

# GLOBAL INITIATIVE FOR ASTHMA

## GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION NHLBI/WHO WORKSHOP REPORT

(Based on a March 1993 Meeting)



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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 today not only in terms of health care costs but also of lost productivity and reduced participation in family life.

Recent advances in science have improved our understanding of asthma and our abilities to manage it effectively. The "International Consensus Report on Diagnosis and Management of Asthma," published in 1992 by the National Heart, Lung, and Blood Institute (NHLBI), presented an approach to asthma therapy that translated these scientific advances into recommendations for clinical management of asthma. Response to the report was significant. Within a year, professional and medical societies in many countries had translated and disseminated the report and its recommendations.

The diversity of national health care service systems and variations in the availability of asthma therapies required, however, that the recommendations be adapted to ensure their appropriateness throughout the global community. In addition, public health officials needed information about the costs of asthma, prevention activities, and education methods so that they could develop asthma care services and programs responsive to the particular needs and circumstances of their countries.

To meet these needs, NHLBI and the World Health Organization (WHO) collaborated in convening workshops to develop information, recommendations, and tools to assist health care professionals and public health officials in appreciating the magnitude of the asthma problem in their countries and in designing and delivering effective asthma management and prevention programs in their communities. Twenty-one workshop participants from 17 countries met three times.

"Global Strategy for Asthma Management and Prevention" is the report of the workshops. Chronic disability and premature deaths can be prevented; people with asthma can have productive and fulfilling lives. The ideas and methods presented in this publication will help public health officials and health care professionals around the world develop strategies to achieve these goals. Highlighted are the new appreciation for the significant role of airway inflammation in the pathogenesis of asthma, the new emphasis on control and prevention in treatment, and the new focus on establishing risk factors for the

development of asthma. This report also emphasizes the continual need to explore ways to improve asthma care and highlights areas for future research investigation.

I would like to acknowledge the educational grants from Abbott Laboratories Inc., ASTA Medica, Astra, Boehringer Ingelheim GmbH, Byk Gulden, Forest Laboratories Inc., Glaxo Research and Development Ltd., Merck & Co., Mitsubishi Chemical Corporation, Norton Healthcare Ltd., Rhône-Poulenc Rorer Pharmaceuticals Inc., Sandoz Pharma Ltd., and Schering-Plough International. 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.

I would also like to acknowledge the superlative work of the workshop participants and the effective leadership of the workshop chair, Dr. Albert L. Sheffer. It was a privilege to bring together physicians and scientists from around the world who shared a remarkable spirit of collaboration as well as commitment to furthering the principles of asthma care for all peoples and nations.

The Global Initiative for Asthma (GINA) was created to prepare scientific reports on asthma, encourage dissemination and adoption of the reports, and promote international collaboration on asthma research. GINA has prepared additional publications since the original printing of the workshop report:

- "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 publications are available from the National Institutes of Health, National Heart Lung, and Blood Institute (Bethesda, Maryland, USA 20892), the Global Initiative for Asthma Secretariate, (Romain Pauwels, M.D., Ph.D., and chair of GINA: Department of Respiratory Diseases, University Hospital, Ghent, Belgium), and the Internet (<http://www.ginasthma.com>).



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# INTRODUCTION

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# CHAPTER

1

## *DEFINITION*

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## KEY POINTS:

- Asthma—whatever 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 predisposition for developing an IgE-mediated 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.

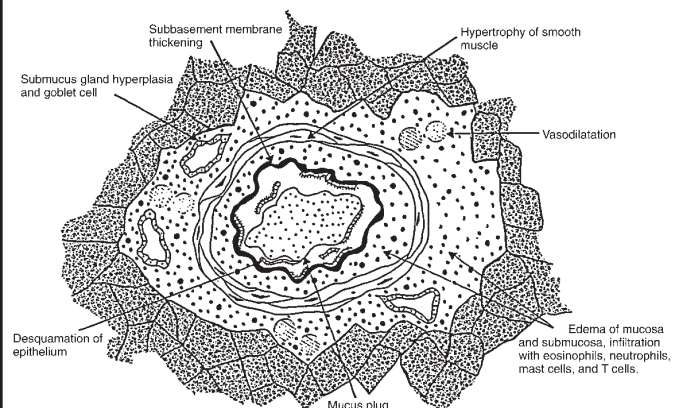
Many attempts have been made to define asthma in terms of its impact on lung function—that is, airflow limitation, its reversibility, and airway hyperresponsiveness (1). But these attempts have been frustrated by a lack of understanding of the mechanisms involved in asthma. Appreciation of the key role of the underlying inflammatory response in asthma leads to a more complete definition of

asthma. This chapter provides the framework for a new definition of asthma based on the underlying pathology of airway inflammation and its relation to disordered lung function. This new view of asthma has profound implications in terms of diagnosis, treatment, and prognosis.

## AIRWAY PATHOLOGY IN ASTHMA

Until recently most information on the pathology of asthma has been obtained from asthma death. Macroscopically in patients who have died of asthma the lung is overinflated, 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 mononuclear cells accompanied by vasodilatation, evidence of microvascular leakage, and epithelial disruption (see figure 1-1) (2). Trophic changes 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) as well as airway wall remodeling. Thus there is evidence of both acute and chronic inflammation that is irregularly distributed throughout the airways (3). An exception is sudden death due to asthma, in which neutrophils may dominate the pathology (4).

Figure 1-1. Pathological Features of Asthma Death



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The relationship between the pathological changes and clinical indices in life has been difficult to obtain. Clinicians have long recognized an association of sputum and blood eosinophilia with asthma (5), 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 (6). In all forms of asthma, there is strong 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 (7). The recent 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 (8). However, T lymphocyte activation is also a feature of other types of airway disease, including chronic bronchitis and bronchiectasis (9). 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 (3). Although the presence and quantification of inflammatory cells in spontaneously produced or saline-induced 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 (10).

In addition to releasing potent mediators that contract airway smooth muscle, increase microvascular leakage, activate different neurons, and stimulate mucus-secreting cells, a number of mediators are released that have the capacity to produce structural changes in the airways. Of particular importance is the targeted attack on the ciliated epithelium, which in places becomes stripped to a single layer of basal cells (11). In an attempt to compensate, epithelial cells and myofibroblasts lying beneath the epithelium proliferate and in doing so lay down interstitial collagens in the *lamina reticularis* of the basement membrane, thus explaining the apparent basement membrane thickening that is characteristic of asthma (12). 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 but neglected components of the disease. Although many of the mediators responsible for these changes to the airway architecture have yet to be defined, cytokines and growth factors seem to be particularly important.

Asthma in childhood and adults is frequently found in association with atopy, which is defined as a largely genetic susceptibility for developing immunoglobulin IgE directed to epitopes expressed on common environmental allergens such as domestic mites, animal proteins, pollens, and fungi (13). As a consequence, the mast cell is sensitized, and when appropriately activated, this leads to the inflammatory response. Atopy occurs in 30 to 50 percent of the population and frequently occurs in the absence of disease. However, when it becomes expressed in the lower airways, atopy is one of the strongest predisposing factors for developing asthma. When expressed in other organs, it gives rise to such diseases as rhinitis, conjunctivitis, eczema (atopic dermatitis), and food allergy. (See the chapter on risk factors.)

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## RELATIONSHIP OF AIRWAY PATHOLOGY TO DISORDERED LUNG FUNCTION

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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 the key factor (see the chapter on mechanisms of asthma). The state of hyperresponsiveness in which the airways narrow too easily and too much 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) or 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, bradykinin) or a combination of both mechanisms (see figures 1-2 and 1-3) (14).

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 expiratory volume in 1 second ( $FEV_1$ ), or by the presence of a plateau and the concentration of agonists at which this occurs (see figure 1-4) (15). Measurement of airway responsiveness has been standardized for histamine and methacholine using aerosol inhalation by tidal breathing (16) or administered in predetermined amounts via a dosimeter (17). For epidemiological purposes, the use of a hand-operated nebulizer has gained popular acceptance (18). 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, the position of the stimulus-response curve being described as the provocative concentration (or dose) of agonist that reduces  $FEV_1$  by 20 percent from baseline ( $PC_{20}$  or  $PD_{20}$ ) (see figure 1-4). Note that the cutoff point between normal or increased responsiveness is dependent on the method used and the population studied and should be adjusted accordingly (19).

The clinical consequences of airway hyperresponsiveness are reflected in an increased variation in airway caliber both within and between days (see figure 1-5) (20). 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 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  $\beta_2$ -agonist is accepted as diagnostic (see figure 1-6) (21). 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 (22). This bronchodilator test method of demonstrating lung dysfunction is of diagnostic help only if the baseline index 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. 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 postexercise being diagnostic (see figure 1-7) (23).

### Airflow Limitation

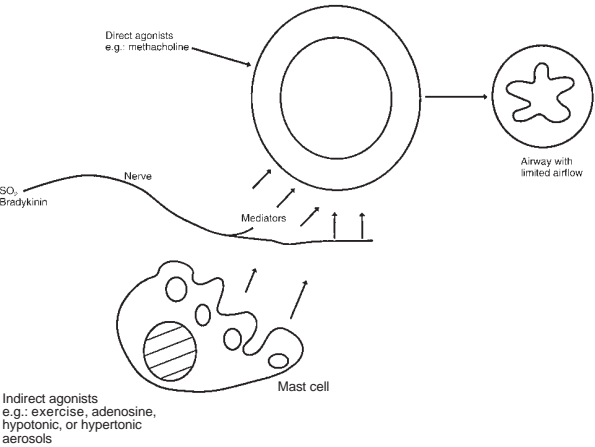
The recurrent episodes of airflow limitation in asthma have four forms. Each relates to the airway inflammatory response (see figure 1-8).

Figure 1-2. Heterogeneity of Airway Hyperresponsiveness in Asthma

Mediator Release	Nerves	Micro-vasculature	Smooth Muscle
Allergen			
Exercise			
Adenosine			
	NKA Substance P		
	Sulfur dioxide		
	PAF		
	Bradykinin		
		Prostaglandins	
		Leukotrienes	
		Histamine	
		Acetylcholine	

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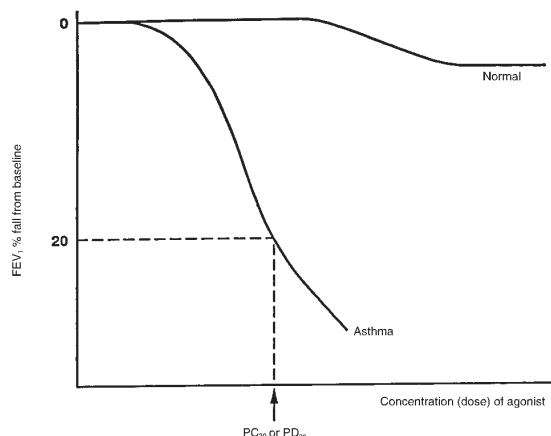
Figure 1-3. Concept of Direct and Indirect Airway Hyperresponsiveness



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- Acute bronchoconstriction.** The mechanism of acute airflow limitation varies according to the stimulus. Allergen-induced acute bronchoconstriction results from the IgE-dependent release of mediators, including histamine, prostaglandins, and leukotrienes from airway mast cells that contract the smooth muscle (24). 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 (NSAID's) is also

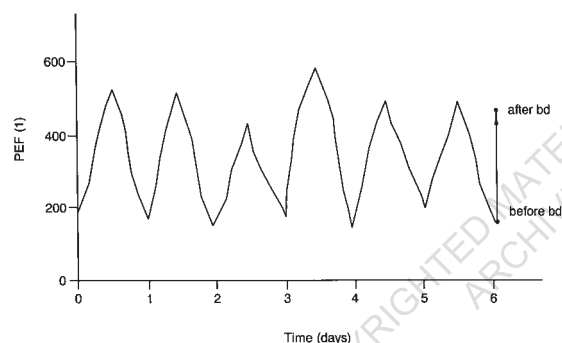
Figure 1-4. Dose-Response Relationship Between Constrictor Agonist and Decrease in an Index of Airway Caliber in Normal and Asthmatic Airways



The position of the curve describes the level of airway reactivity (PEF and FEV<sub>1</sub>). This is frequently defined as the concentration (or dose) that reduces the Index of airway caliber by 20 percent of starting baseline.

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Figure 1-5. 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)

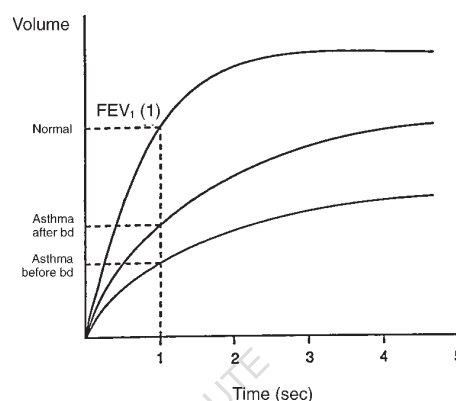


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considered to be the consequence of mediator release (especially leukotrienes), although the precise mechanisms responsible for this have yet to be elucidated (25, 26).

Acute airflow limitation may also occur because airways in asthma are hyperresponsive to a wide variety of stimuli consequent to the underlying inflammation. The mechanisms in this response are described in the preceding section on airway hyperresponsiveness. Many stimuli can cause acute bronchoconstriction, such as inhalation of allergens, exercise, cold air, fumes, and chemicals, and strong emotional expressions like crying and laughing. Their mechanisms for causing

Figure 1-6. Typical Spirometric Tracings From a Normal Subject, a Subject With Asthma, and a Subject With Asthma After Using a Bronchodilator (bd)



Note: Each FEV<sub>1</sub> curve represents the highest of three repeat measurements.

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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.

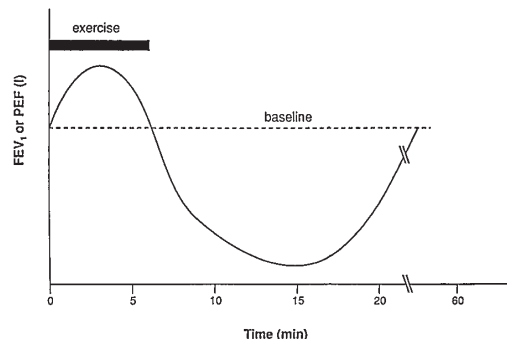
Withdrawal of beta-sympathetic tone through the use of beta-adrenoreceptor antagonists may also produce acute severe bronchoconstriction secondary to the unopposed action of released constrictor mediators (especially acetylcholine) (27).

The acute bronchoconstriction form of airflow limitation is rapidly reversed with an inhaled bronchodilator agent, such as short-acting beta<sub>2</sub>-agonist (21).

- **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 corticosteroids. This component of the asthmatic response 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 reaction (24). 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 phenomena contribute to airway hyperresponsiveness in asthma (28, 29).

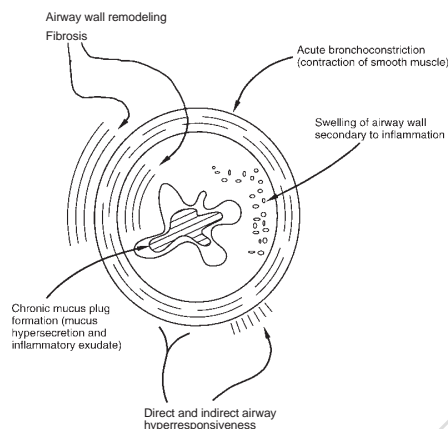


Figure 1-7. The Effect of an Exercise Test on Airway Caliber: Exercise-Induced Asthma Following a Brief Period of Bronchodilation



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Figure 1-8. Factors That Contribute to Airflow Limitation in Asthma



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- **Chronic mucus plug formation.** This more intractable airflow limitation, which has been little studied, usually takes 6 weeks or longer to resolve following the introduction of corticosteroid treatment. It is dominated by increased mucus secretion that, with exuded serum proteins and cell debris, comprises the inspissated mucus plugs characteristically occluding the more peripheral airways in severe asthma.
- **Airway wall remodeling.** Airflow limitation sometimes fails to reverse with corticosteroid treatment. The cellular and molecular basis of this “steroid resistance” may be at the steroid receptor transduction level or may be associated with structural changes to the airway matrix accompanying longstanding and severe airway inflammation.

From a clinical standpoint, airway inflammation is the most likely variable factor to account for varying severity of asthma and is therefore the element most responsive to controlling medications such as sodium cromoglycate,

nedocromil, and corticosteroids. 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 (6). 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 (2). Between these extremes lies the common exacerbation of asthma in which mucosal swelling, excess secretions, and increased airway responsiveness are features of the inflammatory response.

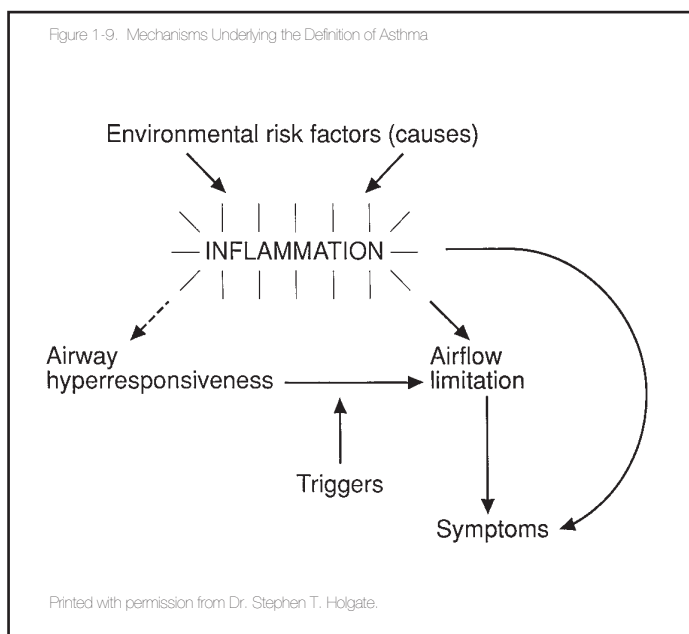
## DEFINITION OF ASTHMA

Asthma may be defined based on pathology and its functional consequences (see figure 1-9). 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. Because there are no well-validated noninvasive measurements of airway inflammation in asthma, the clinician and epidemiologist have had to rely on surrogate indices. 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 play a role, in particular mast cells, eosinophils, and T lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli.

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. Many studies have used questionnaires, which may underestimate or overestimate the prevalence of asthma. For epidemiological purposes the definition of “current asthma” is symptoms of asthma within the last year associated with airway hyperresponsiveness. A measurement of airway responsiveness and serial measurement of PEF as an index of airway caliber add considerably to the confidence with which the inflammatory response of asthma is diagnosed. An increased responsiveness to histamine or methacholine (specific cutoff values depend on method used), a PEF variability

Figure 1-9. Mechanisms Underlying the Definition of Asthma



across 24 hours (amplitude percent mean) of 20 percent or more, and an increase in FEV<sub>1</sub> of 15 percent or more from baseline with an inhaled short-acting beta<sub>2</sub>-agonist are accepted criteria for objectively confirming a diagnosis of asthma (see figures 1-4, 1-5, and 1-6). Note, however, that daily variability in PEF and other indices of airway hyperresponsiveness are not invariably associated with asthma, especially in some children with mild intermittent symptoms (30). Moreover, in any individual with asthma, airway hyperresponsiveness measured by bronchial challenge may vary considerably over prolonged periods and at any given time may not relate well to severity of the asthma assessed both by symptoms and level of airflow limitation (31).

## RESEARCH RECOMMENDATIONS

Being able to sample the airways by endoscopic mucosal biopsy and lavage has greatly increased our understanding of asthma mechanisms, but both techniques have sampling limitations, with biopsies restricted to the proximal airways and lavage to the surface of the airways. Sampling errors in a disorder that varies in its expression at different sites along the bronchial tree may well account for the difficulty that some investigations have found in relating the cellular response to indices of clinical activity. Thus priorities for future investigations related to the definition of asthma include:

- Developing reliable noninvasive surrogate tests to reflect the inflammatory response. This could lessen having to rely purely on measurements of lung function.

- Investigating the relationship of pathological changes to indices of lung function, especially in those patients with highly unstable or chronic indolent asthma in which changes to the neurogenic or structural components of the airway (matrix), respectively, are considered important.

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# CHAPTER

2

# ***EPIDEMIOLOGY***

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## KEY POINTS:

- Asthma is one of the most common chronic diseases worldwide and is increasing in children.
- Asthma occurs in all countries regardless of the level of development but appears to be more common in affluent than in nonaffluent populations.
- The increase in prevalence of asthma may be related to environmental factors, including increasing exposure to allergens and pollutants.
- Asthma can impair quality of life and be a major cause of absence from school and work.
- Data on asthma incidence, morbidity, hospitalization, and mortality are needed from around the world, using standard methodologies, to assist more effective health planning.

Asthma is a problem worldwide. The prevalence of asthma in children varies from almost 0 to 30 percent in different populations. There is good evidence that the prevalence is increasing worldwide, but there are, as yet, insufficient data to determine the likely causes for this increase or for the variations in prevalence among countries. The existing data are biased toward the situation in the Western developed countries from which the most information has been obtained. Health planners are working to develop effective programs for the prevention and management of asthma, but as yet, the impact of asthma management guidelines on large populations is difficult to determine.

This chapter first defines terms needed for asthma epidemiology and then outlines present knowledge about the prevalence, mortality, and morbidity of asthma. The knowledge deficits for these aspects of epidemiology are highlighted. In particular, data about the morbidity and cost effectiveness of different treatments in different countries, including developed countries, are lacking. A checklist that can be used to assess the asthma problem in a locality or country is provided. The chapter concludes with research recommendations. These are aimed at narrowing the gaps in information among countries through homogeneous and well-designed protocols for studying prevalence, mortality, and morbidity, particularly in developing countries.

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## DEFINITIONS

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Terms for which a definition relates to the epidemiology of asthma (1) include the following:

- **Prevalence.** The percentage of the population with a disease, disorder, or abnormality. Cumulative prevalence is the total number of those who have had the disorder at a given time. Point prevalence is the number 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 degree to which quality of life is impaired.
- **Airway responsiveness.** The response of the airways to varying provoking stimuli.
- **Airway hyperresponsiveness.** Airways that narrow too easily or too much in response to a provoking stimulus. In persistent asthma, the airways are hyperresponsive to many different provoking stimuli. Objective parameters are required to assess airway hyperresponsiveness.
- **Atopy.** The propensity, usually genetic, for developing IgE-mediated responses to common environmental allergens.

### Defining Populations

Definitions of affluent, partly affluent, and nonaffluent populations are based on economic grounds:

- **Affluent populations.** These 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 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 afforded. Most of the world's population is partly affluent.
- **Nonaffluent populations.** These are without adequate housing or access to running water and may have an irregular supply of food. Access to health care is inadequate.

- **Migrants.** Persons 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

The difficulties in defining asthma for epidemiologic studies are well known. Despite hundreds of reports on the prevalence and mortality of asthma in widely different populations, the lack of precise definitions of asthma and of standardized methods makes reliable comparison of reported prevalence from different parts of the world problematic. Thus data are not easily compared and provide little information that can be used in health planning or in defining the causative agents. However, a European Economic Community sponsored study (2) of adult asthma and the current International Study of Asthma and Allergies in Childhood (ISAAC), a study in 30 countries around the world in which identical tools are used, will contribute important data that will allow comparisons of prevalence in the near future.

