[688]. In a large pediatric acute asthma study, levabuterol treatment reduced hospitalization rates compared to the racemic albuterol treatment group[689], but length of hospital stay was no different between groups.

Studies of intermittent versus continuous nebulized short acting β_2-agonists, in acute asthma, provide conflicting results. In a systematic review of six studies[643], there were no significant differences in bronchodilator effect or in admissions to hospital between the two groups. In two of the six studies, continuous treatment was associated with a lower heart rate and less fall in serum potassium. Thus, overall there maybe marginal safety benefit to the use of continuous versus intermittent therapy, although it is

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unclear if this is clinically significant. In patients who do require hospitalization, one study[514] found that on-demand therapy led to a significantly shorter hospital stay, fewer nebulizations, and fewer palpitations when compared with regular therapy given every 4 hours. A reasonable approach to inhaled therapy in exacerbations, therefore, would be the initial use of continuous therapy, followed by on-demand therapy for hospitalized patients.

There is no evidence to support the use of intravenous β_2-agonists in patients with severe asthma[644] who are treated with nebulized β_2-agonists.

Epinephrine. A subcutaneous or intramuscular injection of epinephrine (adrenaline) may be indicated for acute treatment of anaphylaxis and angioedema. Epinephrine can be used in the treatment of severe acute exacerbations of asthma if β_2-agonists (inhaled or parenteral) are not available. However, the possibility of adverse effects, particularly among hypoxic patients, is greater. Although epinephrine is sometimes considered if a severe acute exacerbation is not responsive to rapid-acting inhaled β_2-agonist, a more logical approach, based upon the above data, would be to add an intravenous β_2-agonist[507] (**Evidence B**).

Additional bronchodilators.

Ipratropium bromide. A combination of nebulized β_2-agonist with an anticholinergic (ipratropium bromide) may produce better bronchodilation than either drug alone[224] (**Evidence B**), and should be administered before methylxanthines are considered. A number of studies indicate that combination therapy is associated with lower hospitalization rates[518-520] (**Evidence A**) and greater improvement in PEF and FEV_1[519] (**Evidence B**). Similar data have been reported in the pediatric literature[520] (**Evidence A**). However, once hospitalized, The addition of nebulized ipratropium bromide to nebulized β_2-agonist and systemic glucocorticosteroids appears to confer no extra benefit to children with asthma hospitalized following intensive emergency department treatment[645].

Methylxanthines. Methylxanthines have equivalent bronchodilator effect to inhaled β_2-agonists, but because of increased side effects, methylxanthines should only be considered as an alternate therapy[521]. In one study in children with near fatal asthma, intravenous methylxanthines appear to add benefit to those also receiving an aggressive regimen of inhaled and intravenous β_2-agonists, inhaled ipatropium bromide, and intravenous systemic glucocorticosteroids[646].

Systemic glucocorticosteroids. Systemic glucocorticosteroids speed resolution of exacerbations and should be considered integral to the management of all but the mildest (see **Figure 7-9**) exacerbations[522,523,647] (**Evidence A**), especially if:

- The initial rapid-acting inhaled β_2-agonist dose has failed to achieve lasting improvement
- The exacerbation developed even though the patient was already taking oral glucocorticosteroids
- Previous exacerbations required oral glucocorticosteroids.

Systemic glucocorticosteroids administered by ingestion are usually as effective as those administered intravenously and are preferred because this route of delivery is less invasive and less expensive[220,524]. If vomiting has occurred shortly after administration of the oral dose of glucocorticosteroids, then a similar dose should be re-administered. Intravenous administration may be considered if intravenous access is desirable, or if there is possible impairment of gastrointestinal absorption. In patients being discharged from the emergency department, intramuscular administration may be helpful[525,648], especially if there are concerns about compliance.

Systemic glucocorticosteroids require at least 4 hours to produce clinical improvement. A meta-analysis has suggested that doses of systemic glucocorticosteroids equivalent to 60 to 80 mg methylprednisolone or 300 to 400 mg hydrocortisone per day are adequate for hospitalized patients, and even 40 mg methylprednisolone or 200 mg hydrocortisone is probably adequate[523,526] (**Evidence B**). An oral glucocorticosteroid dose of 1 mg/kg daily is adequate for children with mild persistent asthma who present with an acute exacerbation of asthma[649]. There are no convincing data on the proper duration of oral prednisone treatment, although a 10- to 14-day course in adults and a 3- to 5-day course in children is usually considered appropriate (**Evidence D**). Current evidence suggests that there is no benefit to tapering the dose of oral prednisone either in the short term[221] or over several weeks[527] (**Evidence B**).

Inhaled glucocorticosteroids. The optimum increase in maintenance inhaled glucocorticosteroids to prevent an asthma exacerbation is not well defined. Previous guidelines have recommended doubling the dose of inhaled glucocorticosteroids, but there is no evidence to support this recommendation. Higher doses (discussed below) may be appropriate.

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Inhaled glucocorticosteroids are effective as part of combination therapy for asthma exacerbations that have already developed. One study has shown that the combination of high-dose inhaled glucocorticosteroids and salbutamol in acute asthma provides greater bronchodilation than salbutamol alone[528] (**Evidence B**). In addition, inhaled glucocorticosteroids can be as effective as oral glucocorticosteroids at preventing relapses. Patients discharged from the emergency department on prednisone and inhaled budesonide have a lower rate of relapse than those on prednisone alone[522] (**Evidence B**). A high dose of inhaled glucocorticosteroids (2.4 mg budesonide daily in 4 divided doses) achieves a relapse rate similar to 40 mg oral prednisone daily[529] (**Evidence A**). Although cost is a major factor in using inhaled glucocorticosteroids as adjunct therapy, these studies indicate that in patients intolerant of or not willing to take oral prednisone, similar results can be achieved with very high doses of inhaled glucocorticosteroids. Further studies are required to document the potential benefits of inhaled glucocortico steroids in acute asthma[650,651]. This is especially important given the cost effectiveness of a short course of oral prednisone.

Magnesium. Present evidence suggests that intravenous magnesium should not be used routinely in asthma exacerbations, but can help reduce hospital admission rates in selected groups of patients: adults with FEV_1 25 to 30 percent predicted at presentation; adults and children who fail to respond to initial treatment; and children whose FEV_1 fails to improve above 60 percent predicted after 1 hour of care[652,653] (**Evidence A**). Intravenous magnesium is usually given as a single 2-g infusion over 20 minutes. No additional monitoring is required and there are no reported side effects. One study[690] indicated that use of isotonic magnesium as an adjuvant to nebulized salbutamol results in an enhanced bronchodilator response in treatment of severe asthma. Before this therapy is routinely used further studies are needed.

Helium oxygen therapy. Studies that have evaluated the effect of a heliox, combination of helium and oxygen, compared to oxygen alone, on airflow obstruction and dyspnea suggest that this treatment should not be used routinely for mild to moderate asthma[533,534,654] (**Evidence B**), but should be reserved for patients with more severe disease[535] (**Evidence B**). The role of heliox for the treatment of moderate to severe asthma in emergency department patients is uncertain[691].

Other treatments.

- Antibiotics are not routinely required unless there are signs of pneumonia or fever and purulent sputum suggesting bacterial infection, especially if bacterial sinusitis is suspected.
- Inhaled mucolytic drugs have not been shown to benefit treatment of exacerbations, and in severe exacerbations they may worsen cough or airflow limitation.
- Sedation should be strictly avoided during exacerbations of asthma because of the respiratory depressant effect of anxiolytic and hypnotic drugs. Studies show an association between the use of these drugs and avoidable asthma deaths[498,536].
- Antihistamines and chest physical therapy have no established role in the treatment of exacerbations.

Special considerations for infants and young children. Attention to fluid balance may be necessary for infants and young children, who may become dehydrated as a result of increased respiratory rates and with decreased oral intakes during an exacerbation. When treatments offer similar profiles for efficacy and safety, noninvasive procedures are preferred in order to avoid pain and anxiety. Thus inhaled β_2-agonist (delivered by mouthpiece)[655] and oral glucocorticosteroid therapy are preferred to intravenous or subcutaneous therapy, and pulse oximetry is preferred to arterial blood gas measurements.

Criteria for Continuous Monitoring

Factors indicating the need for close and continuous supervision that is provided either in a hospital or dispensary, depending on available facilities, include:

- Inadequate or deteriorating response to therapy within 1 to 2 hours of treatment
- Persisting severe airflow limitation (PEF less than 30 percent of predicted or personal best)
- Past history of severe asthma, particularly if hospitalization and admission to the ICU was required
- Presence of factors indicating high risk of asthma-related death (see above)
- Prolonged symptoms before the current emergency department visit
- Inadequate access at home to medical care and medications
- Difficult home conditions
- Difficulty obtaining transport to hospital in the event of further deterioration.

Criteria for Discharge From Emergency Department versus Hospitalization

Criteria for determining whether a patient should be discharged from the emergency department or hospitalized

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have been succinctly reviewed and stratified based on consensus[537]. Patients with a pretreatment FEV_1 or PEF below 25 percent of the predicted or personal best value, or those with a posttreatment FEV_1 or PEF below 40 percent of predicted or personal best, usually require hospitalization. Patients with posttreatment lung function in the range of 40 to 60 percent predicted can potentially be discharged, assuming adequate followup is available in the community and compliance is assured. Patients with objective evidence of lung function 60 percent predicted or greater can usually be discharged. Health care workers should take account of the patient's prior adherence history and local pressure on inpatient access.

Criteria for Admission to Intensive Care Unit

Admission to an intensive care unit, with consultation of an asthma specialist or a critical care specialist experienced in treating asthma, is indicated if the patient has any of the following:

- Severe asthma with a lack of response to initial therapy in the emergency department or worsening asthma despite adequate therapy
- Presence of confusion, drowsiness, other signs of impending respiratory arrest, or loss of consciousness
- Impending respiratory arrest: hypoxemia despite supplemental oxygen (PaO_2 less than 60 mm Hg (8 kPa) and/or $PaCO_2$ greater than 45 mm Hg (6 kPa), or SaO_2 by oximetry 90 percent in children) (although respiratory failure may occur with either a high or low $PaCO_2$).

Intubation may be needed if there is continued deterioration in clinical features despite optimal therapy, if the patient is exhausted, and/or if the $PaCO_2$ is increasing. There are no absolute criteria for intubating a patient, but it should be done by an experienced physician familiar with the drugs needed and skilled in upper airway management. Rapid-sequence intubation, using succinylcholine and ketamine, is the preferred approach to intubation[538] (**Evidence D**). Cohort studies have shown that controlled hypoventilation is the preferred method of ventilation[539,540] (**Evidence C**), and that using this approach, the historically high rates of complications previously seen with mechanical ventilation can be avoided[541]. If intravenous paralysis is used, there is the risk of the development of myopathy[542] (**Evidence C**). The duration of paralysis should be as brief as possible.