### Questionnaires

Most studies have used questionnaire data that, depending on the definitions used, may underestimate or overestimate the prevalence of the disorder. The standardization of questionnaires has been attempted (2), but questionnaires suffer from potential variable intercultural responses to descriptive terms used. Questionnaire definitions of asthma include "wheeze ever" (the least useful data because responses are influenced by the ability to recall the events) and "diagnosed asthma" (this may be more valuable because of medical certification; however, children in some communities have asthma that has never been diagnosed [3]) (see figure 2-1). To overcome linguistic and cultural differences, use of a video questionnaire may be of interest (4).

### Objective 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 or by exercise challenge, has



**Figure 2-1. Prevalence of Asthma in Children in Studies Using Airway Hyperresponsiveness as a Test**

Country	Study year	Number	Age	Current asthma	Diagnosed asthma	Wheeze ever	Airway hyperresponsiveness	Atopy (SPT)	References
Australia	82 86 91	1,487 1,217 1,575	8 to 10 8 to 11 8 to 11	5.4 6.7 9.9	11.10 17.3 30.8	21.7 26.5 40.7	10.1(H) 10.0(H) 16.0(H)	29.3 31.9 37.9	70 71 72
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	27.2 26.6	22.0(M) 20.0(H) 12.0(E)	45.8	26 73 74
England	80	1,613		8.0#		14.8*	?(H)		3
Wales	89	965		5.3#	12	22.3	8.0(E)		74
Germany	90	5,768	9 to 11	4.2#	7.9		?(C)	?	75
Denmark	87	527	7 to 16	5.3			16.0(H)	31	76
Spain	90	2,216	9 to 14	?		?	6.9(E)		77
Indonesia	81	406	7 to 15	1.2	2.3	14.5	2.2(H)	24.1	78
China	88	3,067	11 to 17	1.9	2.4	6.3	4.1(H)	?30	79
Papua New Guinea	85	257	6 to 20	0	0	1.7	1.0(H)	17	80
Kenya	91	402	9 to 12	3.3	11.4		10.7(E)		81
Australia indig: aborigines	91	215	7 to 12	0.1	0	1.4	2.8(H)	20.5	82

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;  
 C: cold air; SPT: skin prick test.

All figures are a percentage of the population tested.

proved to be the most useful because it defines a group of subjects with clinically important asthma. For these patients, their asthma persists, and they need more treatment than patients with symptoms alone or with airway hyperresponsiveness alone (1). In affluent countries methacholine or histamine challenge remains the method of choice. Exercise challenge, using strict environmental conditions, is also used in some populations, although it does 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 (5-8). 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 at risk for recurrent symptoms. 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 allergy is often associated with asthma, it is important to perform tests allowing the diagnosis of allergy. Skin tests using a standardized panel of allergens relevant for the geographical area (see the chapter on diagnosis and classification) appear to be the easiest method. The measurement of specific IgE is an alternative, although it is more expensive. The measurement of total serum IgE is not a good predictive method for allergy screening.

The characterization of the environment of the patient populations appears to be critical in order to interpret the results of other measurements. The environment can be assessed by quantitating the amount of allergen present in the home (for example, cat allergen and domestic mite allergen in mattress dust), passive smoking, and outdoor air pollution.

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## **PREVALENCE OF ASTHMA**

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Figure 2-1 shows data for the prevalence of current asthma, diagnosed asthma, wheeze ever, airway hyperresponsiveness, and atopy in children. There are many data available for Australia and England, but fewer for other countries (9). There are large differences in prevalence among affluent, partly affluent, and nonaffluent populations, with the highest prevalence found in Australia. Data are insufficient to determine if the differences between affluent and nonaffluent populations are the

consequence of responses to different allergens, to different allergen loads, or to other factors in the environment. Although there has been some suggestion that atopy is less prevalent in patients with high levels of parasitic infections, there is no convincing experimental confirmation.

There are relatively few data for adults. Asthma occurs in all races. Although it is clear that genetic factors are of major importance as predisposing factors in the development of atopy and probably asthma, present evidence (especially regarding increasing prevalence of asthma in developing countries all over the world) suggests that environmental rather than racial factors are important in the onset and persistence of asthma (10).

Even though good epidemiological evidence is difficult to obtain, studies clearly suggest a true increase in asthma prevalence. The prevalence of asthma has increased in the past two to three decades in both children and young adults (11-14) (see figure 2-2). This trend results from a true increase as well as a more recent tendency to label all episodes of wheezing as asthma. (This means that questionnaire estimates of changes over time may not be regarded as reliable measures of true change in the prevalence of asthma.) In children, there is evidence worldwide for an increased prevalence, as figure 2-1 illustrates. In adults the data are more controversial (15, 16).

The reasons for the increase in the prevalence of asthma in children are poorly understood. The increased prevalence of asthma may be due to changes in the indoor or outdoor environment and may involve aeroallergens, especially domestic mites (17-19), and occupational allergens. The introduction of mites in the indoor environment by using blankets (in Papua New Guinea [20]) or by the insulation of houses (21) is probably an important cause. The presence of high quantities of insects (for example, green nimiti moths in Sudan or cockroaches) has also been involved in episodes of asthma symptoms (22-24). Climate is of importance because it is directly related to the amount of allergen present in the environment; for example, a damp and warm climate is favorable to mite and mold growth.

Although links between allergy and asthma have been known for many years, they were recently reemphasized. In some countries, such as Australia and New Zealand, up to 45 percent of children have positive immediate type allergy skin tests, and the prevalence of sensitization to indoor allergens (domestic mites and cat allergens) is positively correlated with both the frequency of asthma and its severity (25, 26). It is possible that the increased

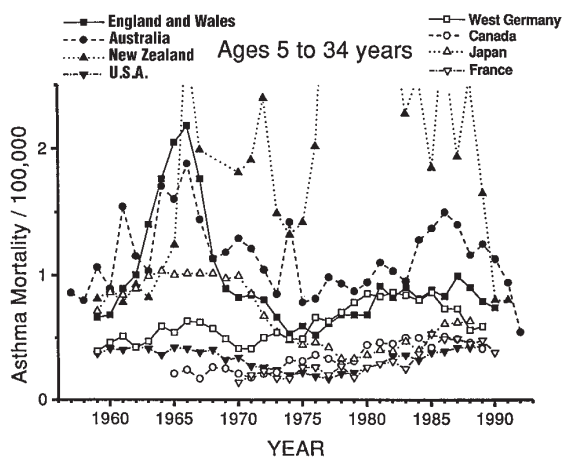


**Figure 2-2. Changes in Prevalence of Asthma or Symptoms in Same Population Studied With Same Method on Two Occasions**

Country	Study year	Number	Age	Current asthma	Diagnosed asthma	References
Australia	82 92	769 795	8 to 11 8 to 11	6.5 9.9	12.9 19.3	70 72
New Zealand	75 89		12 to 18 12 to 18		26.2* 34.0	83 83
Wales	73 88	? 96.5		12 12	6.0 12.0	13 74
United States	71-74 76-80	Large 27,275	6 to 11 6 to 11		4.8 7.6	9 9
Finland	61 89	38.00 0	19 19	0.1 1.8		15 15
France	68 82	814 10,559	21 21		3.3 5.4	84 84
Tahiti	79 84	3,870 6,731	16 13		11.5 14.3	84 84

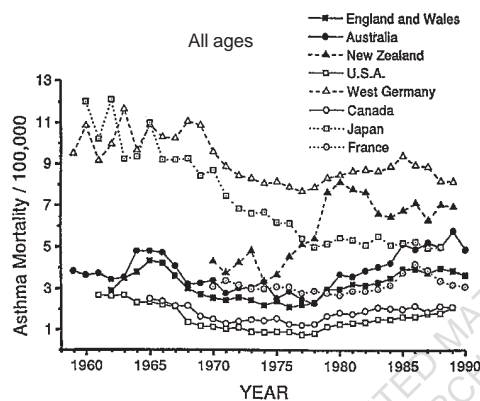
\*Cumulative prevalence of asthma and/or wheeze.

Figure 2-3. Asthma Deaths in 5- to 34- Year-Olds, 1960-90



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Figure 2-4. Asthma Deaths, 1960-90



Printed with permission from Dr. Stephen T. Holgate.

prevalence of allergy and asthma may be caused by the synergistic action of air pollution or tobacco smoking with allergic sensitization (27). Passive smoking in infancy has also been involved in the allergic sensitization to common aeroallergens of boys (28) and in infants with atopic dermatitis (29).

Urbanization appears to be correlated with increases in prevalence of asthma in some populations. For example, in polluted cities in Sweden, the prevalence of allergy has increased (30). Similar observations have been made in Chile where school children living in heavily polluted areas present more often with asthma than those living in less polluted areas, but it is not yet known if the prevalence of asthma or simply the frequency of symptoms is increased (31). The role of air pollution in the development of asthma and allergy was studied by comparing the prevalence of asthma and other allergic 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 (32, 33). The nature of the urbanization factor is unclear because studies have not controlled for indoor allergens, which have been identified as significant risk factors for asthma (25, 26). In Japan, the increased prevalence of allergy to *Cryptomeria japonica* has been attributed to diesel exhausts (34, 35).

The role of dietary factors is under scrutiny (36), but no clear result has been provided. Socioeconomic status within countries may also be involved in the increase in the severity of asthma because of problems in obtaining appropriate medical care and, perhaps, housing environments (37).

## MORTALITY OF ASTHMA

Mortality data are of limited value because they are available for a relatively few countries, and they are rarely available for different populations within the countries. Many factors lead to uncertain reliability of mortality data. First, 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. Second, 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 spite of the unreliability of the data, it is thought that for patients under 35 years of age, the accuracy of diagnosis

on death certificates is over 85 percent (38, 39). Death rates in the 5- to 34-year age group are therefore the most reliable although based on a small number of deaths, for example, 20 to 30 per year in New Zealand. However, according to a recent United States study, death certificate diagnosis of asthma as an underlying cause of death has a low sensitivity but a high specificity (40), 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. 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.

Some data are shown for the past 25 years in figures 2-3 and 2-4 (41, 42). Values 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. In the 1960's there was a rise 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. However, rates in North America, the United Kingdom, and France have been relatively stable compared with those from New Zealand. Nevertheless, deaths have increased by more than 25 percent in the United States and Canada, whereas 20 years ago mortality rates were low compared with other countries. Recent attention has been drawn to the fact that a large part of this increase in the United States occurred in blacks in inner-city (partly affluent) areas (37) and that it occurred in Maoris in New Zealand (42).

Besides artifacts in methodology, several hypotheses have been proposed to explain the failure of most countries to decrease asthma mortality (43).

- An overall increase in the severity of asthma increases the pool of patients at risk for death.
- A failure in management is often observed among young patients who die from their 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. One reason may be that recognition of the therapeutic benefits of inhaled corticosteroids has been recent and has not yet led to a widespread use of these drugs. There are ethnic differences in mortality in New Zealand (42) and in the United States (37) that may indicate racial trends in the severity of asthma, but more probably the trends are due to the low income of these populations. This implies lack of medical care, as in inner cities in the United States. However, the observation that there has been an increase in the prevalence of asthma in young people but no concomitant increase in deaths suggests that perhaps improved therapies are helping to reduce the proportion of young patients who die from asthma.
- Patients and health care professionals are often unable to recognize the severity of an asthma exacerbation, and studies in which the causes of deaths have been retrospectively examined show that, except in the United States, almost all the deaths occur outside the hospital.

- Iatrogenic causes of death may be occurring. The use of isoprenaline forte may have been associated with the increase in deaths in the 1960's. Although retrospective studies, carried out in New Zealand (44) and Canada (45), suggested that high doses of inhaled short-acting beta<sub>2</sub>-agonists might have been associated with increased asthma deaths, a recent meta-analysis indicated that there is a small magnitude of relationship between use of inhaled beta<sub>2</sub>-agonist and death from asthma. Further, the weak association that was noted may be restricted to delivery of the beta<sub>2</sub>-agonist with a nebulizer (46).

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## MORBIDITY

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Few data exist concerning the severity of asthma in populations, but 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 (47).

### Quality of Life

More accurate methods of measuring morbidity are needed, such as measurements of quality of life. 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. 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 asthma patients may not completely appreciate the impact of their asthma 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 mask their restrictions, wanting to "live like others."

Quality of life, or general well-being, is a concept that may be useful for assessing the degree of morbidity caused by asthma. It is assessed by questionnaires that include a large set of physical and psychological characteristics assessing the general functioning and well-being in the context of lifestyle. The questionnaire used must be reliable and valid and must be simple to use in epidemiological as well as clinical settings. However, there is no ideal method to evaluate well-being. Although many quality-of-life scales have been translated into different languages, they may not be useful in developing

countries, and like epidemiological questionnaires, they suffer from potential variable intercultural responses to descriptive terms used. As yet, no questionnaire that is applicable to subjects with asthma in a variety of cultures is available. Quality-of-life scales are either general and not specifically designed for patients with asthma, or they are more specific for patients with asthma but not applicable to the general population.

General health status scales such as the Sickness Impact Profile with 136 items (48) have been proposed. A compromise between lengthy questionnaires and single-item measures of health was also 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) (49). 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 (50), 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 (51-53).

So far, none of these questionnaires has been used to assess quality of life in population studies or to compare the morbidity caused by asthma among racial groups.

### Hospital Admissions

Hospital admission rates have been increasing in children in a number of countries (54, 55). The relationships among changes in prevalence, hospitalization rates, and mortality are unclear (15, 56). Increasing hospital admission rates do not appear to be due to a change in diagnosis, or to admission of patients with less severe asthma, but it may be related to an increased prevalence of asthma as well as to a greater severity of asthma. However, this trend may not fully account for the increase in the severity of asthma because a change in parents' attitude or changes in health care services may influence the rates of hospital admissions. A recent study showed that parents preferred nebulizer treatment, available in hospitals, to other forms of care (55). In Finland, however, asthma has been more frequently treated in outpatient clinics since 1985, leading to a decrease in hospital admissions. The factors underlying increased morbidity may be attributed to the following: increased severity of the asthma itself, undertreatment of patients with anti-inflammatory therapy, overreliance on bronchodilators,

absence of monitoring lung function by serial measurements of peak expiratory flow rate, and delay in seeking medical help during an exacerbation. It seems evident that poverty in affluent countries is a risk factor for increased morbidity (37).

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## NATURAL HISTORY OF ASTHMA

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The evolution of asthma is different depending upon the age of onset and possibly the etiology.

### 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 most common cause of bronchial wheezing is thought to be respiratory viral infections. 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. Those children with asthma continue to wheeze in later childhood. However, 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. In particular, early exposure to domestic mite, *Alternaria*, and animal allergens in high quantities seems to be important (see the chapters on risk factors and on mechanisms of asthma).

During early childhood, wheezing and coughing episodes may occur at infrequent intervals; in some infants wheezing becomes more frequent and the asthma is well established at an early age. A recent study has demonstrated that the majority of 7-year-olds with airway hyperresponsiveness suffered from atopy as infants (57). A study concerning pulmonary 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 in the development of the lung (58), although a subsequent study did not confirm this (59).

### Childhood

The predominant feature associated with asthma in children is allergy, and it appears that domestic mites represent the major allergen causing asthma throughout the world, in both affluent and partly affluent countries (19). The role of viral infections in the etiology of asthma is not clear. In atopic children, viral infections are clearly



important triggers of asthma exacerbations, but there are few data that suggest they directly cause the onset of asthma.

By age 8 years, 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 (60).

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 of spirometric function was impaired among those children with airway hyperresponsiveness and/or allergy to domestic mite or cat allergen (61). Whether this reflects a failure to reach full growth because of asthma or simply the presence of congenitally small lungs is unknown. The influence of the degree of airflow limitation and the cause of the disorder in children is also uncertain.

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 is less optimistic (59, 62, 63). Despite methodological difficulties in the longitudinal studies, it has been estimated that asthma disappears in 30 to 50 percent of children 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. Wheezing in the first year of life is not a prognostic indicator for asthma or for more severe asthma later in childhood. 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 (64).

### 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 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 (63, 65), 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.

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<sub>1</sub> (66, 67). In middle-aged and elderly smokers, it is virtually impossible to separate chronic bronchitis and asthma by means of FEV<sub>1</sub>. 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 years elicits a steeper rate of decline than asthma with an earlier onset (68). Permanent airflow limitation is not rare in adults with asthma as demonstrated by lung function measurements; by CT scan permanent abnormalities of the airways can be observed (69).

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## ASSESSING THE NATIONAL/LOCAL ASTHMA PROBLEM

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How can a health professional discover the extent of asthma problems in his or her locality? Figure 2-5 provides a basic set of research questions to assist in a brief community needs assessment. The checklist's questions could also serve as the beginning of more in-depth research. Figure 2-6 provides a set of survey questions to assess asthma prevalence in a locality.

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## RESEARCH RECOMMENDATIONS

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As asthma increases worldwide, major questions for researchers include the following:

- Is there evidence that asthma is being well treated in any country?
- Is there evidence about the extent to which national or international guidelines are followed and about the means by which they can best be implemented?
- Is it possible to enunciate some principles, based on the

**Figure 2-5. Research Questions/Needs Assessment Checklist for Health Authorities**

### **Prevalence**

- Have asthma prevalence studies been conducted in your country/locality?
- If so:
  - When?
  - What methodology was used?
  - Were they published? In what journal?

### **Mortality**

- What are the annual mortality rates due to asthma in your country/locality in the last 10 years per 100,000 inhabitants —
  - In the total population?
  - In 5- to 34-year-olds?
- Are the data collected from death certificates? Are the data available?

### **Morbidity**

#### *Hospitalization*

- How many persons were hospitalized due to asthma in your country/locality in the last 5 years —
  - In children 0 to 14 years old?
  - In adults (15 years and older)?
- Are the data obtained from the health ministry/department? Other?

#### *Primary care*

- How many outpatient consultations for asthma in primary care departments were there in the last 5 years by district, province, or state —
  - For children 0 to 14 years old?
  - For adults (15 years and older)?

**Figure 2-5 (continued)**

*Incidence*

- How many first-time consultations for asthma were there in primary care departments in the last 5 years —
  - For children 0 to 14 years old?
  - For adults (15 years and older)?

*Quality of life\*:*

- What are the proportions (percent) of mild, moderate, and severe asthma (using the International Consensus Report criteria) in your country/locality?
- What is the availability of medications at the primary care system level for treatment of mild, moderate, and severe asthma? (For names of recommended medications, see figure 7-4.)
- How many emergency consultations per patient with asthma were there in your country/locality per year for the last 5 years?
- How many days were lost due to asthma per year on average per asthma patient for the last 5 years?
- How many days of school were lost because of asthma per year on average per patient for the last 5 years?

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\*In some localities it may be possible to determine quality of life by using the questionnaire suggested by Bousquet (50).

Figure 2-6. Respiratory Health Survey\*

RESPIRATORY HEALTH SURVEY	SCREENING QUESTIONNAIRE																																																																																								
<div style="background-color: black; color: white; padding: 10px; margin-bottom: 10px; text-align: center;"> <b>RESPIRATORY HEALTH SURVEY</b> </div> <p>TO ANSWER THE QUESTIONS PLEASE CHOOSE THE APPROPRIATE BOX IF YOU ARE UNSURE OF THE ANSWER PLEASE CHOOSE 'NO'</p> <p>1. Have you had wheezing or whistling in your chest at any time in the last <u>12 months</u>? IF 'NO' GO TO QUESTION 2, IF 'YES':</p> <p>1.1 Have you been at all breathless when the wheezing noise was present?</p> <p>1.2 Have you had this wheezing or whistling when you did <u>not</u> have a cold?</p> <p>2. Have you woken up with a feeling of tightness in your chest at any time in the last <u>12 months</u>?</p> <p>3. Have you been woken by an attack of shortness of breath at any time in the last <u>12 months</u>?</p> <p>4. Have you been woken by an attack of coughing at any time in the last <u>12 months</u>?</p> <p>5. Have you had an attack of asthma in the last <u>12 months</u>?</p> <p>6. Are you currently taking any medicine (including inhalers, aerosols or tablets) for <u>asthma</u>?</p> <p>7. Do you have any nasal allergies including 'hay fever'?</p> <p>8. What is your <u>date of birth</u>?</p> <p>9. What is <u>today's</u> date?</p> <p>10. Are you male or female?</p> <p>In case we need to contact you again, please write your telephone number below:</p> <div style="border: 1px solid black; padding: 5px; margin-top: 10px;">         Telephone number DAY ( ) _____          EVE ( ) _____ if different       </div> <p>PLEASE CHECK THAT YOU HAVE ANSWERED ALL THE QUESTIONS AND PUT DOWN YOUR CORRECT DATE OF BIRTH AND RETURN THIS QUESTIONNAIRE IN THE STAMPED ADDRESSED ENVELOPE PROVIDED <span style="float: right;"><u>THANK YOU</u></span></p>	<div style="margin-bottom: 10px;">           AREA NUMBER <table style="display: inline-table; border-collapse: collapse;"><tr><td style="border: 1px solid black; width: 20px; height: 20px;"></td><td style="border: 1px solid black; width: 20px; height: 20px;"></td><td style="border: 1px solid black; width: 20px; height: 20px;"></td></tr></table> 1-3            PERSONAL NUMBER <table style="display: inline-table; border-collapse: collapse;"><tr><td style="border: 1px solid black; width: 20px; height: 20px;"></td><td style="border: 1px solid black; 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\*Postal questionnaire developed by P.G. Burney (2).

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present knowledge of the epidemiology of asthma, that can be applied worldwide?

- Is there sufficient evidence about the cause of asthma to start prevention programs?
- If not, what needs to be done?

Priorities for future investigations related to these questions are:

- Extending the studies currently being undertaken in Europe to developing countries and children. The EEC-sponsored study of many European countries and some countries outside Europe (2) is of interest because it uses a single extensive questionnaire that has been translated into many languages, allergy testing, and measurement of airway hyperresponsiveness. This study is attempting to find differences in prevalence of asthma in the 20- to 44-year age group and to identify environmental risk factors. The International Study of Asthma and Allergies in Childhood (ISAAC) currently being conducted in Latin America, Asia, United States, Mexico, Europe, Canada, Australia, and New Zealand will provide much useful information.
- Comparing risk factors (atopy and pollution, in particular) with the development of asthma within the same racial groups in different environmental settings and within different racial groups in the same environmental setting.
- Investigating populations with supposedly low prevalence rates of asthma (for example, Inuits in Canada).
- Defining asthma. When possible, airway hyperresponsiveness measurements should be part of the definition of asthma because questionnaires are not completely specific.
- Characterizing life spans of patients with asthma during longitudinal studies. Such studies will assist in the estimation of cost effectiveness in asthma management and prevention programs.
- Conducting prospective studies to see if drugs can worsen asthma or improve the life expectancy of patients with asthma.
- Finding more accurate methods for measuring morbidity, such as quality of life.
- Conducting epidemiological studies that include quality-of-life measures and compare normal populations with nonselected patients with asthma.