The detailed management of patients requiring mechanical ventilation for acute asthma has been published[543]. In general, the principles of management for the ventilated patient are the same as those for the nonventilated patient: adequate oxygenation, bronchodilator therapy, and systemic glucocorticosteroids. Delivery of bronchodilators, both rapid-acting inhaled β_2-agonists and ipratropium bromide, is best achieved by an inline delivery system using multiple puffs from an MDI. Failure to respond to this treatment should be an indication to use parenteral bronchodilator with close monitoring for arrthymias as outlined above. Given the documented benefit of magnesium sulfate, this should be infused early in the resuscitation phase. The usual dose is 2 g given intravenously over 20 minutes. Patients should have at least daily monitoring of metabolic parameters, especially serum potassium (**Evidence D**).

Discharge From Emergency Department

At discharge several actions are recommended:

- At minimum a 7 to 10 day course of prednisone for adults and a shorter course (3 to 5 days) for children should be prescribed with continuation of bronchodilator therapy.
- The dose of bronchodilator can be gradually reduced, 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 give additive benefit beyond the acute phase and can be quickly discontinued.
- Patients should continue or initiate inhaled glucocorticosteroids.
- During the recovery phase patients should discontinue their long-acting β_2-agonist until their asthma has been reassessed and stability has again been achieved.
- 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 do better than patients discharged without these resources[544,656].
- The factors that precipitated the exacerbation should be identified and avoided.
- The patient's response to the exacerbation should be evaluated, and avoidable factors identified. The action plan should be reviewed and written guidance provided.
- Use of anti-inflammatory therapy during the exacerbation should be reviewed: whether this therapy was increased promptly, by how much, and, if appropriate, why systemic glucocorticosteroids were not added. Consider providing a short course of prednisone to be on hand for subsequent exacerbations.
- The patient or family should be instructed to contact the patient's family primary health care professional or

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asthma specialist within 24 hours of discharge. A follow-up appointment with the patient's family health care professional or asthma specialist should be made within a few days of discharge to assure that treatment is continued until best lung function is reached. Prospective data indicate that patients discharged from the emergency department for followup with specialist care do better that patients returned to routine care[545].

Discharge From Continuous Supervision

There are no absolute criteria for discharge from hospitalization after an acute attack. However, patients should be on discharge medications for at least 12 hours (**Evidence D**), preferably 24 hours, before leaving supervision to assure that the patient's symptoms are controlled on the treatment he or she will take at home. Generally, the following criteria should be met when discharge doses of oral and inhaled medications have been reached:

- Rapid-acting inhaled β_2-agonist is needed no more frequently than every 3 to 4 hours
- Oxygen saturation (by oximetry) is greater than 90 percent in air (or close to the patient's optimal level)
- The patient is able to walk comfortably
- The patient is not waking at night or in the early morning and needing additional bronchodilator
- Clinical examination is normal or near normal
- PEF or FEV_1 is more than 70 percent of predicted or personal best after rapid-acting inhaled β_2-agonist
- The patient is able to use inhaler devices correctly
- Followup and actions outlined above have all been taken.

An exacerbation severe enough to require hospitalization may reflect a failure of the patient's self-management 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, the purposes and correct uses of treatment, and the actions to be taken to respond to worsening symptoms or peak flow values[546,657]. Referral to an asthma specialist should be considered for patients with a history of life-threatening exacerbations or multiple hospitalizations.

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 best lung function is reached. Plans for longer-term treatment, including adjustment of the overall treatment plan, should then be made. Patients who come to the emergency department with an acute exacerbation should be especially targeted for an education program, if one is available.

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PART 6: PROVIDE REGULAR FOLLOWUP CARE

Patients with asthma need regular supervision and support by a health care professional who is knowledgeable about the condition. Continual monitoring is essential to assure that therapeutic goals are met.

While the patient is achieving control of asthma, frequent followup visits are necessary to review home PEF and symptom records, the techniques in using medication, risk factors and methods to control them.

Consultation with an asthma specialist is recommended under certain circumstances when:

- The patient has had a life-threatening asthma exacerbation, has poor self-management ability, or has difficult family dynamics
- Signs and symptoms are atypical or there are problems in differential diagnosis
- Clinical entities complicate asthma (e.g., sinusitis, nasal polyps, aspergillosis, severe rhinitis)
- Additional diagnostic testing is indicated (e.g., skin testing, rhinoscopy, complete pulmonary function studies, provocative studies)
- The patient is not responding optimally to the asthma therapy
- The patient requires Step 3 or 4 care (moderate persistent to severe persistent asthma) to control asthma
- The patient requires guidance on environmental control, consideration of immunotherapy, smoking cessation, complications of therapy, or difficult compliance issues.

Once control is established, regular followup visits (at 1- to 6-month intervals as appropriate) continue to be essential. Health care professionals need to monitor and review the treatment plans, the medications, the patient's management techniques (e.g., for using medicines and peak flow meters, for controlling the environment), and the level of asthma control (PEF and symptom reports). The most appropriate method for followup will depend on the

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SPECIAL CONSIDERATIONS

health care system. A patient visit to a primary health care or specialist office, an outreach worker visit to patient homes, or followup for asthma that is integrated with a visit for another reason (well care, an acute illness other than asthma) can each be a suitable means for providing the ongoing care essential for control of this chronic disorder.