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# CHAPTER

**3**

## ***RISK FACTORS***

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## KEY POINTS:

- Asthma occurs in families. Atopy, the propensity to produce abnormal amounts of IgE in response to exposure to environmental allergens, is considered the strongest identifiable risk factor for the development of asthma.
- Allergen exposure and chemical sensitizers are the most important risk factors for the onset of asthma.
- Contributing factors such as viral infections, small size at birth, diet, tobacco smoking, and environmental pollutants may increase the susceptibility to the development of the disease in predisposed individuals.

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Asthma is a chronic inflammatory disorder of the airways. This chronic inflammation is responsible for increased airway hyperresponsiveness to a variety of stimuli and for the recurrent symptoms and airflow limitation characteristic of asthma. This chapter discusses the risk factors involved in the development or onset of asthma and then the risk factors (triggers) involved in the development of exacerbations.

The chapter begins with an explanation of the causes of asthma. It is not known with certainty what causes the development of asthma, but it appears to be a complex interaction of the following:

- Predisposing factors that give an individual a susceptibility to the disease. These include atopy—the propensity to produce abnormal amounts of IgE in response to environmental allergens.
- Causal factors that sensitize the airways and cause the onset of the asthma. These include inhaled allergens present indoors and outdoors (such as domestic mites, pollens, furred animals, and fungi) as well as inhaled allergens and chemical sensitizers in the workplace.
- Contributing factors that either augment the likelihood of asthma developing upon exposure to a causal factor or may even increase susceptibility to asthma. These include tobacco smoking, air pollution, viral respiratory infections, small size at birth, diet, and parasitic infections. Studies are necessary to clarify the role of contributing factors.

The chapter concludes with a look at triggers—risk factors involved in the development of asthma exacerbations once an individual's airways are sensitized. Triggers include further exposures to causal factors (for example, allergens and occupational agents) that have already sensitized the airways of the person with asthma and that cause recurrent asthma exacerbations by causing both airway inflammation and immediate and/or delayed bronchoconstriction. Triggers also include exposure to exercise, cold air, irritant gases, weather changes, and extreme emotional expression. These factors cannot cause asthma to develop initially, but once it is present, these triggers can exacerbate asthma.

Figure 3-1 summarizes risk factors. The nature of the risk factors is discussed in this chapter; recommendations for managing them in patients with asthma are presented in the chapter on management of asthma.

**Figure 3-1. Risk Factors for Asthma**

**RISK FACTORS THAT LEAD TO THE DEVELOPMENT OF ASTHMA:**

**Predisposing Factors**

- Atopy
- Gender

**Causal Factors**

- Indoor allergens
  - Domestic mites
  - Animal allergens
  - Cockroach allergen
  - Fungi
- Outdoor allergens
  - Pollens
  - Fungi
- Aspirin
- Occupational sensitizers

**Contributing Factors**

- Respiratory infections
- Small size at birth
- Diet
- Air pollution
  - Outdoor pollutants
  - Indoor pollutants
- Smoking
  - Passive smoking
  - Active smoking

**FACTORS THAT EXACERBATE ASTHMA: TRIGGERS:**

- Allergens
- Respiratory infections
- Exercise and hyperventilation
- Weather
- Sulfur dioxide
- Foods, additives, drugs



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## RISK FACTORS INVOLVED IN THE DEVELOPMENT OF ASTHMA

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### Predisposing Factors

Atopy—the propensity to produce abnormal amounts of IgE in response to exposure to environmental allergens—appears to be the strongest identifiable predisposing factor for asthma. Population studies have shown that the majority of children and adults (except those with late-onset asthma) with well-documented asthma are atopic, although asthma may be present in a significant proportion of subjects who cannot be defined as atopic using the current criteria (positive skin tests or increased specific or total IgE). Population studies also showed that the prevalence of asthma increases with increasing levels of IgE, and that those with low serum IgE levels have low prevalence of asthma (1, 2). The prevalence of atopy in the random population ranges from 30 to 50 percent, but the overall prevalence of current asthma in the general population is usually much lower (see the chapter on epidemiology). This suggests that asthma is associated with atopy only in a proportion of atopic subjects. The prevalence of atopy and asthma may vary in different parts of the world.

### *Atopy and Inheritance of Asthma*

Atopic diseases occur in families. Both twin and family studies have convincingly shown that atopy (as measured by allergen skin tests, total and/or specific IgE) is at least partly under genetic control. Further, asthma (identified from the responses to a questionnaire) and airway hyperresponsiveness (as measured with inhalation

challenge tests with histamine, methacholine, or cold air) have been reported to occur in families, but the evidence of genetic control is less convincing (3).

**Genetic control of IgE synthesis.** Atopy may be defined as the production of abnormal amounts of IgE antibodies in response to contact with environmental allergens. Atopy is demonstrated by increased total or specific serum IgE; atopy can be demonstrated most easily by skin prick tests using a battery of standardized allergens, specific for each geographic zone. High serum IgE seems to be inherited as an autosomal genetic recessive trait with an additional polygenic component, whereas different factors seem to govern the specific IgE response (3). This separation has been recently disputed by a study that argued that both high total serum IgE and increased specific IgE are evidence of atopy. The study consequently defined atopy as the presence of a raised total IgE, and/or a positive skin or RAST test to a common aeroallergen. By using these criteria, the study found in both nuclear and extended families that the distribution of atopic subjects is consistent with an autosomal dominant inheritance, which the study then identified with a gene located in chromosome 11 (4). The investigators subsequently observed that this gene may be genomically imprinted, that is, that this gene can exert its effect only if it is derived from the mother (5). Subsequent studies in different populations were unable to confirm these results and have suggested a more complex mode of inheritance of atopy, via multiple genes (6).

**Genetic control of the immune response.** Additional genes determining the specificity of the immune response located in the human leukocyte antigen complex (HLA) may govern the specificity of the immune response to common aeroallergen in some individuals (3, 6). In addition, mutations of the cytokine gene cluster present on chromosome 5 have been hypothesized to predispose subjects to asthma by upregulating the inflammatory response (see the chapter on mechanisms of asthma) (7).

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 developing asthma. Thus, although asthma and atopy may be inherited independently, 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. The probability of nonatopic parents with asthma having a child with asthma seems not different from the risk of the general population, whereas the risk of atopic parents with asthma having a child with asthma is two fold to threefold higher when a family history of asthma is

accompanied by one of atopy (3). Similarly, when both airway hyperresponsiveness and atopy are present in the parents, the prevalence of asthma increases in offspring (3).

### **Gender and Asthma**

Childhood asthma is more prevalent in boys than girls. However, the increased risk for males in childhood seems not to be related to gender but to narrower airways (8) and increased airway tone (9, 10) in boys that predispose them to enhanced airflow limitation in response to a variety of insults. Further support to 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 (11, 12).

In at least one study there was no difference between sexes in children after correcting for atopy, and instead asthma was more prevalent in adult females (13). Further, no difference in prevalence of asthma was observed when correction was made for atopy, suggesting that gender differences in diagnosed asthma in children may be partly explained by gender differences in allergen sensitivities (14).

### **Race and Asthma**

The increase of asthma prevalence in developing countries in different parts of the world suggests that environmental factors may be more important than genetic and racial factors for the development of asthma. The prevalence of wheezing is the same among children of different descent living in London or Australia. Even the much higher prevalence of asthma in black versus white children living in the United States seems more likely to be due to socioeconomic and environmental factors. Thus, even though slight differences in asthma prevalences between different races living in the same region persist after correcting for other factors (15), these differences may be attributable more to socioeconomic conditions, allergen exposures, and dietary factors than to racial predisposition. (See the chapter on epidemiology.)

### **Causal Factors**

Causal risk factors sensitize the airways and cause the onset of the asthma. The most important causal factors of asthma in terms of numbers of people exposed are probably inhaled allergens (from, for example, domestic mites, furred animals, fungi, and pollens). Classification, structure, biology, and nomenclature of allergens have been recently reviewed (16). Allergens sensitize atopic subjects by stimulating the development of specific T lymphocyte clones and the production of specific IgE

antibodies. Once a subject is sensitized (that is, she or he has developed memory T lymphocytes and specific IgE), she or he is predisposed to develop allergic inflammation and asthma exacerbations upon reexposure to the same allergen. Although the IgE-mediated reaction may represent simply one additional mechanism of triggering acute exacerbations of asthma, the population studies showing correlation between prevalence of asthma and long-term allergen exposure (17, 18) and improvement of asthma after cessation of exposure (19) strongly suggested that allergen may indeed cause the onset of asthma by continuously stimulating chronic allergic inflammation of the airways.

The presence of some form of occupational asthma or environmental asthma only in exposed subjects confirms that substances, and particularly allergens, to which a subject becomes sensitized can cause the development of asthma. The studies in Barcelona, where epidemics of asthma exacerbations occurred and were traced to days when soy beans 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. The fact that those who came to hospital were already allergic to the dust suggested that sensitization can occur to low atmospheric concentrations if the allergen is potent enough (20). The risk of sensitization to allergens seems to peak in the first year of life, when exposure occurs in conjunction with the ongoing development of the mucosal immune system (21), although this has not been firmly established.

### **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 carpeted, heated, cooled, and humidified to make them energy efficient—and have become an ideal habitat not only for domestic mites, cockroaches, and other insects but also molds and bacteria.

**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 potential indoor allergen and a major cause of asthma worldwide (22, 23). In communities exposed to a range of mite densities, a relationship between symptoms and mite allergen exposure has been established (18, 24). Exposure to domestic mites in the first year of life correlates with the subsequent development of asthma (23). Although controversial, threshold levels for



sensitization and for exacerbations of acute symptoms have been suggested (22, 25).

The presence of domestic mites has been confirmed on a worldwide basis, and the World Health Organization has recognized domestic mite allergy as a universal health problem.

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 mite bodies, secretions, and excreta and constitute the main source of dust-derived allergens. The principal domestic mite species are the pyroglyphid mites *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Dermatophagoides microceras*, and *Euroglyphus mainei*, which usually account for 90 percent of the mite species in house dust from temperate regions (22). 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° centigrade 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 than *D. pteronyssinus*, and it 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 allergens). These allergenic enzymes have been found in mite fecal pellets. The group II allergens are derived mainly from mite bodies rather than mite feces (*D. pteronyssinus* II, *D. farinae* II). The predominant allergens in house dust are from groups I

and III, and very little group II allergen has been found in dust. Group IV mite allergens have been recently described.

Interestingly, the most important mite allergens have proteolytic activity, and thus they might have an easier access to the immunocompetent cells.

A concentration of mite allergen above 2 mcg Der p I/g of dust group I mite allergen seems to represent a significant risk factor for mite allergy (26).

**Animal allergens.** Household warm-blooded animals release allergens in secretions (saliva), excretions (urine, feces), and danders.

- **Cats.** Cats are potent sensitizers. The principal allergen, Fel d I, is found in cat pelt. The sebaceous secretions are probably the most important source. The allergen, which is carried in small respirable particles, is also a major risk for asthma exacerbations. In the United States, for example, 30 out of 188 asthma patients admitted to the emergency department were allergic to cats compared to 1 out of 202 controls (27). Dust from houses with a cat contains 10 to 1,500 mcg/g of the cat allergen Fel d I; houses without a cat or cleaned after removal of a cat may contain less than 1 mcg/g Fel d I (28). Cat saliva is another source for cat allergen. Allergen has also been identified in voided urine from male cats.

- **Dogs.** Allergic sensitivity to dogs is not as common as 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. This antigen, Ca d I, is present in large concentrations in saliva and can be measured in house dust (29).

- **Rodents.** Many children keep rodents in their bedrooms, 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 (30).

**Cockroach allergen.** In some locations and among some ethnic groups, sensitization to cockroach allergen may even be more common than to the domestic mite. 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 American cockroach (*Periplaneta americana*), German cockroach

**Figure 3-2. Agents Causing Asthma in Selected Occupations**

<u>Occupation or Occupational Field</u>	<u>Agent</u>
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 and feathers
granary workers.....	storage mites, <i>Aspergillus</i> , indoor ragweed, and grass pollen
research workers.....	locusts
fish food manufacturing.....	midges
detergent manufacturing.....	<i>Bacillus subtilis</i> enzymes*
silk workers.....	silk-worm moths and larvae
<u>Plant Proteins:</u>	
bakers.....	flour, amylase*
food processing.....	coffee bean dust, meat tenderizer (papain), tea
farmers.....	soy bean 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)
cotton textile workers.....	cotton dust
nurses.....	psyllium, latex
<u>Inorganic Chemicals:</u>	
refinery workers.....	platinum salts, vanadium
plating.....	nickel salts
diamond polishing.....	cobalt salts
manufacturing.....	aluminum fluoride
beauty shop.....	persulfate
welding.....	stainless steel fumes, chromium salts
<u>Organic Chemicals:</u>	
manufacturing.....	antibiotics, piperazine, methyl dopa, salbutamol, cimetidine
hospital workers.....	disinfectants (sulfathiazole, chloramine, formaldehyde, glutaraldehyde)
anesthesiology.....	enflurane
poultry workers.....	aprolium
fur dyeing.....	paraphenylene diamine
rubber processing.....	formaldehyde, ethylene diamine, phthalic anhydride
plastics industry.....	toluene diisocyanate, hexamethyl diisocyanate, dephenylmethyl isocyanate, phthalic anhydride, triethylene tetramines, trimellitic anhydride, hexamethyl tetramine
automobile painting.....	dimethyl ethanolamine diisocyanates
foundry worker.....	reaction product of furan binder

\*High molecular weight

(*Blatella germanica*), Oriental cockroach (*Blatella orientalis*), Australian cockroach (*Periplaneta australasiae*), and brown-banded cockroach (*Supella supellidum*). Allergens from the German and American cockroach (Bla GI, Bla gII, and Per a I) have been isolated, and their presence in house dust can be measured (31, 32). Allergens from the Asian cockroach (*Periplaneta fuliginosa*) have also been examined (33).

**Fungi.** Molds and yeasts can act as indoor airborne allergens. Among these is *Alternaria*, which is an established risk factor of asthma in different populations and has been associated with the risk of asthma death in the United States (34).

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* (16, 35).

### Outdoor Allergens

The most common outdoor allergens that cause asthma in susceptible people are pollens and fungi.

**Pollens.** Pollen allergens associated with the development of 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. Micronic particles of starch granules are released from pollens, particularly after rainfall, and seem to be responsible for pollen-induced asthma exacerbations (36). 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. Concentrations of Lol p1 (the major allergen from rye grass *Lolium perenne*) above 10 mcg/g in house dust are associated with epidemics of pollen-induced exacerbations of asthma (37), increase of symptoms, increase of airway hyperresponsiveness, and airway inflammation (38).

**Fungi.** Molds and yeasts are also outdoor airborne allergens; *Alternaria* and *Cladosporium* (which are also indoor fungi) are the only fungi that have been established as risk factors for asthma. They tend to be seasonal in temperate zones, where some fungi sporulate on warm, dry summer days and others prefer the rainy nights of fall (39).

### Occupational Sensitizers

Occupational sensitizers are probably the only firmly documented cause of asthma in adults. Subjects develop asthma only after exposure, and in a few cases, asthma is caused and maintained only by the exposure to the sensitizing occupational agent. An extensive list of occupations and sensitizing agents was reported in recent review articles (40). Figure 3-2 provides an abbreviated listing.

Occupational sensitizers are usually classified by high and low molecular weight. High molecular weight sensitizers probably sensitize subjects and cause asthma exacerbations by the same mechanisms as allergens, but the mechanism of action of low molecular weight sensitizers remains largely unknown.

### Drugs and Food Additives

In about 4 to 28 percent (depending on the methodology used) of adults with asthma (particularly in those with nasal polyps and sinusitis), but rarely in children with asthma, aspirin and other nonsteroidal anti-inflammatory drugs (NSAID's) are causal risk factors for asthma. They may also 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 may indeed cause the development of asthma. Once aspirin or nonsteroidal anti-inflammatory drug intolerance develops, it is present for life (41, 42).

Some foods and other ingested substances (such as salicylates, food preservatives, monosodium glutamate, and some food coloring agents) have a recognized effect of causing asthma exacerbations, but the relationship between food sensitivity and the initial development of asthma is uncertain.

### Contributing Factors

Contributing factors augment the likelihood of asthma developing upon exposure to a causal factor; they may even increase susceptibility to asthma.

### Smoking

Tobacco burning, which is an 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.** Children have significant respiratory exposure to adults who smoke. The sidestream smoke, which burns hotter and is more toxic than the smoke inhaled by the tobacco user, is particularly irritating to the respiratory mucosa. The established health effects of involuntary exposure to tobacco smoke include increased lower respiratory symptoms in children (cough, phlegm, and wheeze) as well as an increased risk for asthma and exacerbations of asthma (43-45).

Especially during the first 2 years of life, parental smoking is associated with increased respiratory morbidity, with greater risk from maternal smoking (43-45). Several studies have noted specifically that the risk of asthma appears to increase in children exposed to passive smoking by parents who smoke, especially in those with mothers who smoke (46, 47). A subsequent study could not confirm such association (13).

In one study comparing total IgE levels (a nonspecific marker of atopy), mean IgE levels in the umbilical cord blood were found to be higher in the babies of smoking mothers (48). Another study could not confirm this (46).

**Active smoking.** Smoking may increase the risk of developing occupational asthma in workers exposed to some occupational sensitizers (e.g., acid anhydrides) (49). However, there is little evidence that active smoking is a risk factor for the development of asthma in general.

### **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 outdoor types of 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, mainly in controlled chamber exposure experiments. However, due to 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 pollution exposure 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 (see the chapter on epidemiology), there is little evidence that air pollution is directly responsible for the increased prevalence of asthma in these countries (50-52). The role of air pollution in the development of asthma and allergy was studied by comparing the prevalence of asthma and other allergic 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 (53, 54).

In many countries visible pollutant levels remain very high. In others, levels of visible pollutants have fallen, but invisible pollutants (largely from incomplete combustion of petrol by car engines) have risen. Levels of nitrogen oxides have gone up over the last 10 years (50). These pollutants are known to damage respiratory epithelium, and the damage that they cause may permit other antigens easier entry into the lungs (51, 52), although it is unlikely that they have themselves directly increased the prevalence of asthma. Thus prevalence of asthma seems to be correlated with "urbanization," for example, migration from country to city centers (55). This is another area for research, even though it is likely that such urbanization involves not only exposure to outdoor pollutants but also changes in indoor living environments.

Acute exposure to irritant gases, for example, in the workplace or during accidents, may induce a long-lasting airway hyperresponsiveness called reactive airways dysfunction syndrome. The syndrome shares most of the clinical and physiologic characteristics of asthma (56). However, its pathology, although similar, is not identical, being characterized by increased airway mucosal mononuclear cells and subepithelial fibrosis but not by an increased number of mast cells and eosinophils (57).

**Indoor pollutants.** The contaminants and atmospheric dynamics of indoor air pollution are different from those of outdoor air pollution, with modern construction techniques possibly contributing to a greater indoor pollution. For



example, in insulated, energy-efficient buildings and homes, the turnover of indoor air is 50 percent of the average structure's turnover. Note that 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 using carpets and upholstered furniture). Because very young children spend most time with their mothers indoors, and because residents of developed countries 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 room to room.

Major indoor pollutants are nitric oxide, nitrogen oxides, carbon monoxide, carbon dioxide, sulfur dioxide, formaldehyde, and biologicals such as endotoxin (58). Sources of these indoor pollutants include:

- 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
- 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 material that release isocyanates.

Some data suggest that indoor pollutants may contribute to the development of asthma, but further studies are needed. Among 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.

### ***Viral Respiratory Infections***

There is some evidence that there is a temporal association between viral respiratory infections and the development of asthma in childhood. There is no

evidence that viral respiratory infections directly cause the development of asthma (59), although it is well established that viral respiratory infections can exacerbate asthma—that is, act as triggers.

Several studies have suggested an association between viral respiratory infections, particularly bronchiolitis, in early life and later development of asthma or pulmonary function abnormalities, including airway hyperresponsiveness (see the chapters on epidemiology and diagnosis and 59, 60). Like passive smoking exposure, viral respiratory infections should be considered as one of the risk factors that may contribute to the development of asthma (59).

### ***Small Size at Birth***

Disproportionate fetal growth (large head and small trunk), which is often associated with a birth weight of less than 2,500 grams, may carry an increased risk of developing asthma during childhood or adolescence (15). The mechanism is unclear but may involve reduced airway size and caliber, increased susceptibility to allergen sensitization, increased susceptibility to viral infections, and consequent viral-induced enhanced airway hyperresponsiveness. Disordered nutrition may impair basic immunological mechanisms.

### ***Diet***

The influence of diet on asthma has not been properly examined. Conflicting data have been reported about the protective role of breast feeding for the development of asthma (17, 43, 61, 62). The evidence has also been conflicting, but egg elimination by the mother during pregnancy, and egg elimination in mother and child in the first year of life, appeared to reduce the incidence of atopic diseases (43, 46, 63). In addition, fish in the diet was associated with a lower prevalence of asthma in one retrospective study (17).

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 rather than of the food actually causing asthma.

### ***Parasitic Infections***

Studies that included egg counts suggest that subjects with asthma have a lower parasitic burden than normal subjects. Although epidemiologic studies suggest that asthma is less common where intestinal parasitism is

endemic, case control studies either show no association or an increase in parasitism in people with asthma (64). Therefore, the available data neither refute nor support the theories that parasitic disease either protects against or causes asthma.

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## RISK FACTORS THAT CAUSE ASTHMA EXACERBATIONS: TRIGGERS

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

Triggers also include exposure to exercise, cold air, 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, respiratory infections, exercise and hyperventilation, weather changes, sulfur dioxide, and foods, additives, and drugs as well as 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. 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 (65, 66). Other irritants such as wood smoke, household sprays, volatile organic compounds (e.g., polishes and cooking oils), and air pollutants may also exacerbate asthma.

**Respiratory infections.** In contrast to the lack of evidence of a pathogenetic role of viral infections for the development of asthma, it is well established that viral respiratory infections can exacerbate asthma, particularly in children with asthma under the age of 10 (59). Respiratory syncytial virus, rhinovirus, and influenza virus have been implicated (59), with rhinovirus being implicated in the majority of the exacerbations of asthma in children (67). The role of infections as triggers also appears to be important in adults (68).

Respiratory virus may exacerbate asthma through different mechanisms. One is that viral infections may cause epithelial damage and airway inflammation, both of which events may create asthma symptoms. Another is that virus-specific IgE antibody has been identified for the respiratory syncytial virus and for the parainfluenza virus, and these viruses may be responsible for the generation and release of allergic mediators from human lung cells (69). 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 (see the chapter on mechanisms of asthma) (70).

**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. The mechanisms of exercise-induced airflow limitation are mainly related to changes of the airway mucosa induced by the associated hyperventilation, either cooling or rewarming, or to changes of 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 (71).

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 (72).

**Weather changes.** Adverse weather conditions such as freezing temperatures, high humidity, thunderstorms, 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 (73, 74).

**Sulfur dioxide.** This irritant 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 (73). 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.

**Foods, additives, drugs.** It is widely believed that allergic reactions to foods are common asthma triggers, but documented evidence for this is difficult to find in the literature. Some ingested substances, including salicylates, food preservatives, monosodium glutamate, and some food coloring agents, cause asthma symptoms in some patients (75). One study in England (76) suggested that sodium intake may be related to morbidity and mortality from asthma, although this has not been confirmed.

Preservatives in many beverages (including wine and beer) and in some foods contain metabisulfite, which may release sufficient sulfur dioxide to provoke bronchoconstriction (75).

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAID's) exacerbate asthma in a significant proportion of adults with asthma (up to 20 percent according to some studies), but rarely in children with asthma. The majority of patients first experience symptoms during the third to fourth decade of life (41, 42).

Beta blockers can provoke bronchoconstriction in asthma patients by blocking beta receptors to endogenous catecholamine (42).

**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 that can cause airway narrowing. The panic attacks that are rare but not exceptional in some patients with asthma have a similar effect (77). However, it is important to note that asthma is not a psychosomatic disorder.

**Other factors that may exacerbate asthma.** Rhinitis, sinusitis, and polyposis are sometimes associated with asthma, and the treatment of each of these is often associated with improvement of asthma (78). 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 (78). 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 (79).

Many women complain that their asthma is worse at the time of menstruation, and premenstrual exacerbations have been documented (80). Similarly asthma may improve, worsen, or remain unchanged during pregnancy (81).

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## RESEARCH RECOMMENDATIONS

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Priorities for future investigations related to risk factors of asthma include:

- Searching for the asthma gene(s).
- Identifying the chemical structure and metabolism of the allergens and chemical sensitizers.
- Identifying the role of contributing factors in the development of asthma (e.g., viral infections, drugs, pollutants).
- Identifying the allergens and irritants for each geographical area, particularly in tropical countries.
- Investigating the relationship between asthma and small size at birth.

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# CHAPTER

## 4

# MECHANISMS OF ASTHMA



**KEY POINTS:**

- Asthma is a chronic inflammatory disorder of the airways with recurrent exacerbations.
- Neural control of the airways may be involved in the regulation of the airway inflammatory process and airway caliber.
- Airway inflammation and/or abnormalities of the neural control of the airways may be responsible for recurrent exacerbations of asthma.
- The contribution of the inflammatory reaction or of neural control may vary among patients or in any one patient over time.
- Immunologic and nonimmunologic mechanisms are involved in both the chronic airway inflammation and recurrent exacerbations in asthma.

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 responsiveness, thereby predisposing the airways to narrow in response to a variety of stimuli (see figures 1-8 and 4-1). Characteristic features of the airway inflammation are an increased number of activated eosinophils, mast cells, and T lymphocytes in the airway mucosa and lumen, and an increased thickness of the reticular layer of the basement membrane (subepithelial fibrosis). These changes may be present even when asthma is asymptomatic.

The recurrent episodes of symptoms and reversible airflow limitation that characterize disordered lung function in asthma are associated with an increase in the inflammatory response. Asthmatic reactions induced in the laboratory by allergens and chemical sensitizers 4 to 12 hours after challenge may be used as a model of asthma exacerbations, and when studied in detail, these reactions are associated with a transient increase of neutrophils followed by a more sustained increase and activation of eosinophils and T lymphocytes and by microvascular leakage (see the chapter on definition).

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**AIRWAY INFLAMMATION IN ASTHMA**

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Mechanisms of airway inflammation in asthma involve a cascade of events—the release of immunological mediators in both IgE-dependent, T-lymphocyte-dependent mechanisms and IgE-independent, T-lymphocyte-dependent mechanisms. The net result is the recruitment of inflammatory cells from the circulation, which involves upregulation of endothelial adhesion molecules and their reciprocal ligand expanded on leukocytes.

**Immunologic Mechanisms**

In the majority of cases, asthma is primarily an allergic disorder, that is, a disease that develops and manifests itself dominantly through IgE mechanisms (1).

The immune system is functionally separable into antibody-mediated immunity and cell-mediated processes (2). B lymphocytes produce and secrete specific antibodies, whereas T lymphocytes, in addition to controlling B lymphocyte function, have proinflammatory actions through the expression of cytotoxic activity (CD8+) and the secretion of cytokines.

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 (e.g., dendritic cells, macrophages, and B lymphocytes) and involving the major histocompatibility complex (MHC class II molecules).

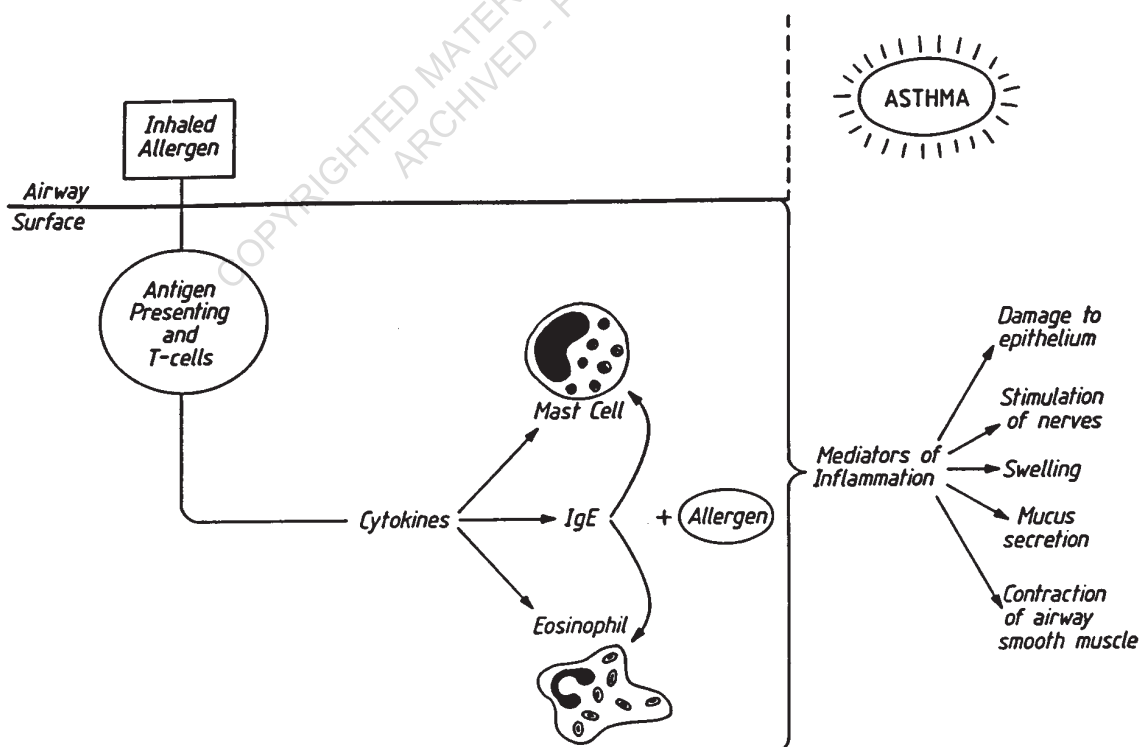
A cognate interaction between allergen presenting B lymphocytes and allergen-specific T lymphocytes involving an array of cell surface receptors and adhesion molecules is responsible for the switching of B lymphocyte synthesis from IgG and IgM to allergen-specific IgE. This process engages CD40 and CD40 L-ligand on B lymphocytes and T lymphocytes, respectively, and is predominantly mediated by interleukin 4 (3-5).

### Inflammatory Mediators

The immunologic cascade and the subsequent inflammatory reaction result from an interaction of inflammatory mediators and cytokines released both by the resident and the infiltrating cells (6-8). Each of the many mediators produced contributes to the development of the characteristic pathological events that occur in asthma and that increase during asthma exacerbations. Together these mediators contribute to the bronchoconstriction, airway hypersecretion, and mucosal

edema that are characteristic of asthma exacerbations. Although some mediators have specific effects, many mediators (e.g., leukotrienes and prostanoids) may have effects on many different cell types. The availability of new mediator-antagonists and synthesis-inhibitors together with refinements in biological detection systems will enable

**Figure 4-1. Interrelationship Between Airway Inflammation and the Development of Symptoms in Asthma, Airway Hyperresponsiveness, and Airflow Limitation**





progress in this field. The role of each mediator and of the interaction among different mediators is under investigation.

### **IgE-Dependent, T-Lymphocyte-Dependent Mechanisms**

B lymphocytes secrete specific IgE under the control of a specific T lymphocyte subtype (Th2) clone developed after exposure to antigen presented by accessory cells. Once sensitized to a specific allergen, reexposure of the tissue to the same allergen augments the production of specific IgE that binds to specific receptors on the membrane of mast cells and also of basophils and eosinophils (Fc epsilon RI), macrophages, eosinophils, and platelets (Fc epsilon RII). Allergens cross-linking specific IgE on the cell surface lead to activation with the release of both preformed (granule derived) and newly generated mediators that are considered to orchestrate the inflammatory cascade (8).

Recently both human mast cells and basophils have been shown to support B lymphocyte IgE synthesis through a combination of IL-4 release and CD40 engagement, suggesting that mast cells and basophils contribute to the induction and maintenance of the tissue allergic reaction through an IgE-dependent, T-lymphocyte-independent mechanism (3).

### **IgE-Independent, T-Lymphocyte-Dependent Mechanisms**

In addition to involving IgE, upon appropriate antigen presentation T lymphocytes may release cytokines, which causes accumulation and activation of leukocytes, particularly eosinophils. In this way they may directly provoke the inflammatory cascade.

Once the subject is sensitized, reexposure to the same antigen causes further activation of specific T lymphocytes that have the capacity both to stimulate IgE production (helper function) and, through the secretion of other cytokines, to attract and activate other leukocytes. Thus, through the latter mechanism, T lymphocytes may directly increase the growth, differentiation, activation, and survival of mast cells. In this sense, activated T lymphocytes are proinflammatory cells in their own right, and thus they are helper cells for promotion of IgE production by B lymphocytes. In addition to protein products capable of stimulating polymorphonuclear leukocytes, activated T lymphocytes are a major source of other cytokines belonging to the five-gene cluster, including granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), IL-4, IL-5, IL-9, and IL-13, which have

pronounced effects on inflammatory cells, and particularly on eosinophils, which dominate the inflammatory picture of asthma (7). In these ways activated T lymphocytes both initiate and propagate allergic inflammation of the airways and, as a consequence, participate directly in the pathological events responsible for exacerbations of asthma (7, 8).

In both mice and humans, at least two distinct T-helper (Th), CD4+ lymphocyte subtypes have been characterized on the basis of their profile of cytokine production (4, 9).

Although both T lymphocyte subtypes secrete IL-3 and GM-CSF, the Th1 subtype preferentially produces IL-2, which stimulates T lymphocyte proliferation and interferon-gamma (IFN-gamma), which inhibits B lymphocyte activation and IgE synthesis by B lymphocytes and tumor necrosis factor beta (TNF-beta) (4, 9). These cytokines are responsible for the development of the classic delayed-type (type 4) hypersensitivity reaction.

The Th2 subtype produces and secretes IL-4, IL-5, IL-9, and IL-13 but not IL-2 or IFN-gamma. Through the specific actions of these cytokines on B lymphocytes, mast cells, and eosinophils, Th2 lymphocytes may lead to the characteristic inflammatory response of asthma (4, 9). In this way, Th2 lymphocytes are believed to be responsible for immediate-type (type 1) hypersensitivity reactions associated with allergic diseases, including asthma. In support of this hypothesis, recent studies have shown that atopic subjects have an increased proportion of Th2 lymphocytes in the peripheral blood and airways (7, 9).

Unlike helper cells, most cytotoxic CD8+ T lymphocytes recognize endogenous antigens, usually presented in the context of MHC class I molecules. This type of cell-mediated immunity is involved mainly in the response to intracellular infectious agents and tumors. However, there is increasing evidence that these cells may also be involved in the inflammatory response of some forms of asthma, including isocyanate sensitivity (10, 11).

T lymphocytes are capable of modulating eosinophil adherence, locomotion, and activation (7, 12) and of stimulating these cells to cause tissue damage. An increased number of activated CD25+ (IL-2 receptor expressing) T lymphocytes and of activated eosinophils and mast cells have been observed in patients with asthma. 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 in asthma of different origins, a hypothesis further supported by the finding of cells expressing IL-5-messenger RNA in bronchial biopsies of

atopic patients with asthma (7, 8). IL-5 is an important regulating cytokine for eosinophils, and its level of expression in the airway mucosa of patients with asthma correlates with markers of T lymphocyte and eosinophil activation (7-9).

### Adhesion Molecules

The mechanism of inflammatory cell recruitment in asthma has been investigated. The increase of neutrophils, eosinophils, and lymphocytes in the airway mucosa during worsening asthma is paralleled by increased expression of specific adhesion molecules on postcapillary venular endothelial cells (7, 12). These include E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). Endothelial adhesion molecules engage the activated form of the complementary ligands (either lectins or integrins) on activated leukocytes. For example, LFA-1 and Mac-1 on T lymphocytes and eosinophils interact with ICAM-1, and VLA-4 with VCAM-1 (7, 12). The upregulation of these molecules by mediators and cytokines is the first step of a cascade of events that enables leukocytes to marginate, cross the postcapillary venule wall, and subsequently migrate to the mucosa.

### Constitutive Cells

Interestingly, it is recognized that in asthma normal resident cells of the airways are able to generate an array of cytokines that may contribute to the chronicity of airway inflammation so characteristic of human asthma, as opposed to allergen-sensitized animal "models" of the disorder. The epithelium is a source of IL-6, IL-8, GM-CSF, IL-beta, and TNF-alpha. The endothelium can generate IL-8, IL-5, and GM-CSF, and fibroblasts are an important source of the mast cell growth factor, cKit-ligand (stem cell factor), and GM-CSF and IL-8 (6). Together, these cytokines may provide a nonimmunological mechanism for augmenting and maintaining the inflammatory response.

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## NEURAL CONTROL OF AIRWAYS

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Several nonspecific stimuli (for example, fog, sulfur dioxide, dust, cold air) provoke reflex bronchoconstriction by stimulating the sensory receptors in the airways. This physiologic defense mechanism may provoke bronchoconstriction in both normal subjects and subjects with asthma. However, in subjects with asthma, the airway response develops at lower levels of stimulation, and the intensity of the airflow limitation response (airway hyperresponsiveness) is more severe compared to normal subjects. In the past, it was believed that an increased activity of the

parasympathetic autonomic nervous system could be responsible for the airway hyperresponsiveness in asthma (13). Subsequent work has shown that although this mechanism may be involved, it is not a major cause of airflow limitation in asthma (14).

The system of innervation of the airways now is seen as much more complex. In addition to the classic cholinergic and adrenergic mechanisms, nonadrenergic-noncholinergic neural pathways have been described in human airways (14). The demonstration of an extensive network of nerve fibers containing potent peptides, in addition to classic neurotransmitters, has revived interest in the possible abnormalities of the neural control of airways in the pathogenesis of asthma (14).

Substance P (SP), neurokinin A (NKA), neurokinin B (NKB), calcitonin gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP) are the best characterized neuropeptides. Some irritants, in addition to causing a vagally mediated reflex bronchoconstriction, stimulate the sensory nerves, especially the nonmyelinated sensory C-fiber endings, to release SP, NKA, and other related neuropeptides, with wide-ranging effects in the airways. Neuropeptides may contribute to the development of most of the characteristic features of asthma exacerbations, including mucus hypersecretion, smooth muscle contraction, plasma extravasation, inflammatory cell activation, and adhesion. Neutral endopeptidase (NEP) is an enzyme present on the surface of the cells containing receptors for neuropeptides (for example, airway epithelial, smooth muscle, and endothelial cells). NEP cleaves and inactivates neuropeptides, thereby limiting their concentration at cell surface receptors and modulating the target response. An increased release of excitatory neuropeptides, a decreased activity of neutral endopeptidase, or both might be involved in asthma exacerbations. Neutral endopeptidase activity is, however, not decreased in mild persistent asthma (15-17).

Vasoactive intestinal peptide has been localized in the airway efferent cholinergic nerves, where it acts as a cotransmitter with acetylcholine, and it may therefore function as a braking system for cholinergic bronchoconstriction. In asthma, a primary defect of nonadrenergic-noncholinergic innervation seems unlikely, although airway inflammation may cause a functional defect in this system. In the airways of patients with asthma, inflammatory cells, such as eosinophils, neutrophils, and mast cells, may release a variety of peptidases (e.g., tryptase) that have the capacity to degrade VIP. The consequent exaggerated reflex cholinergic bronchoconstriction could contribute to the development of airway hyperresponsiveness associated

with airway inflammation.

Nitric oxide (NO) is a reactive gas formed from arginine both in neuronal and nonneuronal tissue through the action of nitric oxide synthase. In asthma, there is evidence to suggest that the inducible (steroid suppressible) form of this enzyme is upregulated in the epithelium (18). Nitric oxide is a potent vasodilator and also a bronchodilator. Nitric oxide is probably the neurotransmitter of nonadrenergic-noncholinergic inhibitory nerves (19), which may be involved in the regulation of airway and pulmonary blood flow and in immune regulation. Thus abnormalities of its production and/or breakdown may be relevant in the pathophysiology of asthma (20).

Whether abnormalities of the neural control of airways play a role in the development of airway inflammation, airway hyperresponsiveness, and airflow limitation in asthma remains to be established. The availability of potent and selective inhibitors and antagonists should help in resolving these issues.

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## ASTHMA SYMPTOMS

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Characteristic symptoms of asthma are cough, chest tightness, wheezing, and dyspnea. Different patients experience different combinations—and varying intensities—of these symptoms. Cough is probably caused by stimulation of the sensory nerves by inflammatory mediators, and it is a particularly important symptom of cough variant asthma and in children with asthma (21). Chest tightness and wheezing are most likely due to airflow limitation (22). Dyspnea (literally difficult breathing) probably reflects the increased work of breathing and the increased activity of the respiratory muscles, changes in lung compliance, and direct neuronal stimulation by relevant inflammatory mediators.

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## AIRFLOW LIMITATION IN ASTHMA

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Many factors may contribute to airflow limitation in asthma, including direct and indirect (neural) contraction of smooth muscle, edema, mucus plug formation, and airway wall remodeling; each is related to the inflammatory process. The many factors contributing to airflow limitation may vary within and among individuals with asthma, and this leads to a marked variability of clinical presentation. This leads

to the hypothesis that asthma is not a single disease but rather a common disorder or clinical expression of different pathogenic mechanisms.

Acute bronchoconstriction may occur as a consequence of hyperreactive airways and be provoked by inhaled allergen through the release of mast cell mediators. Direct measurements of mediators in bronchoalveolar lavage and the use of specific inhibitors and antagonists suggest that leukotrienes (C4 and D4), prostaglandins (PGD<sub>2</sub>, TxA<sub>2</sub>, and PGF<sub>2</sub>-α), and histamine are the most relevant mediators of airflow limitation induced by inhaled allergens. Exercise or hypertonic saline may also provoke acute airflow limitation by directly (not through IgE) stimulating the release from mast cells of some of the same mediators. The response is most likely caused by the action of these mediators on smooth muscle rather than through vasodilation or edema formation. Neural reflexes may serve to augment these responses through the release of neuropeptides and the upregulation of effector cell receptors within the inflammatory microenvironment.

### Reversible Airflow Limitation and Airway Hyperresponsiveness

A characteristic feature of asthma is reversible airflow limitation. The daily variability of the degree of airflow limitation correlates with the degree of airway hyperresponsiveness (23). It has therefore been suggested that similar mechanisms are responsible for both of these characteristic features of asthma.

The reversible airflow limitation and the transient increase of airway responsiveness associated with exacerbations of asthma are probably caused by an acute inflammatory reaction in the airways. In fact, not only has acute airway inflammation been shown to occur during asthma exacerbations, but also symptoms, lung function changes, and increase in airway responsiveness are prevented or reversed by anti-inflammatory agents (23).

Most subjects with asthma have airway hyperresponsiveness even when they are asymptomatic and after effective anti-inflammatory treatment capable of abolishing daily variability of airflow limitation and reversing airway inflammation. This component of airway hyperresponsiveness, which is long lasting and poorly reversible either spontaneously or with treatment, may be attributed to enhanced neural pathways or airway remodeling, that is, to permanent structural or functional changes of the resident airway cells (24, 25).

## Irreversible Airflow Limitation

It is clearly established that irreversible airflow limitation develops in some asthma patients. This may be caused by increase of airway wall thickness due to accumulation of inflammatory cells, edema, increased thickness of smooth muscle, subepithelial fibrosis and remodeling of the airway wall, obstruction of the airway lumen by exudate and mucus, and changes of the elastic properties of the airway walls or loss of the interdependence between the airways and the surrounding parenchyma (26). In most asthma patients, the hypertrophy of airway smooth muscle is more pronounced in the central airways, but in a subgroup of patients, it also extends to peripheral bronchioles (27, 28).

The natural history of asthma is difficult to examine, particularly when the risk factors that cause asthma and asthma exacerbations cannot be identified (see the chapter on epidemiology). In this respect, occupational asthma has provided some useful information. If exposure continues after diagnosis, occupational asthma does not resolve but instead persists or may even worsen as shown by increased airway responsiveness and development of chronic airflow limitation (29). The majority of patients with occupational asthma do not fully recover even after several years of cessation of exposure. Recent studies have shown that persistence of occupational asthma is associated with continued airway inflammation, suggesting that once initiated the inflammatory process may continue even in the absence of environmental exposure. However, some of the characteristic features of asthma pathology (including subepithelial fibrosis) may reverse after cessation of exposure to the sensitizing agent (30).

## BLOOD GAS ABNORMALITIES IN ASTHMA

Stable and well-controlled asthma is usually associated with normal blood gases, even when a significant ventilation-perfusion mismatch is present (31). In some patients mild hypocapnia and respiratory alkalemia are associated with normal oxygen tension or with mild hypoxemia, probably because of a hyperventilation compensatory to the underlying hypoxemia. Asthma exacerbations are associated with a variable combination of hypoxemia and hypocapnia, hypoxemia and normo- or hypercapnia, and acidosis, depending on the severity (31). Hypoxemia is most likely caused by alteration of the distribution of the ventilation due to peripheral airway inflammation, but hypercapnia is most likely caused by failure of the respiratory pump (32).

## NOCTURNAL ASTHMA

Being awakened at night by cough, wheeze, or breathlessness, or experiencing chest tightness at night or first thing in the morning is characteristic of asthma. These symptoms disrupt sleep and impair daytime performances. Increased parasympathetic tone and decreased nonadrenergic airway dilating activity, together with increased functional residual capacity and enhanced nocturnal airway inflammation, are likely to play a role in the pathogenesis of nocturnal airflow limitation (33). Allergens present in bedding, decreased mucociliary clearance, nocturnal hypoventilation or hyperventilation, and gastroesophageal reflux also may contribute to the development of nocturnal asthma.