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

PREGNANCY

During pregnancy the severity of asthma often changes and patients may require close followup and adjustment of medications. Retrospective and prospective studies have suggested that during pregnancy in approximately one-third of women asthma becomes worse; in one-third asthma becomes less severe; and in the other one-third it remains unchanged[547-549].

Although concern exists with the use of medications in pregnancy, poorly controlled asthma can have an adverse effect on the fetus, resulting in increased perinatal mortality, increased prematurity, and low birth weight[548,549]. The overall perinatal prognosis for children born to women with well-managed asthma during pregnancy is comparable to that for children born to women without asthma[550]. 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 drugs used to treat asthma and rhinitis–with the exception of alpha-adrenergic compounds, brompheniramine, and epinephrine–there is little to suggest an increased risk to the fetus. Appropriately monitored theophylline, sodium cromoglycate, inhaled beclomethasone dipropionate, and inhaled β_2-agonists are not associated with an increased incidence of fetal abnormalities. Inhaled steroids have been shown to prevent exacerbations of asthma specifically in pregnancy[551,552] (**Evidence B**). Acute exacerbations should be treated aggressively in order to avoid fetal hypoxia. Treatment should include nebulized rapid-acting β_2-agonists and oxygen; systemic glucocorticosteroids should be instituted when necessary. As in other situations, the focus of asthma treatment must remain on control of symptoms and maintenance of normal lung function.

All patients require adequate opportunity to discuss the safety of their medication, but this is especially important for women who plan to become pregnant and expectant mothers. 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 will provide important additional reassurance[547,553].

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 many factors, including the severity of asthma at the time of surgery, the type of surgery (thoracic and upper abdominal pose the greatest risks), and the type of anesthesia (general anesthesia with endotracheal intubation carries the greatest risk). These variables need to be assessed prior to surgery by history, physical examination, and especially measurement of pulmonary function. If possible, this evaluation should be undertaken several days before the surgery to allow time for additional treatment. In particular, if FEV_1 values are less than 80 percent of the patient's personal best, a brief course of glucocorticosteroids is required to reduce airflow limitation[554,555] (**Evidence C**). Furthermore, patients who have received systemic glucocorticosteroids within the past 6 months should have systemic coverage during the surgical period (i.e., 100 mg hydrocortisone every 8 hours intravenously) and rapidly reduced within 24 hours following surgery. Prolonged glucocorticosteroid therapy may inhibit wound healing[556] (**Evidence C**).

PHYSICAL ACTIVITY

For a majority of patients with asthma, physical activity is an important trigger of asthma exacerbations. For some patients, it is the only trigger. This condition, in which postexertional airflow limitation resolves spontaneously within 30 to 45 minutes following physical activity, is referred to as exercise-induced asthma (EIA). Some forms of exercise, such as running, are more potent triggers[557]. EIA may occur in any climatic condition, but it increases substantially in breathing dry, cold air and is less common in hot, humid climates[558].

EIA is one expression of airway hyperresponsiveness, not a special form of asthma. EIA often indicates that the patient's asthma is not properly controlled; therefore,

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appropriate anti-inflammatory therapy generally results in the reduction of exercise-related symptoms. For those patients who still experience exercise-induced asthma despite appropriate therapy and for those in whom exercise-induced asthma is the only manifestation of asthma, the inhalation of rapid-acting β_2-agonist before exercising is the most effective treatment for preventing asthma exacerbations. Many other compounds (sodium cromoglycate, nedocromil, anticholinergic agents, theophylline, inhaled glucocorticosteroids, antihistamine H_1-antagonists, leukotriene modifiers, and long-acting β_2-agonists) have been demonstrated to modulate EIA. Training and sufficient warming up also reduce the incidence and severity of exercise-induced asthma[559,560]. In people with asthma, physical training can improve cardiopulmonary fitness without changing lung function. It is not known whether this improved fitness translates into improved quality of life[560] (**Evidence B**).

Because the treatment of EIA is so effective, there is no need for patients to avoid physical activity. Instead, a goal of asthma management is to enable most patients to participate in any activity they choose without experiencing symptoms. In addition, physical activity should be part of the therapeutic regimen of subjects with EIA. Physical training decreases the ventilation necessary to maintain a certain level of activity; because the severity of EIA depends on ventilation, a well-trained subject with EIA experiences postexertional symptoms only at a higher degree of physical activity than before training. Therefore, it is important to recommend that sports and physical activity should not be avoided in patients with EIA[560].

RHINITIS, SINUSITIS, AND NASAL POLYPS

Upper airway diseases can influence lower airway function in some patients with asthma. Although the mechanisms associated with this relationship have not yet been fully established, recent studies have shown that inflammation plays a critical role in the pathogenesis of rhinitis, sinusitis, and nasal polyps, just as in asthma.

Rhinitis

Asthma and rhinitis often coexist in the same patient[561]. Common allergens such as house dust mites, animal danders, and, less commonly, pollen and aspirin or other NSAIDs can affect both the nose and bronchi[562-564]. Studies of the temporal relationship between the onset of rhinitis and that of asthma have shown that rhinitis frequently precedes the development of asthma[565]. The majority of patients with asthma–75 percent of those with allergic asthma and over 80 percent of those with nonallergic asthma–present with symptoms of seasonal or perennial allergic rhinitis[561,566].