## RESEARCH RECOMMENDATIONS

Priorities for future investigations related to mechanisms of asthma include:

- Exploring the genetics of asthma, e.g. the physiologic mechanisms that are genetically altered and predispose a subject to develop asthma (immune response, inflammatory cascade, neural control).
- Identifying the mechanisms through which causal risk factors lead to the development of asthma, e.g., sensitizing allergens and chemicals.
- Identifying the mechanisms through which risk factors that are triggers cause asthma exacerbations:
  - Sensitizing allergens and chemicals
  - Secondary immune reactions
  - Airway inflammation
  - Neural control of airways
  - Other.
- Identifying the mechanisms of chronicity of asthma.

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# CHAPTER

**5**

## ***DIAGNOSIS AND CLASSIFICATION***

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### KEY POINTS:

- Asthma is underdiagnosed and undertreated throughout the world.
- Asthma can be diagnosed on the basis of symptoms. In addition, measurements of lung function greatly enhance diagnostic confidence.
- Lung function measurements that are most helpful for the diagnosis of asthma are the bronchodilator response to an inhaled beta<sub>2</sub>-agonist, the variation in airflow limitation measured by peak expiratory flow (PEF) monitoring, and the airway response to exercise provocation in children.
- Classifying asthma severity is important in guiding therapeutic recommendations.
- Measurements of allergic status are a valuable addition to the diagnosis of asthma 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 subject to occupational exposure.
- Asthma screening programs may be considered in children and occupationally at-risk groups.

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 in the underdiagnosis of asthma is in the nonspecific nature of the symptoms that 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 is diagnosed as variant forms of bronchitis and, as a consequence, treated inappropriately and ineffectively with successive courses of antibiotics and cough medications (2). 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.”

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## CLINICAL DIAGNOSIS

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### History and Measurements of Symptoms

A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, chest tightness, and cough, worse particularly at night and in the early hours of the morning. However, in themselves these common symptoms are not diagnostic. Figure 5-1 highlights questions for 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 (3, 4). What is important is a history of recurrent exacerbations (or attacks) often provoked by factors such as allergens, irritants, exercise, and virus infections. Under some circumstances, especially in patients with very responsive airways, asthma triggers may produce profound bronchoconstriction that rapidly gives rise to a life-threatening exacerbation. Other useful clinical markers of asthma are the relief of symptoms spontaneously and more specifically by bronchodilator and anti-inflammatory treatments. Seasonal variability of symptoms and a positive family history of asthma and atopic disease are also helpful diagnostic guides.

Measurements of symptoms and lung function are important parameters for assessing the characteristics of the patient's asthma. Various symptom scores have been developed in order to quantify the symptoms (5). Many of these symptom scores have not been thoroughly validated. Symptom scores can, however, be a useful tool to follow up individual patients. They should be adapted to the age and the cultural background of the patient.

### Physical Examination

Because asthma symptoms are variable throughout the day, the physical examination of the respiratory system may appear normal. 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. It follows that clinical signs of dyspnea, airflow limitation (wheeze), and hyperinflation are more likely to be present if patients are examined during symptomatic periods and in the morning prior to the administration of a bronchodilator drug.

Some patients with asthma may have normal auscultation but significant airflow limitation when measured objectively, probably due to predominant involvement of the smaller airways. Airway sounds (wheezing) may be absent in severe asthma exacerbations, but usually patients in this state 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. Assessment of such symptoms as dyspnea and wheezing by physicians may also be inaccurate. Measurements of lung function provide direct assessment of airflow limitation and, by measuring variability, indirect assessment of airway hyperresponsiveness. However, although some relationship has been established between laboratory indices of airway hyperresponsiveness and peak expiratory flow variability, they are not interchangeable. For example, PEF variability may respond rapidly to corticosteroid treatment, whereas histamine or methacholine airway responsiveness reverses over a slower time course. Nevertheless, measurements of airflow limitation, its reversibility (see figures 1-4 and 1-6), and its variability (a.m.-p.m. PEF variability of 20 percent or more) are considered critical in establishing a clear diagnosis of asthma (see figure 1-5) (6). 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. Both of these measurements depend on

### **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 cough or wheeze after exercise?
- Does the patient have a cough, wheeze, or chest tightness 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?

### **Figure 5-2. International Union Against Tuberculosis and Lung Disease (IUATLD) Asthma Questionnaire**

- 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?

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).

Measurement of FEV<sub>1</sub> and FVC is undertaken during a forced expiratory maneuver using a spirometer. 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<sub>1</sub> less than 1 liter. Predicted values of FEV<sub>1</sub>, 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<sub>1</sub>, 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<sub>1</sub>, a useful assessment of airflow limitation can be obtained as the ratio of FEV<sub>1</sub> to FVC. In the normal lung, flow limitation on forced expiration results in FEV<sub>1</sub>-FVC ratios of greater than 75 percent and in children possibly greater than 85 percent. Any values less than these are suggestive of airflow limitation, with the lower the ratio the more severe the limitation. Spirometry is helpful for monitoring the activity of the asthma 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 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.

Probably the most important innovation to aid in the diagnosis and subsequent treatment of asthma is the peak expiratory flow meter. For most patients, PEF correlates well with FEV<sub>1</sub>, and 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 true asthma. Regular home monitoring is useful because it can help patients detect early signs of deterioration—i.e., of an

exacerbation. By the time wheezing can be detected with a stethoscope, the PEF may have decreased by as much as 25 percent or more (7). Several studies have demonstrated that patients' symptom reports are unreliable indicators of airflow limitation (8, 9). 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 (10). However, this is not the case with all patients. One study showed that symptoms preceded the onset of declines in lung function (11).

Increasingly peak flow meters are becoming available on health service prescription. PEF meters are also useful in clinic and primary health care settings for ongoing supervision of asthma if spirometry is impractical (see figure 1-5).

Careful instruction is required because PEF measurement, like FEV<sub>1</sub> and FVC measurement, is effort dependent. A peak flow meter may be used regularly to obtain an accurate picture of asthma throughout the day and over weeks and months to assess severity and monitor the course of asthma. The severity of asthma is not only reflected in the level of baseline airflow limitation but also in its variability, particularly across 24 hours (see figure 1-5). Ideally PEF should be measured first thing in the morning when values are usually close to their lowest and last thing at night (preferably after inhaling a short-acting bronchodilator—if the patient is using bronchodilators) when values are usually at their highest. The most robust and sensitive method of describing diurnal PEF variability is as the amplitude (difference between the prebronchodilator morning value and postbronchodilator value from the evening before) expressed as a percentage of the mean daily PEF value (12).

$$\text{Daily variability} = \frac{\text{PEF evening} - \text{PEF morning}}{1/2 (\text{PEF evening} + \text{PEF morning})} \times 100$$

To acquire information about variability, patients can be asked to record their peak flow either in tabular form or on easily read charts at least twice a day for a period of 1 to 2 weeks with a request that they record values both before and 10 to 15 minutes after inhalation of a standard dose of an inhaled short-acting beta<sub>2</sub>-agonist, if the patient is using this medication.

A diurnal variation in PEF of more than 20 percent is diagnostic of asthma, the magnitude of the variability being broadly proportional to disease severity (see figure 1-5) (12). However, it should be noted that in mild intermittent

asthma (especially in children) 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 corticosteroids. 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 treatment plans that are responsive to asthma severity, and the course of asthma can be effectively monitored. Furthermore, patient adherence to the treatment may be enhanced by observing objectively their responses to therapy.

Although long-term peak flow monitoring for most patients with persistent asthma can be valuable and may be an ideal, this may not always be possible for reason 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 (stepdown or stepup). 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 (13).

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 a patient presenting with severe symptoms and gross lung dysfunction differ from those for the asymptomatic patient found to be just above the diagnostic cutoff value for PEF variability (greater than 20 percent). For the asymptomatic patient at least one additional test result with a value in the asthmatic range is desirable. It is under these conditions that measurements of airway hyperresponsiveness can help diagnose asthma, but these measurements alone have low specificity. The presence of an allergic component identified by skin testing or measurement of specific IgE adds little to the diagnosis of asthma but can help in identifying its risk factors—causes and triggers.

Although measurements of airway responsiveness may be used to identify asthma, there is some overlap with rhinitis

and causes of lower airflow limitation other than asthma, such as cystic fibrosis, bronchiectasis, and chronic obstructive pulmonary disease. The use of airway hyperresponsiveness as an index of underlying asthma has recently been shown in a prospective study showing that 20 percent of young asymptomatic adults or 45 percent of asymptomatic subjects with a PD<sub>20</sub> less than 3.2 micromoles developed symptomatic asthma within 2 years (14). This raises important issues as to whether completely asymptomatic or preclinical asthma exists and as to whether or not it should be treated. Only when there is information on the long-term outcome of asthma will it be possible to assess the importance of preclinical asthma. Deliberate provocation of the airways with a suspected sensitizing agent may also be helpful in establishing causality, especially in the occupational setting, but it is not recommended for routine use, largely on the grounds of safety (13, 15). Similarly, antigen provocation should not be used to establish a diagnosis of asthma but only to establish an environmental cause.

Evidence of airway inflammation may also be revealed by examining spontaneously produced or hypertonic saline-induced sputum for eosinophils and metachromatic cells (16). However, there is a clear need to develop further noninvasive discriminant measurements of airway inflammation.

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 more clear. 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 a short-acting beta<sub>2</sub>-agonist and a corticosteroid 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 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.

### Measurements of Allergic Status

Skin tests with allergens represent the primary diagnostic tool in allergy. Prick tests are the most commonly used for diagnosis 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 is of great value but does not surpass skin tests and is more expensive. The main limitation of these two methods is that a positive test does not necessarily mean that the disease is allergic in nature, as some nonallergic individuals have specific IgE antibodies without any allergic symptoms. The relevant exposure and its relation to symptoms must be confirmed by the patient history. Measurements of total IgE or allergen-specific IgG4 in serum has no value in the diagnosis of allergy. Bronchial challenges are time consuming, possibly harmful to the patient, and only rarely used for diagnostic purposes.

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## PARTICULARLY DIFFICULT DIAGNOSTIC GROUPS

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As already noted, asthma is frequently misdiagnosed, and as a consequence, inappropriate treatment is given. 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

Asthma in childhood can present a particularly difficult problem largely because episodic wheezing and cough are among the most common symptoms encountered in childhood illnesses, particularly in the under-3-year-old (2). Although health care professionals are increasingly encouraged to make a positive diagnosis of asthma whenever recurrent wheezing, breathlessness, and cough occur (particularly if associated with nocturnal and early morning symptoms), the underlying nature of the disorder's process may differ in infants from that in older children and adults (17). 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, particularly below age 5, the greater the possibility of an alternative diagnosis for 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 intrathoracic airways, and foreign body aspiration. Chest radiography is important as a diagnostic test to exclude alternative causes. 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 investigations, such as a sweat test to exclude cystic fibrosis, measurements of immune function, and reflux studies.

Among those with no alternative diagnosis, there is the possibility that the problem does not have a uniform underlying pathogenesis (2). 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 (18, 19). 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 (20) and thus may differ mechanistically from the more established chronic inflammatory condition that underlies asthma in older children and adults.

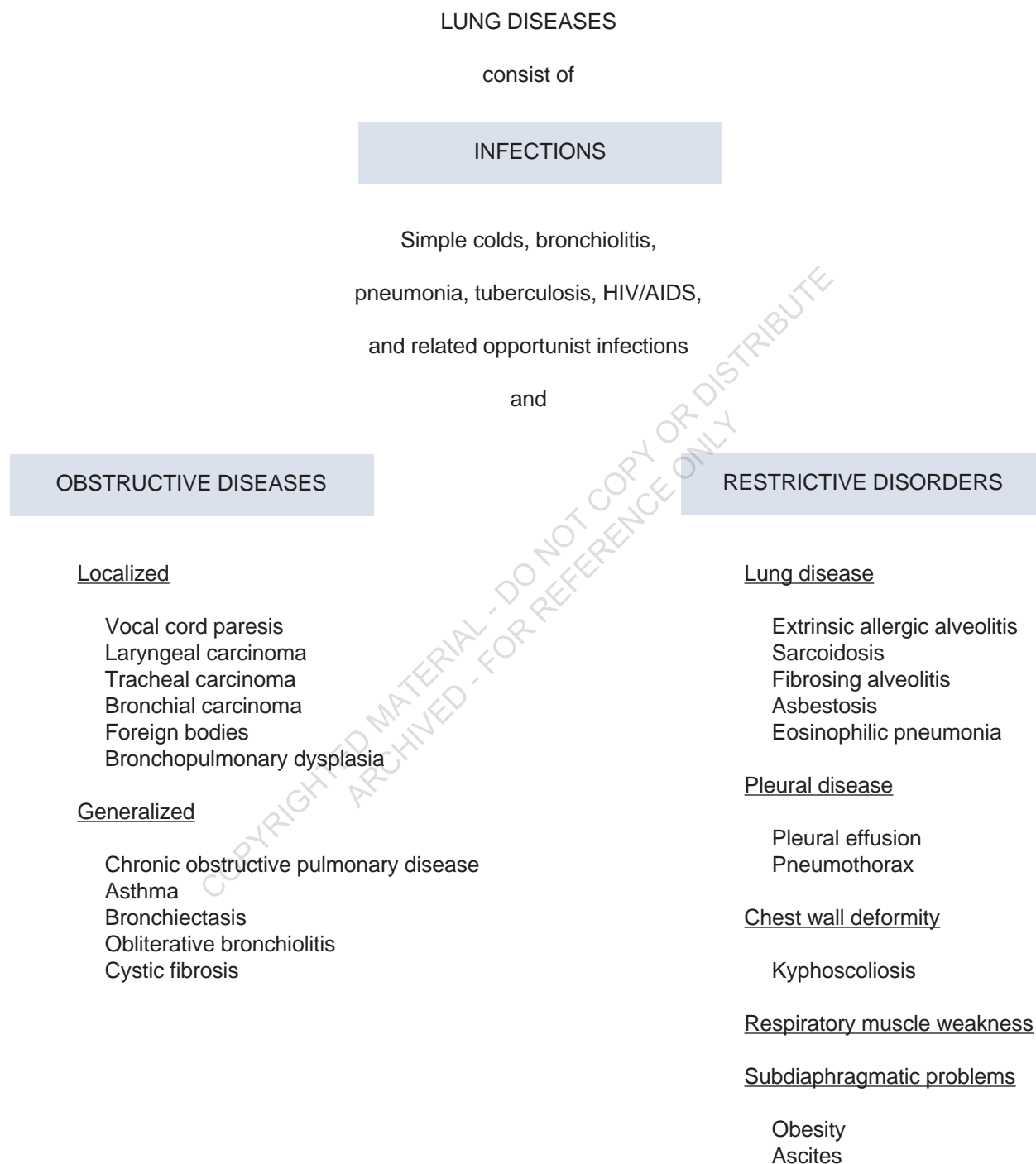
Other infants with asthma have an atopic background often associated with eczema and develop symptoms later in infancy that persist through childhood and into adult life (21). In these children, characteristic features of airway inflammation can be found even in infancy. However, there are no practical, clinical tests that can be done to establish the presence of airway inflammation. Only associated atopic problems can be used as a guide to prognosis. Early age (under 2 years) of onset of wheeze is a poor predictor of continuing problems in later childhood (2, 18, 19).

It is likely that the issue of asthma associated with recurrent virus-related episodes and the later development of persistent asthma requires further study. Apart from the confusion over etiological mechanisms of asthma in childhood, there is also considerable reluctance in establishing a diagnosis and, as a consequence, initiating 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), 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 drugs and bronchodilators rather than antibiotics, and it is for this reason that health care



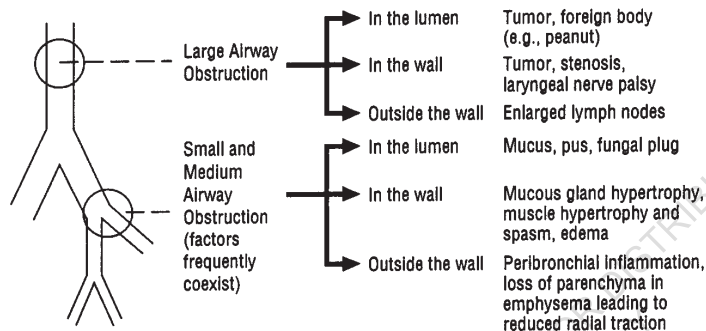
**Figure 5-3. Overview of Lung Diseases**



**Figure 5-4. Differential Diagnosis of Obstructive Airway Disease**

**WITH AIRWAY-TYPE SYMPTOMS  
OF COUGH, WHEEZING, BREATHLESSNESS, AND  
AIRWAY NARROWING (OBSTRUCTIVE SPIROMETRY, PEF)**

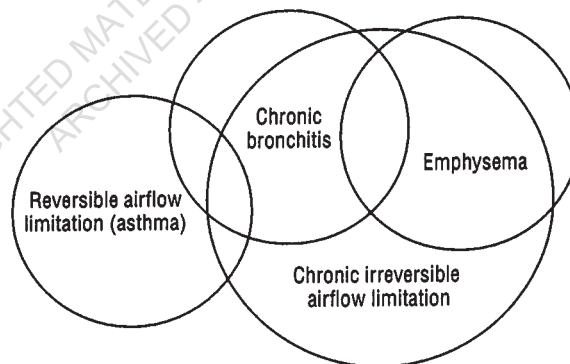
**ALWAYS THINK: IS OBSTRUCTION  
LOCALIZED OR GENERALIZED?**



If generalized be sure to differentiate

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**Figure 5-5. Venn Diagram Showing the Interrelationship Among Chronic Bronchitis, Airflow Limitation, Emphysema, and Asthma**



Venn diagram showing the interrelationship among chronic bronchitis, airflow limitation, emphysema, and asthma. An overlap is shown because with time and under treatment some of the airflow limitation associated with asthma may become fixed, and in "irreversible" airflow limitation a small degree of response to bronchodilators is often shown.

A steroid may be necessary to place an individual in the left- or right-hand side of the Venn diagram.

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professionals are encouraged to use the word "asthma" rather than other terminology to describe this syndrome.

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 forms of presentation of asthma in childhood. The presence of recurrent nocturnal cough in an otherwise healthy child should raise awareness of asthma as a probable diagnosis. Although repeated infections of the sinuses, tonsils, and adenoids may explain nocturnal coughing, the occurrence of this symptom awakening the child in the early hours of the morning is almost always diagnostic of asthma.

Under the age of 5 years, the diagnosis of asthma has to rely largely on clinical judgment based on a combination 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 (22), it can therefore only be recommended as a research tool. A trial of treatment is probably the most confident way in which a diagnosis of asthma can be secured in children (and in many adults as well). Prognostic features include a family history of asthma or eczema and presence of eczema in a young child with respiratory symptoms (19).

Children ages 4 to 5 years can be taught to use a PEF meter and obtain reliable readings. However, unless there is careful parental supervision over when and how the measurements are made, PEF recording in childhood can be unreliable (23). The use of diary cards to record symptoms, PEF, and treatment has proved invaluable for the new asthma management strategies and is discussed in the chapter on management.

Some children with asthma present only with exercise-induced symptoms. In this group, or when there is doubt over the existence of low-grade asthma in childhood, exercise testing is helpful. A 6-minute running protocol is easily performed in clinical practice, and when used in conjunction with measurements of airflow limitation ( $FEV_1$  or PEF), it can be most helpful in establishing a firm diagnosis of asthma (see figure 1-7) (24), especially if the cough produced by the exercise is similar to that occurring spontaneously at night.

### **Asthma in the Elderly**

Another group of patients in which the diagnosis of asthma (late onset) is either not made or is missed occurs in the elderly (25). Although structural damage to the lung consequent upon smoking and lifelong exposure to

inhaled environmental insults targets this age group with such diseases as bronchitis, emphysema, and fibrosing lung disease, 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. Thus it follows that the diagnosis of asthma and chronic bronchitis purely on the basis of symptoms is fraught with difficulties. The presence of 15 percent or more reversibility in PEF spontaneously, after inhalation of a bronchodilator or in response to a trial of corticosteroid therapy, favors a diagnosis of asthma.

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

Later in life, chronic airflow limitation and elevated serum IgE levels appear to be independent determinants of airflow limitation, although they may interact (26). This has led to the growing view that chronic obstructive airway (pulmonary) disease associated with lifelong 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 (27). When doubt exists, a trial of oral corticosteroids in which a greater than 15 percent improvement in PEF or  $FEV_1$  occurs accompanied by improvement in symptoms and reduced bronchodilator requirement usually confirms asthma as a cause of chronic respiratory symptoms. However, in patients with low PEF and in those who also have chronic obstructive pulmonary disease, continuous oral corticosteroid treatment for up to 4 weeks may be necessary. In such patients, an asthma (reversible) component carries a much better prognosis (28).

The elderly are particularly susceptible to episodes of wheezing, breathlessness, and cough caused by left ventricular failure (sometimes mistakenly labeled cardiac asthma) (25). The presence of increased symptoms with exercise and at night may add to the diagnostic confusion. A careful history and 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 (see the chapter on risk factors and figure 3-2). 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 chronic obstructive pulmonary disease and is therefore either not treated at all or treated inappropriately. Ideally the diagnosis requires a defined occupational history, especially in relation to exposure to 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 occupationally related asthma may be successfully achieved by lung function measurement, such as specific bronchial provocation testing, and serial measurement of PEF at work and away from work (single measurements are less sensitive than serial measurements). The increasing recognition that many forms of occupational asthma persist, or continue to deteriorate, even in the absence of continued exposure to the offending agent, 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 pollen and ragweed. Seasonal asthma is usually associated with allergic rhinitis. This type of asthma may occur only intermittently, with the patient being entirely asymptomatic between seasons. Or it may occur as a seasonal worsening of asthma symptoms in a patient with moderate to severe asthma.

### Cough Variant Asthma

Yet another group of patients whose asthma can sometimes be missed are those with cough variant asthma who seldom if ever present with wheeze (29). These patients have cough as their principal, if not only, symptom. Frequently this occurs at night; consequently examinations during the day are normal. For these patients, documentation of variability in lung function together with a search for sputum eosinophils and diagnostic challenge to reveal hyperresponsiveness are particularly important. Within this group is a small subgroup of patients who cough and have sputum eosinophils but who also have apparently normal indices of lung function when assessed by spirometry. In some of these patients, nocturnal administration of long-acting bronchodilators may be diagnostic.

Individuals with hypertension treated by angiotensin-converting-enzyme (ACE) inhibitors, and individuals with gastroesophageal reflux, postnasal drip, or chronic sinusitis, may develop a cough that resembles cough variant asthma.

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## DIFFERENTIAL DIAGNOSIS

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Asthma is one of the most common causes of respiratory symptoms, but it is only one cause of lung disease (see figure 5-3). An important step in ensuring diagnosis of asthma is the demonstration of reversible and variable airflow limitation, preferably by spirometer.

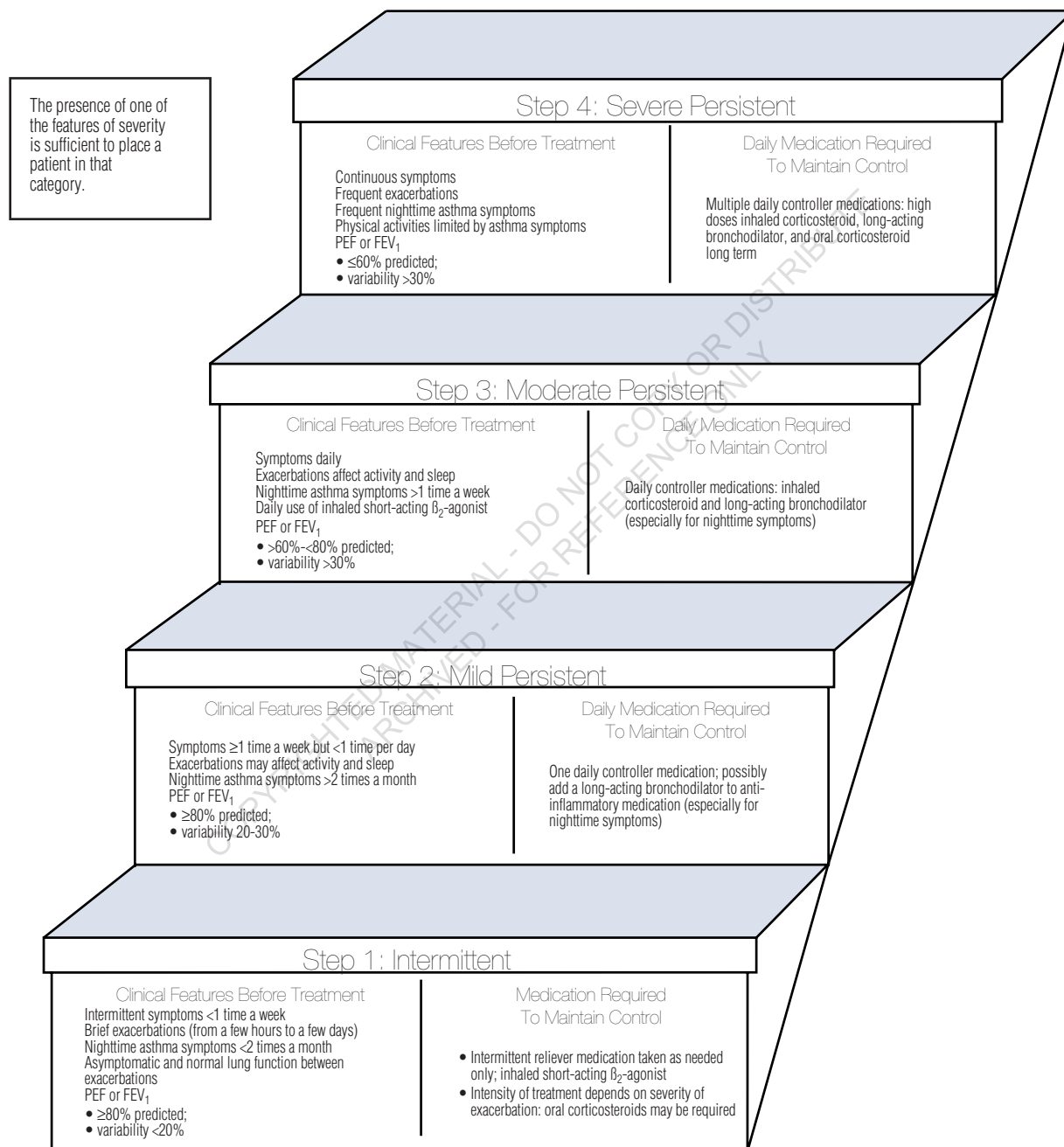
Although in children asthma and acute respiratory infections produce wheezing consequent upon widespread airway involvement, the respiratory symptoms may also arise from localized airway obstruction, which must always be considered in the differential diagnosis (figure 5-4).

In developing countries, acute respiratory infections are one of the most common causes of death in children worldwide, usually in the form of bacterial pneumonia (30). This contrasts with the situation in developed countries where most acute respiratory infections are due to viruses. Wheezing is a common symptom of acute respiratory infection, particularly in that form carried by viruses with a predilection for the smaller airways. The first episode of wheezing in an infant under 6 months of age is probably due to bronchiolitis. At 18 months it is more likely that the child has asthma and should be treated accordingly. The child's response to antiasthma medication can be helpful for the diagnosis.

In adults the overlap of syndromes that cause diffuse

**Figure 5-6. Classification of Asthma Severity**

Classify Severity  
of Asthma





airflow limitations can best be described in the form of a Venn diagram (figure 5-5). Asthma superimposed upon chronic bronchitis and emphysema is a common problem in past or present smokers. A corticosteroid trial is helpful in determining the level of reversible inflammation in chronic obstructive pulmonary disease.

## CLASSIFICATION OF ASTHMA

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

### Etiology

From mechanistic and therapeutic standpoints it is appropriate to differentiate the factors that induce inflammation and its associated airflow limitation and hyperresponsiveness from those that provoke acute bronchoconstriction in hyperresponsive individuals. Because the term “asthma” often is used to reflect the disordered state of lung function produced by risk factors leading to development of asthma as well as the acute exacerbations caused by a variety of triggers, considerable confusion exists over the choice of drugs used in its treatment. Because of a lack of understanding of the underlying process in the past, the focus has been on the more observable aspects of asthma—that is, on acute exacerbations of bronchoconstriction and airflow limitation. This led to the strong emphasis on the use of bronchodilators for management of all aspects of asthma. Now with the current knowledge that airway inflammation underlies both acute and chronic aspects of asthma, a shift in approach has occurred toward the preventive use of avoidance strategies and anti-inflammatory drugs in a determined attempt to focus primarily on the underlying disease process rather than only on the acute consequences.

Many attempts have been made to classify asthma according to etiology, particularly with regard to environmental sensitizing agents. Such a classification is severely hampered by the existence of a group of patients in whom no environmental cause can be identified. Conversely, patients with asthma caused by a known sensitizing large molecular weight agent (e.g., rodent proteins) include those whose symptoms are associated with atopy. However, in addition to IgE mechanisms, sensitizing occupational agents may produce asthma through other cellular and immunological mechanisms that do not depend on the immediate hypersensitivity response. Identification of a specific environmental cause for asthma in an individual patient should be part of the clinical assessment because it enables the use of

avoidance strategies in asthma management. The recent association found between serum IgE levels and indices of asthma in all age groups, including individuals who are nonatopic, raises the possibility that all forms of this disorder relate to a mucosal inflammatory response initiated by environmental or other antigens (31).

### Severity

No single test allows us to precisely classify the severity of the disorder. However, combining measurements of symptoms and the measurements of lung function yields a useful characterization of the disorder by its severity.

A classification of asthma based on severity is of importance when decisions have to be made about management. 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 (32). Both the level of airflow limitation and its variability enable asthma to be subdivided by severity into intermittent, mild persistent, moderate persistent, and severe persistent (see figure 5-6) (33). These descriptions of asthma severity are useful because asthma therapy has a stepwise approach in which the level of therapy is increased as the severity of the asthma increases.

The severity of an acute exacerbation of asthma is often underestimated by patients, their relatives, and their health care professional. This is largely because of 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 (34, 35). It is important to recognize that any patient with asthma, however mild on a chronic basis, may have an acute severe asthma exacerbation. Specific factors have been identified that are associated with a higher risk of asthma mortality, and these include a previous history of acute life-threatening attacks, hospitalization within the previous year, psychosocial problems, a history of intubation for asthma, recent reductions or cessation of corticosteroid therapy, and noncompliance with recommended medical therapy. Populations who are low income, are medically underserved, live in the inner city, or have cultural differences are at especially high risk (35). Deaths usually occur because of a failure to appreciate the severity of an exacerbation and to initiate appropriate emergency treatment that includes the early introduction of anti-inflammatory drugs.

### Time Trends of Airflow Limitation

Asthma may also be classified according to time trend

patterns of airflow limitation monitored by PEF measurements (36). 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, in contrast to persistent asthma, which is characterized by daytime and nocturnal PEF variability, frequent symptoms, and airway hyperresponsiveness. Some patients with longstanding persistent asthma with an irreversible component fail to achieve normal lung function despite intensive therapy with corticosteroids. The term "brittle asthma" is sometimes used to describe patients with highly responsive airways and extreme day-to-day variability in airway obstruction, and these patients are particularly at risk for sudden, severe, and life-threatening exacerbations.

## ASTHMA SCREENING

Population screening for asthma is not of proven cost effectiveness. However, screening of selected groups for asthma is a realistic but not widely used practice. Children seem a particularly important group in whom a successful diagnosis could lead to early effective intervention and perhaps to improved prognosis. Screening measures for most industries are of limited value, but screening of work forces prior to exposure or potential exposure to high molecular weight animal or plant occupational sensitizing agents could be beneficial. Asthma screening for the armed forces, for other highly physically demanding occupations, and for those persons wishing to become athletes may also be helpful to ensure that the individual with asthma gets appropriate asthma therapy to enable full participation. School medical examinations and immunization programs might be ideal opportunities to look for asthma and initiate treatment. Although spot measurements of FEV<sub>1</sub> or PEF may be sufficient to detect moderate or severe asthma, screening to detect mild asthma requires a questionnaire of symptom assessment over a 12-month period, PEF monitoring, or provocation testing with exercise or other stimulus.

## RESEARCH RECOMMENDATIONS

Priorities for future investigations related to diagnosing asthma include:

- Developing methodology for the early detection of asthma (preclinical asthma), particularly in infants.

- Developing and validating symptom questionnaires that are applicable for diagnosis and followup of asthma.
- Developing noninvasive test(s) of airway inflammation for use in diagnosis, monitoring the disorder's activity, and evaluating treatments.
- Determining the basis of asthma with unknown etiology.
- Determining markers in childhood asthma to identify whose asthma will improve.
- Investigating the long-term outcome of airway inflammation in relation to the appearance of chronic obstructive pulmonary disease.
- Developing common diagnostic criteria for occupational asthma.
- Establishing PEF normal values for all ethnic characteristics.
- Determining the consequences on long-term lung health in a population if asthma is not adequately diagnosed.

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# CHAPTER

6

# *PREVENTION*

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## KEY POINTS:

- Prevention of asthma involves both the prevention of the initial development of asthma (primary prevention) and the prevention of exacerbations in those who already have the condition (secondary prevention).
- Primary prevention methods have considerable potential to prevent the development of asthma, and urgent investigation is required. Reducing exposure to indoor allergens, particularly domestic mites, is one of the most promising measures for future preventive action, especially for infants. Avoidance of passive smoking, especially by infants, is very likely to be beneficial. Avoidance of vehicle emission pollutants by people of all ages warrants consideration.
- Secondary prevention includes both pharmacologic and nonpharmacologic interventions and is discussed in the chapter on management of asthma.
- The subject of primary prevention represents a major research challenge for the next decade.

The challenge of the last 10 years has been to better understand what is happening within the airways of those with asthma so that treatment may be used to maximum effectiveness. The challenge for the present is to organize asthma care effectively and to ensure that both patients and health care professionals are educated to make the most of the excellent treatments available. The challenge of the future is to understand why more people are developing asthma and take steps to prevent the onset of the condition in at-risk individuals. It is possible that within 10 years we may have advanced our understanding of asthma to the extent that we can compare the costs and advantages of a communitywide asthma prevention program versus the cost of lifelong medication for those who develop asthma.

Prevention of asthma can be both primary and secondary:

- The goal of primary prevention—the focus of this chapter—is to prevent development of the condition of asthma.

- The goals of secondary prevention (discussed in the chapters on management of asthma and education and delivery of care) are to prevent exacerbations of asthma in those who already have the condition and avoid deterioration in lung function or death from the condition.

Preventing the development of a condition is clearly a more attractive option than treating an established condition. Although advances have been made in understanding prevention in relation to passive smoking and occupational asthma, primary prevention is as yet an area of unproven benefit. Much more research is needed.

This chapter discusses primary prevention strategies in relation to indoor, outdoor, and workplace environments; smoking; birth weight; infections; and nutrition and diet. Also included are suggestions for communitywide primary prevention programs.

## PRIMARY PREVENTION STRATEGIES

The tendency to develop asthma, along with a tendency to develop the associated atopic conditions of eczema and hay fever, is inherited probably on several genes (1, 2) (see the chapter on risk factors). The apparent increase in prevalence of these conditions over the last few decades (see the chapter on epidemiology) is unlikely to reflect an alteration in genetic constitution and may instead be connected to industrialization and Western lifestyle. More likely is the probability that a greater proportion of those who inherited the tendency to the condition are having that tendency activated so that they manifest the disease. Thus a combination of environmental and lifestyle factors may play a role.

Primary prevention strategies directed at adjusting the environment of those at risk of developing asthma are more feasible than altering a genetic component. Some such environmental manipulations may apply only to high-risk infants; other primary prevention measures merit study for all.

A high-risk infant may be identified as one born to two atopic parents, or to a family in which one parent is atopic (3, 4). The age and length of time that an at-risk infant is particularly vulnerable may be important. Twin studies in which each twin was brought up in a different environment have emphasized the importance of this interaction of the environment with genetic factors (5, 6).

## Indoor Environments

The very young spend most time with their mothers, and they also spend considerable time indoors. New building methods (better insulation, less natural ventilation), new building materials, and changes in indoor furnishings (especially in the use of carpets, mattresses, and upholstered furniture) may have increased the quantity of allergens (especially domestic mites) to which young children are exposed. The degree of such exposure has been shown to correlate with an increased prevalence of childhood asthma (7-9). The same probably applies to adults (10). Further research is needed to evaluate whether manipulation of the home environment could serve as a primary preventive strategy for some of those at risk. Reducing exposure to domestic mites, especially for infants, appears to be a highly promising preventive measure because evidence suggests that domestic mite allergen is a major causal risk factor for asthma.

## Tobacco Smoking

Cross-sectional studies of children and teenagers have found an increased risk of asthma if one or both parents were cigarette smokers (11-16). In longitudinal studies these findings have been confirmed, and the relative risk has been around 2 (17-21). Several studies showed a correlation between degree of exposure and the development of asthma (22). It is thus possible that initiatives aimed at reducing smoking in females, and especially smoking during and just after pregnancy, may have some effect on the prevalence of asthma.

In adults, active smoking is associated with the presence of higher total IgE levels, and in certain situations, especially occupational, such smoking may predispose to sensitization by agents known to be causal risk factors in asthma (23).

## Outdoor Environments

In many countries visible pollutant levels remain very high. In other countries, levels of visible pollutants have fallen, but levels of invisible pollutants (largely from incomplete combustion of petrol by car engines) have risen. Levels of nitrogen oxides have gone up over the past 10 years (24). These substances are known to damage respiratory epithelium (25), and although it is unlikely that nitrogen oxides have themselves directly increased the prevalence of asthma, the damage that they cause may have permitted other antigens easier entry into the lungs. One study showed that the prevalence of exercise-induced asthma varied in different parts of Zimbabwe, but it was more common in urban areas (26). Similar investigation

has shown an increase in the prevalence of asthma with migration from bush to townships and to city centers (27). This is an area for further research, although it is likely that such urbanization involves not only exposure to pollutants but also changes in indoor living environments (especially in the use of carpets, upholstered furniture, and mattresses).

## Workplace Environments

Many agents in the workplace can sensitize the airways and cause asthma (see figure 3-2 in the chapter on risk factors). Prevention of exposure to such agents, immediate removal if exposed, and total avoidance of future contact can prevent this occupational type of asthma. Atopic patients might have a slightly higher risk of developing occupational asthma if exposed to certain high-molecular-weight sensitizers in the workplace. Atopy as well as tobacco smoking may predispose some workers to higher risk in specific occupations, but screening measures are believed to be of limited value in most industries (28). Prevention of sensitization by adequate occupational hygiene measures is most important.

## Small Size at Birth

Disproportionate fetal growth (large head and small trunk), which is often associated with a birth weight of less than 2,500 grams, may carry an increased risk of developing asthma during childhood or adolescence (29). The mechanism is unclear but may involve virally induced enhanced airway hyperresponsiveness, or disordered nutrition may impair basic immunological mechanisms. Avoiding prematurity and other causes of small size at birth by improved maternal care and better maternal nutrition may be helpful.

## Infections

Viral respiratory infections may predispose young children to recurrent bronchitis or bronchiolitis, and several investigations have shown that as many as 50 percent of such children have diagnosed asthma in later life (30, 31). Although there is no evidence that viral infections directly cause the onset of asthma, there is a suggestion that they may contribute to its development. Measures to prevent such infections may in the future be important as a primary preventive measure and might include steps to improve nutrition and to avoid overcrowding in nurseries and kindergartens. Vaccination against respiratory syncytial virus and other infective agents may be possible in the future.

## Nutrition and Diet

Although disordered nutrition may predispose to infection, and small size at birth is associated with an increased rate of asthma, there is no clear evidence that dietary manipulation may be useful as a primary preventive strategy for asthma at this time. However, a retrospective study observed that fish in the diet was associated with a lower prevalence of asthma (32). Another study suggested that when the mother eliminates eggs from her diet during pregnancy, and when both mother and child eliminate eggs in the first year of life, the incidence of such atopic diseases as eczema may be reduced (33-35). However, opinion is divided on this issue, and no recommendation can be made at this time.

Breast feeding is to be recommended for many reasons, and its use and the avoidance of additional animal protein (especially cow's milk) in early infancy appear logical in at-risk infants because some studies (although not all) suggest these actions may reduce the prevalence of atopy (36). It remains controversial as to whether breast feeding also reduces the incidence of asthma (22, 32, 37).

## Other Areas for Consideration and Research

It has been suggested that asymptomatic adolescents shown to have airway hyperresponsiveness carry an increased risk of the subsequent development of asthma (38). Other preasthmatic conditions may exist, and further research is needed to determine whether interventions would be beneficial if such preasthmatic states could be identified.

## SUGGESTIONS FOR A PRIMARY PREVENTION PROGRAM

A possible (and speculative) future program for the communitywide primary prevention of asthma might include:

- Activities designed to reduce the exposure of the newborn to domestic mites and cat allergen. Further research is needed to determine optimal methods for reducing domestic mite growth; current possibilities such as use of mattress covers and discouraging use of carpets and upholstered furnishings are discussed in the chapter on management of asthma.
- Activities directed against smoking during pregnancy.

- Activities directed against exposing infants and young children to passive smoking.
- Improved maternal nutrition during pregnancy.
- Reduction in pollution produced by vehicle emissions.

These are, it is emphasized, speculative activities for which there is currently no definite evidence of value, but they are likely to be areas in which a primary prevention campaign may be more cost effective by preventing the development of asthma and avoiding lifelong treatment.

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# CHAPTER

7

## ***A SIX-PART ASTHMA MANAGEMENT PROGRAM***

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## KEY POINTS:

- Asthma is a chronic inflammatory disorder of the airways. This inflammation causes recurrent episodes of symptoms, variable airflow limitation, and increased airway responsiveness. The most effective management is to prevent this inflammation by eliminating the causal factors.
- Asthma can be effectively controlled in most patients, although it cannot be cured.
- The major factors contributing to asthma morbidity and mortality are underdiagnosis and inappropriate treatment.
- The goal of management is to achieve control of asthma, which is 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) beta<sub>2</sub>-agonist
  - No limitations on activities, including exercise
  - Peak expiratory flow (PEF) circadian variation of less than 20 percent
  - (Near) normal PEF
  - Minimal (or no) adverse effects from medicine.
- Any asthma more severe than mild, intermittent asthma is more effectively controlled by treatment to suppress and reverse the inflammation than by treatment only of acute bronchoconstriction and related symptoms.
- Effective control of asthma can be accomplished by a six-part asthma management program:
  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 or control asthma triggers
  4. Establish individual medication plans for long-term management
  5. Establish plans for managing exacerbations

## 6. Provide regular followup care.

- The choice of management should be guided by the severity of the patient's asthma, the benefits and the risks of each treatment, the cost effectiveness, and the availability of the various forms of asthma treatment. Cultural preferences and differing health care systems need to be considered.
- A stepwise approach to pharmacologic therapy—in which the number and frequency of medications increase as the need for asthma therapy increases—is recommended. The aim is to accomplish the goals of therapy with the least possible medication.
- Although in many countries traditional methods of healing are used, their efficacy has not yet been established and their use can therefore not be recommended.

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 a new understanding of asthma and its treatment. It is now appreciated that asthma is a chronic disorder with progressively developing chronic airway inflammation leading to recurrent episodes of such airway responses as airflow limitation, mucus production, and cough (see the chapters on definition, risk factors, and mechanisms of asthma). 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. Further, the recommendations are based on the "International Consensus Report on Diagnosis and Management of Asthma" (6).

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 or control asthma triggers
4. Establish individual medication plans for long-term management
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**

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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.

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

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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**

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 questionnaires can be a sensitive method for detecting a deterioration of asthma (7). 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.

## 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 (see the chapter on diagnosis and classification). 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.

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 and 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 (9-12).

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 two or three 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 (13-15). 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.

The variability of PEF provides a reasonable index of asthma stability and severity. The variability should be calculated from at least two values (morning and evening) (15). The variability of PEF may be calculated from the formula (9, 16):

$$\text{Daily variability} = \frac{\text{PEF evening} - \text{PEF morning}}{1/2 (\text{PEF evening} + \text{PEF morning})} \times 100$$

**Using PEF measurements to manage asthma.** To help patients manage their asthma at home, a system of PEF zones can be used. 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. A suggested plan for a zone system for asthma management, using PEF and symptom measurements, is presented in Part 4: Establish Medication Plans for Long-Term Management.

**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.

### **Measurement of Arterial Blood Gases**

Arterial blood gas measurement provides important information for assessing the severity of an asthma exacerbation (see the chapter on mechanisms of asthma). During an asthma exacerbation, the uneven distribution of inspired gas owing to heterogeneity of the inflammatory response and its effect on lung function throughout the bronchial tree may lead to gross disturbances of ventilation-perfusion ratios (17). During a mild-moderate acute exacerbation, the primary gas exchange defect is hypocapnia, and hypoxemia develops as the exacerbation worsens. Although the occurrence of hypercapnia is low, its identification in an acute exacerbation is helpful because of its association with severe abnormality and high mortality and because of the potential need for mechanical ventilation. Respiratory acidosis may also develop in a small number of patients and may be severe, especially in children.

Although not necessary for all patients, arterial blood gas measurements should be considered for patients in the emergency department, particularly if there is a severe asthma exacerbation (e.g., with FEV<sub>1</sub> or PEF less than 40 percent of predicted), a decreased oxygen saturation, and/or a failure of the PEF to respond to initial treatment. However, treatment, and particularly oxygen treatment, should not be delayed because of the time necessary to obtain blood gas measurements.

Pulse oximetry provides measurement of oxygen saturation that can help assess the severity of an acute exacerbation and monitor a patient's response to acute therapy. The more extensive information obtained through blood gas determinations may be important, particularly if the pulse oximetry is normal in the presence of other indications of a severe exacerbation, a situation that can arise because cardiac output may be inordinately elevated during a severe asthma exacerbation and the degree of



hypoxemia may not accurately reflect the underlying degree of ventilation-perfusion mismatch. Pulse oximetry should not replace close supervision. No studies have yet demonstrated that pulse oximetry is a sufficiently valid monitoring system during asthma exacerbations.