Both asthma and rhinitis are considered to be inflammatory disorders of the airway, but there are some differences between the two conditions in terms of mechanisms, clinical features, and treatment approach. Although the inflammation of the nasal and bronchial mucosa is sustained by a similar inflammatory infiltrate, including eosinophils, mast cells, and T lymphocytes, there are differences in the mechanism of obstruction related to structural differences between the nose and the bronchi[567]. In rhinitis, nasal obstruction is largely due to hyperemia of blood vessels, while in asthma reversible airway obstruction is mostly due to airway smooth muscle contraction. In asthma airway mucosal inflammation causes epithelial shedding, increased thickening of the reticular layer of the subepithelial basement membrane, and hypertrophy of the airway smooth muscle[568]. In perennial rhinitis, the epithelium is usually not shed[569].

Treatment of rhinitis may improve asthma symptoms[570,658] (**Evidence A**). Anti-inflammatory agents including glucocorticosteroids, cromones, leukotriene modifiers, and anticholinergics are effective in both conditions. However, differences in treatment for the two conditions exist: some medications are selectively effective against rhinitis (e.g., α-agonists) and others against asthma (e.g., β-agonists). Others, such as the H_1-antagonists, are more effective in rhinitis than asthma (**Evidence A**)[571].

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 provoke asthma. Diagnosis of sinusitis requires either X-ray or CT scan confirmation; clinical findings of sinusitis are often too subtle to make the diagnosis[572]. Antibiotic therapy of sinusitis has been associated with short- to medium-term improvement in symptoms. Such therapy is more likely to be effective if the antibiotics are given for at least 10 days[573] (**Evidence B**). Treatment should also include medications (topical nasal decongestants or topical nasal glucocorticosteroids) to reduce nasal congestion. However important these treatments are, they remain adjunct to primary asthma therapy[565,571].

Nasal Polyps

Nasal polyps associated with asthma and rhinitis, and often with aspirin sensitivity[574], are seen primarily in

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patients who are over 40 years old, and they are more prevalent in patients who have negative skin tests. Various studies have shown that 7 to 15 percent of patients with asthma have nasal polyps, with the highest frequency of polyps seen among those over 50 years old. The same studies show that between 36 and 96 percent of aspirin-intolerant patients have polyps and 29 to 70 percent of patients with nasal polyps referred to ENT departments and allergy clinics, respectively, have asthma[574,575]. Children with nasal polyps should be assessed for cystic fibrosis and immotile cilia syndrome. Nasal polyps are remarkably responsive to glucocorticosteroids, and topical steroid therapy has a well-established role in the management of this condition[571]. Patients who have chronic nasal obstruction that persists in spite of treatment may benefit from surgery, although the role of nasal and sinus surgery in the management of nasal polyps has not been precisely established.

OCCUPATIONAL ASTHMA

Asthma is the most common occupational respiratory disorder in industrialized countries[576]. Occupational asthma is defined as asthma caused by exposure to an agent encountered in the work environment. Over 300 specific occupational agents are associated with asthma[577,578-580]. It has been estimated that occupational factors are associated with about 1 in 10 cases of adult asthma, including new-onset disease and aggravation of pre-existing asthma[576]. Occupations associated with a high risk for occupational asthma include farming and agricultural work, painting (including spray painting), cleaning and janitorial work, and plastic manufacturing[577].

Two types of occupational asthma are recognized: immunologically mediated and nonimmunologically mediated. Immunologically mediated occupational asthma is more common and has a latency period of months to years after the onset of exposure[581-583]. The mechanisms by which a variety of occupational agents induce sensitization and asthma are largely unknown, but IgE-mediated allergic reactions, and possibly cell-mediated allergic reactions or both, are involved[584,585]. Nonimmunologically mediated occupational asthma, or irritant-induced asthma, has no latency. Reactive airway dysfunction syndrome (RADS) is the best example of irritant-induced asthma. Typically asthma symptoms associated with airflow obstruction and/or airway hyperresponsiveness occur within 24 hours following accidental exposure to a high concentration of an irritant gas, fume, or chemical in a previously healthy subject and last for at least 3 months[586].

A diagnosis of occupational asthma should be considered in every adult patient with new or worsening asthma. Detection of asthma of occupational origin requires a systematic inquiry about the patient's occupation and exposures as part of the clinical history. Improvement of symptoms away from work and worsening of symptoms on returning to work suggest an occupational relationship. 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 by objective means. One 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[582,587,588]. This method is often used by itself, but additional monitoring of nonallergic airway hyperresponsiveness will ensure that changes in PEF with changing work exposure are actually reflect occupational asthma. There are very few centers with facilities for specific inhalation testing to confirm an occupational asthma diagnosis.

Once the diagnosis is established, complete avoidance of the relevant exposure is the ideal management[581,582,589]. Occupational asthma may not be completely reversible 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[590,591]. Continued exposure may lead to increasingly severe and potentially fatal asthma exacerbations[592], a lower probability of subsequent remission, and, ultimately, permanently impaired lung function[593]. 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.

Atopy and tobacco smoking may increase the risk of occupational sensitization in some workers in specific occupations. Screening individuals for atopy is of limited value in preventing occupational asthma[581]. The most important method of primary prevention of occupational asthma is elimination or reduction of exposure through substitution, and by adequate occupational hygiene measures.

RESPIRATORY INFECTIONS

Respiratory infections have an important relationship to asthma as they provoke wheezing and increased symptoms in many patients. Epidemiological studies have found that respiratory viruses[594], possibly chlamydia, and mycoplasma[659] but seldom other bacteria[595], are the

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infectious microorganisms associated with increased asthma symptoms. The respiratory virus that most commonly causes wheezing in infancy is respiratory syncytial virus[50], while rhinoviruses, which cause the common cold, are the principal triggers of wheezing and worsening of asthma in older children and adults[596]. Other respiratory viruses, such as parainfluenza, influenza, adenovirus, and coronavirus, are also associated with increased wheezing and asthma symptoms[597].
A number of mechanisms have been identified to explain wheezing and increased airway responsiveness with respiratory infections, 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[598]. 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[599].

Treatment of an infectious exacerbation follows the same principles as in other asthma exacerbations; that is, rapid-acting inhaled β_2-agonists and the early introduction of oral glucocorticosteroids or increase in inhaled glucocorticosteroids are recommended. Because increased asthma symptoms can often last for weeks beyond the infection, anti-inflammatory treatment should be continued for weeks to ensure adequate control.

GASTROESOPHAGEAL REFLUX

The relationship of increased asthma symptoms, particularly at night, to gastroesophageal reflux remains an issue of debate, although this condition is nearly 3 times as prevalent in all patients with asthma[600-603]. Most of these patients also have a hiatal hernia; furthermore, the use of methylxanthines may increase the likelihood of symptoms by relaxing the lower esophageal ring.

Diagnosis can best be made by simultaneously monitoring esophageal pH and lung function. Medical management should be given for the relief of reflux symptoms as it is often effective and includes eating smaller, more frequent meals; avoiding food or drink between meals and especially at bedtime; avoiding fatty meals, alcohol, theophylline, and oral β_2-agonists; using H_2-antagonists or proton pump inhibitors; using drugs that increase lower esophageal pressure; and elevating the head of the bed. Surgery is reserved for the severely symptomatic patient with well-documented esophagitis and failure of medical management; it is not successful for everyone. It should be demonstrated that the reflux causes asthma symptoms before surgery is advised for patients with asthma[602,603].

The role of antireflux treatment in asthma control is unclear as it does not consistently improve lung function, asthma symptoms, nocturnal asthma, or the use of asthma medications in subjects with asthma but without clear reflux-associated respiratory symptoms. Subgroups of patients may benefit, but it appears difficult to predict which patients will respond to this therapy[604].

ASPIRIN-INDUCED ASTHMA (AIA)

In 4 to 28 percent of adults with asthma, but rarely in children with asthma, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) cause asthma exacerbations. The variability depends on the diagnostic criteria[605].

The course of the disease and its clinical picture are characteristic[606]. The majority of patients first experience symptoms during the third to fourth decade of life. The typical patient experiences intense vasomotor rhinitis characterized by intermittent and profuse rhinorrhea. Over a period of months, chronic nasal congestion occurs, and physical examination often reveals nasal polyps. Asthma and intolerance to aspirin develop during subsequent stages of the illness. In these individuals, asthma runs a protracted course. The intolerance presents itself as a unique picture: within an hour following ingestion of aspirin, an acute asthma exacerbation develops, often accompanied by rhinorrhea, conjunctival irritation, and scarlet flush of the head and neck. These reactions are dangerous; indeed, a single therapeutic dose of aspirin or other anticyclooxygenase agent can provoke violent bronchospasm, shock, loss of consciousness, and respiratory arrest[606,607].

Persistent inflammation with marked eosinophilia, epithelial disruption, cytokine production, and upregulation of adhesion molecules is found in the airways of patients with AIA[608]. Eosinophilic infiltration of airway tissue is a central feature of AIA. Eosinophils are 4 times more numerous in AIA patients than in aspirin-tolerant subjects with asthma, and 15 times more numerous than in people without asthma[609]. The airway expression of interleukin-5 (IL-5), which is known to be involved in the recruitment, activation, maturation, and survival of eosinophils, is markedly increased in patients with AIA[609]. These patients, whose asthma is characterized by increased production of cysteinyl leukotrienes, also exhibit an overexpression of leukotriene C4 (LTC4) synthase in the bronchi. This phenomenon is explained partly by a genetic polymorphism of the LTC4 synthase gene found in 70 percent of patients with AIA[610], a common promoter variant that creates a

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predisposition to aspirin-sensitive asthma by reinforcing the effector mechanism of bronchoconstriction. However, the exact mechanism by which aspirin acts on cyclooxygenase to trigger bronchoconstriction remains unknown.

Not all of the offending drugs produce adverse reactions with the same frequency. This depends on a drug's anticyclooxygenase potency and dosage as well as on the individual sensitivity of the patient[564].

Although a patient's clinical history may raise suspicion of AIA, the diagnosis can be established with certainty only by aspirin challenge, conducted only where facilities for cardiopulmonary resuscitation exist. There are no *in vitro* tests suitable for routine clinical diagnosis. If confirmation of an AIA diagnosis is necessary, patients are challenged when their asthma is in remission and their FEV_1 is greater than 70 percent of predicted or personal best. Oral challenge tests are hazardous and carry a risk of provoking a severe reaction; they should be replaced by the safer inhalational challenge with lysine-aspirine[611]. Nasal challenge is less sensitive but safer than inhalation testing and can be used as an initial test of aspirin intolerance[612]. All challenges should be carried out in the morning in the presence of a highly trained and experienced physician and with emergency treatment available. The reaction is considered positive if at least a 15 percent decrease in FEV_1 or PEF occurs, accompanied by symptoms of bronchial obstruction and irritation of nose or eyes. In the absence of these clinical findings, the reaction is considered positive only if a fall in FEV_1 or PEF greater than 20 percent occurs.