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## **PART 3: AVOID OR CONTROL ASTHMA TRIGGERS: NONPHARMACOLOGICAL SECONDARY PREVENTION**

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The identification and control of triggers—asthma risk factors that cause exacerbations of asthma—are important steps in asthma management. Avoidance or control of triggers can prevent exacerbations and reduce symptoms and requirements for medications and thus is considered nonpharmacological secondary prevention. Avoidance of some triggers (e.g., domestic mites) may, in the long term, decrease airway inflammation and hyperresponsiveness (4). In addition, taking prompt measures to avoid further exposure to chemical sensitizers as soon as a patient's occupational asthma is recognized helps prevent the development of irreversible airflow limitation. This may possibly apply to exposure to other triggers such as allergens, pharmacologic agents, and viral infections. Additional triggers include indoor and outdoor air pollutants, changes in environmental temperature or humidity, and physical changes such as exercise, cold air, and strong emotional expression.

The discussion in this section focuses on controlling exposure to allergens, pollutants, and pharmacologic agents. Exercise, cold air, and emotional expression are a part of a normal lifestyle; asthma treatment should be adapted so that these exposures can be tolerated without symptoms (see the following section, Part 4: Establish Medication Plans for Long-Term Management). For children, viral respiratory infections are a common trigger, and these are discussed in part 4 of this chapter (in Special Considerations for Children).

### **Environmental Control Measures**

Environmental control measures to reduce exposure to indoor and outdoor allergens and air pollutants should be applied as much as possible because they can help prevent exacerbations and reduce the need for pharmacologic treatment.

### ***Avoidance of Indoor Allergens***

The occurrence of asthma symptoms is closely related to the amount of environmental allergens (18). Thus indoor environmental control measures to reduce exposure to allergens are important, even though it is rarely possible to achieve complete control.

Among the wide variety of allergens that occur within human dwellings are domestic mites, animal allergens (furred animals), cockroach allergen, and fungi. Avoidance of such allergens should be seen as the primary anti-inflammatory treatment for asthma. The presence of domestic mites has been confirmed on a worldwide basis, and exposure to mite allergens in early childhood is known to be an important causal risk factor for development of asthma (18). The World Health Organization has recognized domestic mite allergy as a universal health problem (19), although in some locations, and among some ethnic groups, sensitization to cockroach allergen may be even more common.

**Domestic mites.** Reducing mite populations is a difficult task. Ideal is removing the habitat of mites and making what remains inhospitable for them. Methods to reduce the number of mites have mainly been developed for affluent countries, and very little is known about the influence of different types of housing in partly affluent and nonaffluent countries on mite populations. However, the introduction of blankets has been shown to increase the number of mites in homes dramatically.

Most attention should be directed to the patient's bedroom, although if possible the whole apartment or house should be treated. Mattresses, box springs, and pillows should be encased appropriately not only to contain the allergen but also to deprive mites of an external source of humidity and food. Bed linens and blankets should be washed regularly (once a week) in hot water (over 55° C) to ensure mite killing. The same effect may be obtained by sun-drying, but no data are available that support this assumption. Ideally, the carpet should be removed and replaced by vinyl or polished wooden floor boards. If it is impossible to remove the carpet, it can be completely covered by polyethylene sheeting, taped to the skirting board. Vacuum cleaning removes loose dust but has no effect on the number of live mites in the carpet (the mites attach themselves to the fibers). Curtains should be washable at 55° C. Children's soft toys can be a potent source of domestic mite allergen and either should be removed, washed in hot water, or deep frozen once a week. Vinyl, leather, or plain wooden furniture is preferred; it should not



be fabric covered (20). Ambient humidity can be reduced with dehumidifiers or air conditioning. Maintaining a low humidity level (less than 50 percent) is desirable.

Room air cleaning devices include the HEPA (high-efficiency particulate air) unit, a commonly used mechanical filter. The role of these devices is not defined.

Acaricides (substances that kill mites via chemical action), including benzyl benzoate, pyrethroids, pirimiphos methyl, and liquid nitrogen, are being used but have no proven effect at present. They can therefore not be recommended. Both benzyl benzoate and tannic acid (a 3 percent solution denatures domestic mite allergen) are very effective in vitro, although the difficulty of applying them so that they reach deep into the pile or padding of furniture or carpets reduces their effectiveness. The efficacy of acaricides is influenced by a variety of factors within each home and by the delivery systems, and these issues have not as yet been adequately addressed. Long-term exposure to acaricides requires rigorous safety and toxicity studies. Application of chemical acaricides to bedrooms where children have prolonged contact (via mattresses, pillows, carpets) is not generally recommended. Further, available data do not justify the use of fungicides in the control of domestic mites.

**Animal allergens.** Furred, warm-blooded animals, including small rodents, produce dander, urine, and saliva that can cause allergic reactions. Removal of such animals from the home is important; at a minimum, animals should be kept out of the sleeping area. If a cat is present in the home and cannot be removed, washing it weekly appears to reduce the allergen load (21).

**Cockroach allergen.** Cockroaches are controlled by regular thorough cleaning of infested homes and by the use of pesticides. If pesticide sprays are used, they should be used when the person with asthma is not present. This will help the person avoid the irritating spray. Professional help may be required for this difficult problem.

**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. Using a dehumidifier and cleaning the unit frequently can significantly reduce both mold and bacteria. In addition, air conditioning not only reduces humidity and filters large fungal spores but also effectively lowers the mold and yeast count indoors. Care should be taken to make sure dehumidifiers or air conditioners do not become contaminated with mold and mildew and thus form a new source of allergens or nonspecific irritants. In tropical and subtropical climates fungi might 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 are particles derived from plants (pollen from algae, grasses, weeds, trees) and fungi (spores from molds, mushrooms, shelf fungi). The outdoor allergens that most often produce symptoms in susceptible people are pollens and mold spores, but the thresholds required for clinical impact remain to be determined. Although such common allergens as outdoor pollen and molds are impossible to avoid completely, exposure may be reduced by closing windows and doors, remaining indoors when pollen and mold counts are highest, and using air conditioning if possible. A 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. It also increases the frequency and severity of respiratory symptoms in children with asthma. Parents of children with asthma should be advised to not smoke and to not allow smoking in rooms their children use. Of course, all patients with asthma should be advised to not smoke.

The major indoor air pollutants are respirable particles, nitric oxide, nitrogen oxides, carbon monoxide, carbon dioxide, sulfur dioxide, formaldehyde, and biologicals such as endotoxin (22). Preventing and controlling indoor air quality problems—except by cigarette smoke avoidance—can be expensive and time consuming. 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 must 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.

## ***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 of air pollutants such as ozone, nitrogen oxides, acidic aerosols, and particulate matter and symptoms and exacerbations of asthma (23).

On occasion, weather and atmospheric conditions create a period of intense air pollution in a defined geographic area. The following guidelines are recommended for patients with asthma during such air pollution episodes:

1. 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.
2. Avoid smoking and smoke-filled rooms.
3. Avoid exposure to dust and other irritants such as hair spray, paint, exhaust fumes, or smoke from any fire.
4. Avoid exposure to persons with respiratory infections.
5. 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 short-acting bronchodilator beforehand in order to prevent acute symptoms.
6. If it appears that the air pollution episode will persist or worsen, it may be a good idea to leave the polluted area temporarily.
7. The health care professional and patient should formulate special plans to be followed with regard to medication used and medical evaluation.

### ***Avoidance of Occupational Exposure***

A large number of substances have been identified as occupational allergens and as risk factors that can cause asthma, and levels above which the sensitization occurs frequently have been proposed for many chemicals. However, once a patient has been sensitized, the level of sensitizer necessary to induce symptoms may be extremely low (24-27), and the 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. 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.

### ***Food Avoidance***

Food allergy is a rare cause of asthma exacerbations and occurs primarily in young children. However, food avoidance should preferably not be recommended before a positive double-blind food challenge has been made

(28). For people with a history of severe anaphylactic reactions, skin testing might be helpful, but it should be done with great caution. A food challenge in such patients should be conducted only in a specialty clinic under careful and close supervision. A food challenge may be difficult or impractical, in which case a trial elimination and reintroduction of the suspected food may provide insight. The trial may be repeated for additional insight. However, close monitoring of the patient's asthma during the trial is essential in order to prevent unnecessary food restriction.

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 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 (29, 30). Beta-blocker drugs administered orally or by eye drops may exacerbate bronchospasm and in general should not be used by patients with asthma (31). If they are used, close medical supervision is essential.

### ***Vaccination***

Patients with moderate to severe asthma might be advised to receive an influenza vaccination every year. This may diminish the likelihood for viral respiratory illness to cause exacerbations of asthma (32). The purification of the vaccine preparations has made adverse reactions to the vaccine less frequent.

### ***Specific Immunotherapy***

The role of specific immunotherapy, using subcutaneous injections of allergen solutions, in asthma management is under continual investigation (33, 34). Currently available asthma management strategies with patient education, avoidance measures, and pharmacologic treatment usually provide good control of asthma. Specific immunotherapy is directed at treating the underlying allergy; it may be considered when avoiding allergens is not possible and when appropriate medication

is not available or fails to control asthma symptoms. Specific immunotherapy has been demonstrated to be effective in asthma caused by grass pollen, domestic mites, animal dander, or *Alternaria* allergy, but only when standardized extracts are used under carefully controlled and monitored circumstances. Specific immunotherapy can be dangerous and should only be performed by health care professionals specially trained for this form of treatment.

It is essential to consider several factors in order to appreciate the value of specific immunotherapy in comparison with other available therapeutic methods:

- Potential severity of the allergic asthma to be treated
- Efficacy of available immunotherapy
- Cost and availability of each type of treatment
- Risk of morbidity and mortality due to asthma compared to the risk of the treatments.

To minimize risk and improve efficacy, the following suggestions are made:

- Specific immunotherapy needs to be prescribed by health care professionals trained in the diagnosis of allergy and able to manage systemic reactions if anaphylaxis occurs.
- Patients with multiple allergen sensitivities and/or nonallergic triggers may not benefit from specific immunotherapy.
- Specific immunotherapy is more effective in children and young adults than later in life.
- It is essential for safety reasons that the patient with asthma should be asymptomatic at the time of the injections because lethal and adverse reactions are more often found in patients with severe airflow limitation.
- Patients should remain in the health care professional's office under close supervision for 30 minutes following administration of the allergen extract.
- FEV<sub>1</sub> or PEF with pharmacological treatment should be at 70 percent or greater of the predicted value, for both efficacy and safety reasons.

The duration of specific immunotherapy is still a matter of debate. After a 3-year specific immunotherapy course, the effect of the treatment may last for several years.

Although specific immunotherapy may be administered by oral or sublingual routes, there are no convincing controlled studies as yet that show their effectiveness in asthma. Specific immunotherapy with extracts of undefined allergens (house dust, bacteria, foods, *Candida albicans*, insect bodies, other dusts) should no longer be used.

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## PART 4: ESTABLISH MEDICATION PLANS FOR LONG-TERM MANAGEMENT

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In establishing a medication plan to achieve and maintain control of asthma, there are three considerations:

- The medications
- A stepwise approach to pharmacologic therapy
- An asthma management zone system for patients.

### 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. They include anti-inflammatory agents and long-acting bronchodilators. **Anti-inflammatory agents and, more specifically, inhaled corticosteroids are at present the most effective controllers.** Antiallergic agents may also be controllers, although there are insufficient data about use of these agents in the long-term management of asthma. Controllers have been variably labeled as prophylactic, preventive, or maintenance medications. It must be stressed that few clinical studies have addressed the question of how effective these medications are in getting asthma under complete control and in serving as pharmacologic secondary prevention measures. 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. Anti-inflammatory agents may interrupt the development of airway inflammation and have a prophylactic and suppressive action (35-37). It appears that antiallergic agents might have an inhibitory effect on the allergic

response. Bronchodilators act principally to dilate the airways by relaxing airway smooth muscle. Although bronchodilators reverse and/or inhibit bronchoconstriction and related symptoms of acute asthma, they do not reverse airway inflammation and hyperresponsiveness. Several long-term clinical studies have shown that in asthma long-term treatment with anti-inflammatory agents is more effective than long-term treatment with bronchodilators for long-term control of symptoms, improvement of lung function, and decrease of airway responsiveness (1-3, 38, 39).

**Relievers** include short-acting bronchodilating medications that act quickly to relieve bronchoconstriction and its accompanying acute symptoms such as cough, chest tightness, and wheezing. 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. This section also discusses traditional methods of healing; these are not recommended for asthma therapy because they are as yet insufficiently studied, but they are discussed because they may be popular with some patients. The next sections, which present a stepwise approach to pharmacologic therapy and a zone system of asthma management, offer recommendations to guide selection of medications and dosages for appropriate asthma therapy.

### **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 (40). Some of the drugs that are effective in asthma can only be used via inhalation because they are not absorbed when given orally. The onset of action of bronchodilators given via inhalation is substantially shorter than when administered orally.

Aerosolized medications that are used to treat asthma are available as pressurized metered-dose inhalers (MDI's), breath-actuated MDI's, dry powder inhalers (DPI's), and nebulized or "wet" aerosols. Patients should be instructed in the use of a metered-dose inhaler or alternative device, and their technique should be checked regularly (see the chapter on education and the delivery of care).

The major disadvantage of pressurized metered-dose inhaler therapy is that training and skill are required to

coordinate activation of the drug through inhalation. For the patient who has difficulty using a metered-dose inhaler, a spacer improves delivery (41). The spacer device allows discharge of the drug into a chamber where particles of medications are held in suspension for 3 to 5 seconds. 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 corticosteroids. Further, the use of spacers for the delivery of inhaled corticosteroids has been shown to decrease the systemic bioavailability of corticosteroids and the risk of systemic side effects (42). Some (although not all) investigations suggest that high doses of short-acting beta<sub>2</sub>-agonists administered from metered-dose inhalers using spacer devices achieve bronchodilation equivalent to that effected by nebulization in treating severe exacerbations (43).

Breath-actuated aerosols might be helpful for patients who have difficulty using the pressurized MDI (44).

Dry powder inhalers do not utilize freon propellants. These devices have potency similar to standard metered-dose inhalers. Dry powder inhalers 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. Further studies are needed to evaluate the usefulness of DPI's and to compare different types.

Dry powder inhalers are more ecological because they do not utilize chlorofluorocarbons (CFC's), but storage of some dry powder formulations may be more difficult in humid climates. Production of CFC's is likely to be severely restricted in developed countries within the next 2 years. Exemption from the Montreal agreement (which bans CFC production) for medical usage is likely. Newer non-CFC-propelled inhalers will be introduced, and an increased use of dry powder inhalers in some countries is also expected.

Nebulized or "wet" aerosols generated by an air compressor are particularly useful for children under 5 years of age and in the treatment of acute severe asthma in which respiratory insufficiency could impair inhalation from a metered-dose inhaler or dry powder inhaler.

**Special considerations for children.** Metered-dose inhalers are often difficult for children to use correctly, and therefore can be recommended only when the prescription is accompanied by thorough and repeated instruction. The use of spacer devices with a valved septum allows children as young as 2 to 3 years of age to use the MDI



after careful training. A device that combines a face mask with a spacer may also decrease the age at which MDI's can be used. A good inspiratory effort is required for the dry powder systems; the lower age limit for the devices will vary. In general, they are most suitable for children over 5 years old. During acute exacerbations, young children may have particular difficulty using the MDI, with or without a spacer device. Under such circumstances, nebulizers are appropriate. Nebulizers are of value to children under 2 years of age, older children who have difficulty with the MDI or dry powder techniques, and those prone to severe exacerbations. There are few controlled studies of nebulizer treatment in this age group; thus knowledge of dose requirements is limited (45, 46).

### **Controller Medications**

Controller medications—medications used daily on a long-term basis to achieve and maintain control of persistent asthma—include inhaled corticosteroids, systemic corticosteroids, sodium cromoglycate (cromolyn sodium), nedocromil sodium, sustained-release theophylline, long-acting inhaled beta<sub>2</sub>-agonists, long-acting oral beta<sub>2</sub>-agonists, and possibly ketotifen, other oral antiallergics, and experimental/other medications. Inhaled corticosteroids are at present the most effective controller medications.

#### **Inhaled corticosteroids.**

- *Mode of administration*—Inhaled.
- *Mechanisms of action*—Inhaled corticosteroids are anti-inflammatory medications. The exact mechanisms are not fully understood. Many have been proposed; important among these are interference with arachidonic acid metabolism and the syntheses of leukotrienes and prostaglandins, reduction in microvascular leakage, inhibition of cytokine production and secretion, prevention of the directed migration and activation of inflammatory cells, and increased responsiveness of beta receptors of the airway smooth muscle. Several studies have now demonstrated that treatment with inhaled corticosteroids during 1 month or more significantly reduces the pathological signs of airway inflammation in asthma (35-37).
- *Role in therapy*—Corticosteroids 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, reducing symptoms, reducing frequency and severity of exacerbations, and improving quality of life (1, 3, 47-49). Long-term high-dose

regimens of inhaled corticosteroids are useful for the treatment of severe persistent asthma because they both reduce the need for the long-term use of oral corticosteroids and have significantly fewer systemic adverse effects.

- *Side effects*—Local adverse effects from inhaled corticosteroids include oropharyngeal candidiasis, dysphonia, and occasional coughing from upper airway irritation, but these effects may often be prevented by using spacer devices (50). Mouth washing (rinse with water, gargle, and spit out) after inhalation may also prevent oral candidiasis. The risk for systemic effects of inhaled corticosteroids is dependent on the potency of the corticosteroid 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. The systemic effects will therefore differ among the different inhaled corticosteroids and depend also on the different delivery systems that are used. As noted, the use of spacers decreases the systemic bioavailability of corticosteroids and the risk of systemic side effects. Although the clinical relevance of all systemic effects of long-term treatment with inhaled corticosteroids has not yet been established, some recent studies suggest that doses above 1 mg a day of beclomethasone dipropionate (BDP) or budesonide or possibly equivalent doses of other inhaled corticosteroids may be associated with systemic effects, including skin thinning and easy bruising, adrenal suppression, and decrease of bone metabolism (51-54).

The clinical significance of the adrenal suppression or the decrease in osteoblast activity during treatment with high doses of inhaled corticosteroids is not yet known. Controlled, short-term knemometry studies and controlled, prospective long-term (2- to 6-year) parallel group studies have demonstrated that treatment with inhaled budesonide in daily doses up to 400 to 600 mcg using a spacer does not adversely affect growth in children with asthma (54, 55). However, 800 mcg of budesonide per day reduces short-term lower leg linear growth in children with mild asthma in knemometry studies. The clinical relevance of this needs further study because prospective long-term studies of the effects of these doses on children with severe asthma have not been performed. Treatment with 400 mcg beclomethasone per day reduces short-term lower leg linear growth as assessed by knemometry, and recent controlled, prospective group parallel controlled studies also indicated that this treatment given without a spacer may reduce intermediate-term statural growth in children with mild asthma (56), although many intermediate-term



studies involving more than 1,000 children have not been able to confirm this effect. However, these studies seem to have been on patients with more severe asthma and did not include a control group not receiving beclomethasone. No firm conclusions can be made about the effect of inhaled corticosteroids on final height, although the studies addressing that question indicate that children with asthma usually attain a normal final height. Any considerations about the use of inhaled corticosteroids must also take account of the fact that severe asthma can, in itself, cause delayed growth in later childhood and early adolescence (57).

There are no data on the possible effect of inhaled corticosteroids on pulmonary tuberculosis or on calcium metabolism and bone growth in malnourished populations.

Inhaled corticosteroids 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, as always, be weighed against the (probably limited) risk of this form of treatment.

### **Systemic corticosteroids.**

- *Mode of administration*—Oral (ingested) or parenteral.
- *Mechanisms of action*—As for inhaled corticosteroids, the exact mechanisms are not fully understood. The proposed mechanisms are also the same.
- *Role in therapy*—A burst or cycle of oral corticosteroids (5 to 7 days) may be used as "maximum therapy" to achieve control of a patient's asthma. This may be useful either when initiating long-term therapy for a patient with uncontrolled asthma or during a period when the patient experiences a gradual decline in his or her condition.

Long-term oral corticosteroid 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, however, that the therapeutic index (effect/side effect) of long-term inhaled corticosteroids is always better than any form of long-term oral or parenteral corticosteroid therapy in asthma (58).

If oral corticosteroids 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 corticosteroids such as prednisone, prednisolone, or methylprednisolone are preferred

because of their minimal mineralocorticoid effect, their relative 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 corticosteroids should be given once in the morning every other day. This generally allows sufficient control of the asthma and minimizes the systemic side effects. Some patients with very severe asthma may, however, need daily and even twice-daily therapy with oral corticosteroids.

- *Side effects*—The systemic side effects of long-term use of oral corticosteroids may be decreased—and a similar antiasthma effect maintained—by administering oral corticosteroids on an alternate-day schedule (one dose in the morning of every other day). The systemic effects of long-term oral or parenteral corticosteroid treatment include osteoporosis, arterial hypertension, diabetes, hypothalamic-pituitary-adrenal axis suppression, cataracts, obesity, skin thinning leading to cutaneous striae and easy bruisability, and muscle weakness.

Although it is rare, adrenal failure may occur when a patient is withdrawn from long-term suppressive doses of oral corticosteroids. Any such withdrawal should thus be observed for clinical and laboratory evidence of adrenal insufficiency.

In addition, caution and close medical supervision are recommended when considering the use of systemic corticosteroids 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 corticosteroid therapy for asthma and the patient has never been treated with effective antituberculosis drugs, then the patient should also be given chemoprophylaxis with isoniazid. Data are not yet sufficient to make recommendations concerning the use of high-dose inhaled corticosteroids in patients with asthma who also have tuberculosis.

Fatal herpes virus infections have been reported among patients who are exposed to these viruses while taking systemic corticosteroids, even short bursts. If a patient is exposed to varicella, the following actions should be considered: discontinue the systemic corticosteroids, give the patient zoster immunoglobulin, and consider acyclovir therapy if the patient develops progressive varicella (59). Oral corticosteroids 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.

### **Sodium cromoglycate (cromolyn sodium).**

- *Mode of administration*—Inhaled.
- *Mechanisms of action*—The exact mechanisms of action of sodium cromoglycate are not fully understood, although this nonsteroidal anti-inflammatory medication will partly inhibit the IgE-mediated mediator release from human mast cells in a dose-dependent way (60), and it has a cell-selective and mediator-selective suppressive effect on other inflammatory cells (macrophages, eosinophils, monocytes) (61).
- *Role in therapy*—Administered prophylactically, sodium cromoglycate inhibits early- and late-phase allergen-induced airflow limitation and acute airflow limitation after exposure to exercise, cold dry air, and sulfur dioxide. The long-term effects of sodium cromoglycate on the chronic inflammatory changes in asthma have not been directly demonstrated, except for one study in which prolonged treatment with cromoglycate was associated with a significant decrease in the percentage of bronchial lavage eosinophils (62), and studies on nonspecific hyperresponsiveness have inconsistently shown a benefit. Sodium cromoglycate may be used as long-term therapy early in the course of asthma (63). It reduces symptoms and the frequency of exacerbations. There is insufficient knowledge about the mechanisms of action to predict those patients who will achieve a beneficial response to sodium cromoglycate; any patient may benefit, although some consider the drug most efficacious in mild-moderate allergic asthma (64). A 4- to 6-week trial of sodium cromoglycate therapy may be required to determine efficacy in individual patients.
- *Side effects*—As a rule, sodium cromoglycate produces only minimal side effects, such as occasional coughing upon inhalation of the powder formulation.