Once aspirin or NSAID intolerance develops, it is present for life. Patients with AIA should avoid aspirin, all products containing it, and other analgesics that inhibit cyclooxygenase and hydrocortisone hemisuccinate[613]. However, such avoidance does not prevent the progression of the inflammatory disease. Where a non-steroidal is strongly indicated, the use of cyclooxygenase (COX-2) inhibitor may be considered with appropriate physician supervision and patient observation for at least one hour[660-662] (**Evidence B**). Glucocorticosteroids continue to be the mainstay of therapy, and leukotriene modifiers may be useful for additional control of the underlying disease[564,614] (**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[615]. After aspirin desensitization, daily ingestion of high doses of aspirin reduces inflammatory mucosal disease symptoms, especially in the nose, in most patients with AIA[564].

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.

Risk factors for the occurrence of anaphylaxis include a prior history of anaphylaxis, the presence of atopy, unstable steroid-dependent asthma, allergen immunotherapy, and the concomitant use of beta-blockers or ACE inhibitors[616].

Symptoms of anaphylaxis include flushing, pruritis, urticaria, and angioedema; upper and lower airway involvement such as stridor, dypsnea, wheezing, or apnea; dizziness or syncope with or without hypotension; and gastrointestinal symptoms such as nausea, vomiting, cramping, and diarrhea. The differential diagnoses of acute anaphylaxis include acute urticaria, asthma, angioedema, ischemic heart disease, cardiac arrhythmia, shock, and seizure. Exercise-induced anaphylaxis, often associated with medication or food allergy, is a unique physical allergy and should be differentiated from exercise-induced asthma[617].

Airway anaphylaxis could account for the sudden onset of asthma attacks and the relative resistance of attacks to acute doses of β_2-agonists in severe "brittle" asthma[618,619]. 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, aqueous epinephrine, injectable antihistamine, intravenous glucocorticosteroid, 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 preloaded epinephrine[616].

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CHAPTER

8

RESEARCH RECOMMENDATIONS

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Asthma, a chronic lung disease that affects people of all ages, races, and ethnic groups, is a growing concern throughout the world. As a result, there has been a considerable research interest in a number of areas: (1) understanding the underlying pathophysiologic mechanisms that lead to asthma; (2) identifying risk factors and evaluating appropriate methods of risk factor avoidance; (3) evaluating existing management strategies and developing new therapeutic approaches; and (4) developing and evaluating strategies to improve asthma control and patients' quality of life. The development and evaluation of methods to incorporate new research findings into patient care, and the identification of measures of the socioeconomic impact of asthma care, have also contributed to the impressive progress in asthma control that has been achieved in the past decade. Yet much work remains to be done and many research avenues to be explored. This chapter provides a brief sketch of some of the important research questions that need answers. Special attention must be given to overcoming barriers to the implementation of asthma management programs in developing countries where resources are limited.

1. **Genetics of Asthma:** Family clustering of asthma and allergy suggests a genetic basis for the disease. However, the progressive increase in the prevalence of asthma witnessed in the last two decades is most likely related to an interaction of environmental factors with genetic susceptibility, since the genetic background of the population has not changed significantly over this period. Further work is needed to clarify how genetic susceptibility interacts with the timing of environmental exposure and of exposures that stimulate the immune system (e.g., *in utero* or during the first days of life) to cause or predispose individuals to asthma. Defining these interactions is key to developing effective prevention strategies. The genetic basis of the variability in individual responses to asthma treatments (pharmacogenetics) is an important new area of exploration.

2. **Pathogenesis and Mechanisms of Asthma:** Additional research is needed to broaden understanding of the molecular, cellular, and immunologic mechanisms that lead to asthma and affect its severity and chronicity. A better understanding of the events that initiate, direct, and perpetuate the development of airway inflammation in response to both immunologic and nonimmunologic stimuli may lead to the identification of new targets for treatment. In addition, reliable, noninvasive surrogate tests that reflect the inflammatory response in asthma are needed. Investigating the relationship of pathological changes to indices of lung function and improving understanding of what constitutes airway remodeling are important priorities. A promising area of investigation involves mechanisms regulating the function of airway receptors, as evidence suggests that a defect in beta-adrenergic receptors could contribute to the development of asthma and may lead to a more severe clinical course of the disease.

3. **Prevention:** Intervention strategies for the primary prevention of asthma remain in the realm of speculation and hypothesis, yet primary prevention may well be achievable if targets for intervention can be identified. Secondary prevention measures, such as those related to reducing exposure to known allergens and environmental insults, require continued examination in carefully controlled clinical investigations, in several different populations and socioeconomic settings, to determine their impact on reducing asthma symptoms and acute exacerbations.

4. **Burden of Asthma:** Epidemiologic and socioeconomic studies have the potential to help health planners define risks and document the costs and benefits of improved management guidelines. However, to achieve these outcomes, data on asthma incidence, severity, hospitalization, and mortality are needed. Epidemiologic investigations can also aid in identification of environmental exposures that influence the rate of decline in lung function and increased airway hyperresponsiveness.

5. **Diagnosis and Monitoring:** Development and validation of methods for early diagnosis, monitoring, and evaluation of asthma treatment are needed, with special attention to methods appropriate for use in infants and young children.

6. **Asthma Guidelines:** Research is needed to determine the impact of national asthma programs and asthma guidelines at national, district, and local levels in both developed and developing countries. Whether guidelines are useful as a basis for audit, for setting standards, and for education should be explored. Measures to assess outcomes of asthma care need to be continually evaluated.

7. **Patient Education and Delivery of Care:** Although the efficacy of guided self-management has been demonstrated for patients with asthma, numerous issues have yet to be clarified including the amount of detail needed; use of this strategy in people of different ages, ethnicities, and socioeconomic backgrounds; and use and cost-effectiveness in different settings,

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including health care facilities, schools, and the patient's home. Studies to examine the most effective and efficient roles for patients, physicians, and other health care professionals in guided self-management and to determine the best way to integrate this strategy into primary medical care should be conducted. The effective use of guided self-management in developing countries requires special attention, due to problems of literacy, cultural attitudes, and barriers to medical care including the availability and cost of medications. It is also important to clarify the relative effectiveness of interventions delivered by different health care professionals and the impact of asthma support groups, telephone help lines, and new methods of communication and education such as e-mail and interactive multimedia. The impact of these interventions on patients' quality of life should be included in measurements of program effectiveness.

8. **Severe Asthma:** It has been estimated that 5 to 10 percent of patients with asthma have severe disease that is unresponsive to typical therapies. The genetic, molecular, cellular, and immunologic events that lead to severe asthma are unknown. The natural course and causes of severe asthma need to be defined.

9. **Alternative Medicine:** In many parts of the world, "alternative" or "traditional" therapies have been reported to be of use in the treatment of asthma. The most widely used therapies are acupuncture, homeopathy, herbal medicine, and Ayurvedic medicine (which includes transcendental meditation, herbs, and yoga). However the use of these therapies in asthma has not been validated by controlled clinical trials, and their mechanisms of action are not clearly understood. However, these therapies warrant scientific investigation to assess their efficacy and their relation to currently recommended management approaches.

10. **Asthma Management:** In the past two decades, the implementation of effective asthma treatments has made it possible for people with asthma to live fully active lives. However, additional research on new therapeutic approaches, and continued work on currently available medications, remains essential. Evaluation of combination therapies, effective therapeutic doses in children and adults, interaction of asthma medication with other medications (especially in elderly patients), and continued comparison of various classes of medications in well-controlled randomized clinical trials are key to future progress in asthma management.

There are several other areas related to asthma management that should be investigated:

- The long-term effects of asthma therapy on the natural history of asthma and on lung function require investigation.
- The efficacy of the step approach to asthma care, as recommended in this document, needs to be examined in large populations of asthma patients using a variety of outcome measures, including quality of life.
- The potential side effects of long-term use of inhaled glucocorticosteroids in both children and adults need to continue to be monitored.
- The risk of side effects from inhaled glucocorticosteroids needs to be examined in malnourished children.
- A number of studies indicate a benefit from action plans that include an increase in inhaled glucocorticosteroids early in an asthma exacerbation. Although this concept has gained wide clinical endorsement, randomized controlled trials are required.
- Long-term studies of leukotriene modifier therapies should be undertaken.
- The efficacy and applicability of the recommendations for the management of acute asthma exacerbations in different health care systems need to be studied.
- New inhaler devices are being developed and introduced at regular intervals. These require careful evaluation and studies of cost-effectiveness.

11. **New Approaches to Asthma Treatment:** Several new therapeutic agents have been developed to target specific components of the inflammatory process in asthma, although they have not yet been proven to be particularly effective. Targets of these agents include IgE antibodies, cytokines, chemokines, and vascular adhesion molecules. Future developments might include better forms of immunotherapy and treatments targeting the remodeling of structural elements of the airways.

IgE antibodies: The concept that IgE plays a critical role in asthma pathogenesis has driven the

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development of IgE blockers, which are currently being introduced into clinical use. However, much remains to be learned about the role of IgE in asthma and the genetic and environmental influences that lead to its production. Over the next few years, the emerging experience with anti-IgE in patients will provide a more complete understanding of the mechanisms by which IgE contributes to disease, as well as the therapeutic potential of its inhibition.

Cytokines: Increasing knowledge of the pathophysiologic roles of various cytokines in atopic diseases has provided the basis for the development of novel therapies. Approaches to cytokine inhibition include blocking transcription factors that lead to cytokine expression; inhibiting cytokines after their release; cytokine receptor antagonism; and inhibiting signaling pathways that are activated after cytokine-receptor binding. The proinflammatory cytokines interleukin (IL)-5, IL-4, IL-13, and tumor necrosis factor-α (TNF-α) are among the targets of these new therapies.

Chemokines and vascular adhesion molecules: It is now widely accepted that T lymphocytes play a primary role in orchestrating the processes of airway inflammation through their capacity to generate a range of cytokines encoded by genes in the IL-4 gene cluster on the long arm of chromosome 5. Additional cytokines derived from mast cells and eosinophils also play key roles, especially TNF-α, which is responsible for initiating the upregulation of vascular adhesion molecules involved in the recruitment of eosinophils and other inflammatory cells from the circulation. The importance of CXC and CC chemokines as local chemoattractants and activating stimuli is also recognized. As more is learned about these factors, it will be interesting to determine whether this knowledge will lead to specific clinical applications in asthma.

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The Global Initiative for Asthma is supported by educational grants from:

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