### **Nedocromil sodium.**

- *Mode of administration*—Inhaled.
- *Mechanisms of action*—In in vitro and in vivo studies in animal and human models of asthma, this anti-inflammatory pyranoquinoline is 4 to 10 times more potent than sodium cromoglycate in preventing induced bronchoconstriction in animal models of asthma and in humans (65, 66). Although the precise mechanism of action is not fully understood, it has been shown that nedocromil inhibits activation of, and mediator release from, several types of inflammatory cells. It also inhibits neuronal pathways. No long-term effect on the chronic

inflammatory changes in asthma has yet been demonstrated for nedocromil.

- *Role in therapy*—As with sodium cromoglycate, this medication may be used as maintenance therapy early in the course of asthma. Clinical trials in adult patients with asthma show that therapy with nedocromil sodium has a rapid effect on symptoms, improves lung function, and reduces nonspecific airway responsiveness (38, 67, 68). Clinical trials with nedocromil sodium are ongoing in childhood asthma and show an efficacy similar to that in adults (69).
- *Side effects*—Treatment with nedocromil sodium is not associated with any significant adverse effects.

**Sustained-release theophylline.** This is the principal methylxanthine used in asthma therapy.

- *Mode of administration*—Oral (ingested).
- *Mechanisms of action*—Theophylline is a bronchodilator that may have extrapulmonary effects, including anti-inflammatory effects (70). The precise pharmacological mechanism of action of theophylline is not clear, although theophylline significantly inhibits both the early and late asthma reactions following the inhalation of allergen. Two studies have shown that theophylline influences chronic asthma inflammation (71, 72). Most studies can only show a small effect on airway hyperresponsiveness.
- *Role in therapy*—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 (73).

Note, however, that because theophylline has the potential for significant adverse effects (see the discussion of side effects that follows), appropriate dosing and monitoring are essential. Due to this risk, and the difficulty of monitoring therapy, theophylline is regarded in some countries as a therapy that should be reserved for use after inhaled corticosteroids and inhaled beta<sub>2</sub>-agonists fail to 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 and especially of nocturnal asthma symptoms.

- **Side effects**—Theophylline has the potential for significant adverse effects, although these can generally be avoided by appropriate dosing and monitoring. Individual patient needs will vary, but a general approach is to aim for a steady-state serum concentration for theophylline of between 5 and 15 mcg per mL (28 to 85 mcM) during long-term theophylline treatment. Generally, serious toxic effects do not occur at these serum concentrations.

Monitoring of serum concentrations is advised when theophylline therapy 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 known to alter theophylline metabolism exist (e.g., febrile illness, pregnancy, liver disease, congestive heart failure, and the use of certain drugs, including cimetidine, certain quinolones, and macrolides).

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 (74). Cardiopulmonary effects include tachycardia, arrhythmias, and, occasionally, stimulation of the respiratory center.

**Long-acting inhaled beta<sub>2</sub>-agonists.** These newer long-acting beta<sub>2</sub>-agonists, which include formoterol and salmeterol, have a duration of action lasting more than 12 hours. (Most short-acting beta<sub>2</sub>-agonists have a 4- to 6-hour duration of action.)

- **Mode of administration**—Inhaled.
- **Mechanisms of action**—Long-acting inhaled beta<sub>2</sub>-agonists are bronchodilator medications. Like other beta<sub>2</sub>-agonists, they relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability, and may modulate mediator release from mast cells and basophils (75, 76). Long-acting inhaled beta<sub>2</sub>-agonists appear to inhibit allergen-induced early and late asthmatic responses and the increase in histamine-induced airway responsiveness. However, biopsy studies show that the chronic airway inflammation is not modified by treatment with long-acting inhaled beta<sub>2</sub>-agonists. Therapy with long-acting inhaled beta<sub>2</sub>-agonists, like aerosol or inhaled therapy with any beta<sub>2</sub>-agonist, is comparable to, or better than, oral therapy in producing bronchodilation.
- **Role in therapy**—Although the position of long-acting inhaled beta<sub>2</sub>-agonists in asthma therapy has not been clearly defined, and further clinical trials are necessary, clinical studies have indicated that chronic treatment with long-acting beta<sub>2</sub>-agonists improves symptom score, decreases nocturnal asthma, improves lung function, and decreases the use of short-acting inhaled beta<sub>2</sub>-agonists (77-80). Because long-term treatment with long-acting inhaled beta<sub>2</sub>-agonists does not appear to influence the persistent inflammatory changes in asthma, this therapy should be accompanied by anti-inflammatory medications. Long-acting inhaled beta<sub>2</sub>-agonists may be considered when standard introductory doses of inhaled corticosteroids fail to achieve control of asthma, especially nocturnal symptoms, and before raising the dose of inhaled corticosteroids (81). Some asthma specialists prefer to add long-acting inhaled beta<sub>2</sub>-agonists only after a trial of higher doses of corticosteroids continues to reveal symptoms or a need for short-acting inhaled beta<sub>2</sub>-agonists three to four times a day or more.
- Long-acting inhaled beta<sub>2</sub>-agonists may also be used to prevent exercise-induced asthma and may provide longer protection than the short-acting beta<sub>2</sub>-agonists.
- **Side effects**—Therapy with long-acting inhaled beta<sub>2</sub>-agonists causes fewer systemic adverse effects—such as cardiovascular stimulation, skeletal muscle tremor, and hypokalemia—than oral therapy.

### Long-acting oral beta<sub>2</sub>-agonists.

- **Mode of administration**—Oral (ingested).
- **Mechanisms of action**—Long-acting oral beta<sub>2</sub>-agonists (sympathomimetics) are bronchodilators. Like other beta<sub>2</sub>-agonists, they relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability, and may modulate mediator release from mast cells and basophils (75, 76).
- **Role in therapy**—Long-acting oral beta<sub>2</sub>-agonists may be helpful in controlling nocturnal symptoms of asthma. They may be used as an addition to inhaled corticosteroid, cromolyn sodium, or nedocromil therapy when standard doses of these medications do not sufficiently control nocturnal symptoms.
- **Side effects**—Possible side effects include cardiovascular stimulation, anxiety, pyrosis, and skeletal muscle tremor. Adverse cardiovascular reactions may also occur with the combination of oral beta<sub>2</sub>-agonists and theophylline.



### Oral antiallergic compound—ketotifen.

- *Mode of administration*—Oral (ingested).
- *Mechanisms of action*—The mechanism of action of this antiallergic H<sub>1</sub>-antagonist has not been clearly established, but it is recognized to have an inhibitory effect on the allergic response. That is, ketotifen may inhibit mast cell activation or mast cell mediator release. Other pharmacologic activities of ketotifen have mainly been shown in in vitro and in vivo animal models (82).

The efficacy of ketotifen has not been sufficiently documented. Several studies have inconsistently shown that ketotifen inhibits the early asthma reaction following allergen challenge. Only one study, using high doses of ketotifen, demonstrated that the drug inhibits the late asthma reaction (83). No long-term effects on the chronic inflammatory changes in asthma have been demonstrated.

- *Role in therapy*—The controlled clinical studies comparing the therapeutic efficacy of ketotifen in asthma to placebo or cromoglycate have had variable results. Most studies suggest that ketotifen, given in a dose of 2 mg daily in adults and in a similar or half the dose in children, results in a slow but significant improvement of asthma symptoms and reduction in the need for concomitant antiasthma medication (84). Most significant results are obtained in children and young atopic adults (85). The clinical benefits are in general most clearly observed after more than 2 months of treatment.
- *Side effects*—The most frequent side effect is sedation, especially in the initial treatment period and in adults. Ketotifen may also cause weight gain.

**Other oral antiallergic compounds.** Among oral antiallergic compounds introduced in some countries for the treatment of mild-moderate allergic asthma are tranilast, repirinast, tazanolast, pemirolast, ozagrel, azelastine, 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 antiallergic compounds in the long-term treatment of asthma. Selective H<sub>1</sub>-antagonists (such as terfenadine and astemizole) have only minor effects on asthma management and are generally not recommended for the long-term treatment of asthma.

- *Side effects*—Sedation is potentially a side effect of compounds with H<sub>1</sub>-antagonistic activity. Other serious side effects have not yet been reported for this very heterogeneous class of drugs.

### Experimental/other medications.

- *Mode of administration*—Oral (ingested).
- *Role in therapy*—Therapeutic regimens to reduce oral corticosteroid dependence among patients with severe asthma may include such medications as troleandomycin, methotrexate, and cyclosporin, as well as other immunosuppressive treatments. These medications are experimental and should be used only in selected patients under the supervision of an asthma specialist. The potential steroid-sparing effect may not outweigh the risk of serious side effects. Gold has not been demonstrated to be effective in the treatment of asthma.
- *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 hematologic, teratogenic, and pulmonary effects.

### Reliever Medications

Reliever medications—medications that act quickly to relieve bronchoconstriction and its accompanying acute symptoms—include short-acting inhaled beta<sub>2</sub>-agonists, systemic corticosteroids, inhaled anticholinergics, short-acting theophylline, and short-acting oral beta<sub>2</sub>-agonists.

### Short-acting inhaled beta<sub>2</sub>-agonists.

- *Mode of administration*—Inhaled.
- *Mechanisms of action*—Short-acting inhaled beta<sub>2</sub>-agonists (sympathomimetics) are bronchodilators. Like other beta<sub>2</sub>-agonists, they relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability, and may modulate mediator release from

mast cells and basophils (75, 76). Therapy with short-acting inhaled beta<sub>2</sub>-agonists, like aerosol or inhaled therapy with any beta<sub>2</sub>-agonist, is comparable to, or better than, oral therapy in producing bronchodilation.

- **Role in therapy**—Short-acting inhaled beta<sub>2</sub>-agonists are the medication of choice for treatment of acute exacerbations of asthma and for the pretreatment of exercise-induced asthma. Short-acting inhaled beta<sub>2</sub>-agonists are used to control episodic bronchoconstriction.

Although long-term use of short-acting inhaled beta<sub>2</sub>-agonists is common, regularly scheduled (as opposed to taken as needed) therapy with specific inhaled beta<sub>2</sub>-agonists has recently been associated with diminished control of asthma (86, 87). Thus, although further studies are required (88), it is recommended that regularly scheduled short-acting inhaled beta<sub>2</sub>-agonist treatment be kept to a minimum.

Note that frequent or regularly scheduled use of short-acting inhaled beta<sub>2</sub>-agonists for long-term management of asthma does not adequately control asthma symptoms, peak flow variability, or airway hyperresponsiveness (1-3, 47). An increased use—or even a daily use—of the short-acting inhaled beta<sub>2</sub>-agonist 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 beta<sub>2</sub>-agonist treatment during an exacerbation mandates medical attention and may indicate the need for short-term oral corticosteroids.

- **Side effects**—Therapy with short-acting inhaled beta<sub>2</sub>-agonists causes fewer systemic adverse effects—such as cardiovascular stimulation, skeletal muscle tremor, and hypokalemia—than oral therapy.

### Systemic corticosteroids.

- **Mode of administration**—Oral (ingested) or parenteral.
- **Mechanisms of action**—As for inhaled corticosteroids, the exact mechanisms are not fully understood. The proposed mechanisms are also the same.
- **Role in therapy**—Although onset of action of these medications is 4 to 6 hours, they are important in the treatment of acute severe 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 generally continued for 3 to

10 days following initial treatment of the exacerbation. A typical short course of oral corticosteroids for an exacerbation is 20-40 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 corticosteroids can be stopped or tapered.

- **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 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 postganglionic efferent vagal pathways (89). When inhaled, these agents produce bronchodilation by reducing intrinsic vagal tone to the airways. They also block reflex bronchoconstriction caused by inhaled irritants. They do not diminish the early and late allergic reaction or the reactions after exercise.

In asthma, inhaled anticholinergics are less potent bronchodilators than inhaled beta<sub>2</sub>-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 short-acting beta<sub>2</sub>-agonist for exacerbations of asthma (90). Note that ipratropium bromide's benefits 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 and tremor from short-acting beta<sub>2</sub>-agonists.
- **Side effects**—Inhalation of ipratropium or oxitropium can cause a dryness of the mouth and a bad taste.

### Short-acting theophylline.

- **Mode of administration**—Oral (ingested) or parenteral.
- **Mechanisms of action**—Theophylline is a bronchodilator



that is, in general, less efficient than an inhaled beta<sub>2</sub>-agonist. Short-acting aminophylline or theophylline, which is not in sustained-release preparations, is less effective in controlling symptoms of persistent asthma because of the fluctuation of the serum theophylline concentration.

- **Role in therapy**—Short-acting theophylline may be considered for pretreatment for exercise-induced asthma and for relief of symptoms (although its onset of action is considerably longer than short-acting beta<sub>2</sub>-agonist). The role of theophylline/aminophylline in treating exacerbations remains controversial. Short-acting theophylline may provide no additive bronchodilator effect over adequate doses of short-acting beta<sub>2</sub>-agonists, but it may benefit respiratory drive or respiratory muscle function and prolong or sustain the response to short-acting beta<sub>2</sub>-agonist between doses (91, 92).
- **Side effects**—As already noted, theophylline has the potential for significant adverse effects, although these can generally be avoided by appropriate dosing and monitoring. No theophylline should be administered to patients already on long-term treatment with sustained-release theophylline unless the serum concentration of theophylline is known.

### Short-acting oral beta<sub>2</sub>-agonists.

- **Mode of administration**—Oral (ingested).
- **Mechanisms of action**—Short-acting oral beta<sub>2</sub>-agonists are bronchodilators that relax airway smooth muscle.
- **Role in therapy**—Short-acting oral beta<sub>2</sub>-agonists are appropriate for use in patients 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.

### Traditional Methods of Healing

Although alternative and complementary medicines—traditional methods of healing—may be popular with some patients, they have as yet been insufficiently researched, and their effectiveness is largely unproven. However, their use merits consideration (93). A recent study in one country showed that the use of unconventional therapy is far greater than generally expected (one-third of patient population), and it is associated with considerable

individual health care expenditure (94). 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. A problem is the holistic approach taken in traditional methods of healing, not just the medication per se, and the resulting difficulty in attributing any observed effects. For example, the Chinese traditional medicine approach to asthma involves acupuncture, herbal remedies, and strict advice on diet and lifestyle. Furthermore, the psychotherapeutic benefit of a holistic approach cannot be excluded.

Although traditional healing methods cannot be recommended for asthma therapy until they have been studied more rigorously, the most widely known methods, which include acupuncture, homeopathy, herbal medicine, and Ayurvedic medicine, are described here.

**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 (93, 95-102). 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 (103). Acupuncture is not entirely innocuous. A large outbreak of acupuncture-associated hepatitis B, bilateral pneumothorax, and burns have been described (104-107).

**Homeopathy.** Homeopathy, propounded in the late 18th century, has two principles in the management of diseases: the law of similars and the use of infinitesimally small doses. This dilution principle is taken to the degree that no molecules of the original medicine are still present

in the solution. Asthma, a disorder in which objective measurements are available, was not the subject of any substantive work using homeopathy. This yet-unexplained form of treatment must be regarded as unproven for asthma (108, 109). Nevertheless, it 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. However, a word of caution is necessary. Homeopathic treatment may contain potent pharmacological agents—as in, for example, “Dumcap” and “Franal”—that may account for its efficacy and that may lead to adverse side effects (110).

**Herbal medicine.** Several modern treatments have their origins in the folk medicine tradition, for example, adrenergic drugs, atropine, and sodium cromoglycate, which were 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.

Work is continuous in trying to identify the active compounds of plants used as folk remedies and their mode of action in the treatment of lung diseases, including asthma (111). Recently, several active compounds were extracted from onions, from *Galphinia glauca* (used in Central and South America), from *Adhatoda vasico* (used in India), and from *Picorhyza kurroa* (a herb that grows in the Himalayan area). These active compounds exert a wide spectrum of pharmacologic activities. 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 venoocclusive 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.

**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 (93, 112). 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 2 weeks there was no difference between the two groups regarding lung function, symptom score, and inhaler use (113). 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 (114, 115). The negative ion generator in a room has several disadvantages, including production of ozone (a respiratory irritant).

**Other methods.** Reports of the effects of hypnosis and suggestion, naturopathy, osteopathy, 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) need for p.r.n. (as needed) beta<sub>2</sub>-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.

Figure 7-1. Asthma Treatment Modalities: Comparison of Estimated Effects, Risk for Serious Side Effects, and Cost

Drug	Control of chronic asthma symptoms over weeks to months	Relieve exacerbations over minutes or hours	Serious Side effects long term	Cost per month**
Inhaled corticosteroids*	+++	—	+ <sup>2</sup>	
Oral corticosteroid (prednisolone)*	++	++(over hours)	+++	
Cromoglycate*	+	—	—	
Nedocromil	+	—	—	
Inhaled beta <sub>2</sub> -agonist—short acting*	+/-	+++	?	
Inhaled beta <sub>2</sub> -agonist—long acting	++	+++	?	
Oral beta <sub>2</sub> -agonist*	+/-	++	+	
Theophylline—sustained release*	+	++	++	
Inhaled anticholinergic	—	++	—	
Ketotifen	+ <sup>1</sup>	—	—	
Oral antiallergics	?	—	—	
Immunotherapy	+/-	—	++ <sup>3</sup>	

\* Listed on WHO List of Essential Drugs.

\*\* This column is to be filled in by each individual country or region based on calculations using figure 7-2 because costs vary widely among countries and regions. Further, estimating the relation of cost and effect should consider the severity of the asthma. See also the chapter on socioeconomics.

<sup>1</sup> Applicable to children.

<sup>2</sup> Applicable to high doses.

<sup>3</sup> Anaphylaxis is a marked risk.

**Figure 7-2. Calculations of the Cost Per Year of Long-Term Treatment for Patient With Mild Persistent Asthma Living in Belgium. The Prices Are Given Independent of Health Insurance.**

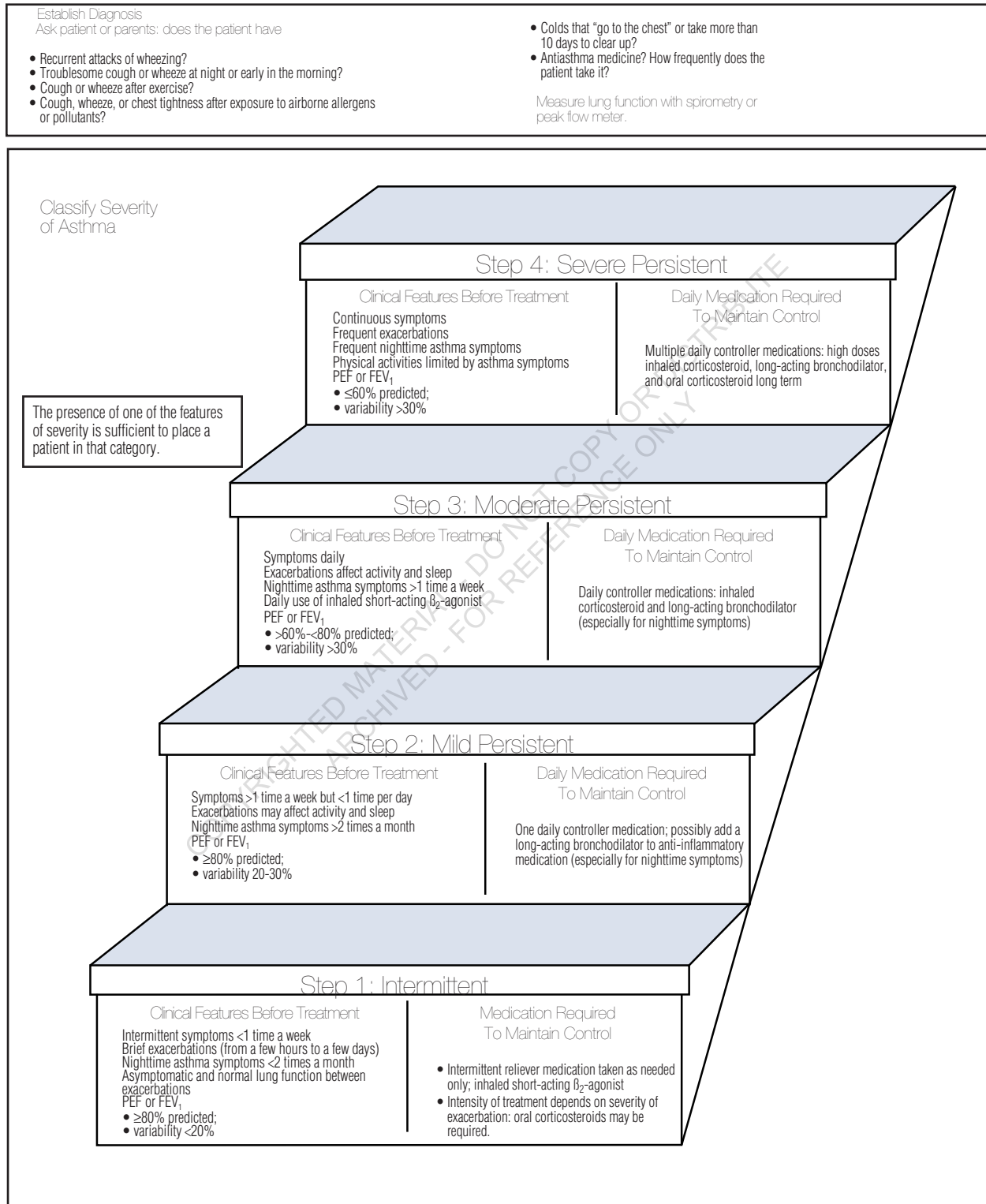
	B	C	D	E	F	G	H	I	J
Medication	Dose	Weight	Doses per unit	Price per unit	Price per dose	Recommended dosage per day	Doses per day	Cost per day U.S. \$	Cost per year U.S. \$
Formula				Belgium Franc	E × D		G/B	(F × H)/Curr per U.S. \$	1 × 365
<b>Controllers</b>									
Beclomethasone*	250	mcg	80	781	10	500	2	0.53	193
Budesonide*	200	mcg	100	1028	10	400	2	0.55	202
Cromoglycate	5	mg	112	646	6	40	8	1.25	455
Inhaled beta <sub>2</sub> -agonist long-acting									
Not available in Belgium.									
Sustained-release theophylline	300	mg	60	328	5	600	2	0.30	108
Sustained-release terbutaline	5	mg	30	214	7	10	2	0.39	141
<b>Nedocromil</b>									
Not available in Belgium.									
Oral prednisolone	5	mg	20	90	5	10	2	0.24	89
Ketotifen	1	mg	50	682	14	2	2	0.74	269

\*Inhaled corticosteroids available in Belgium.

Relievers**									
Salbutamol Inhaled	100	mcg	200	246	1	800	8	0.27	97
Terbutaline Inhaled	250	mcg	200	325	2	1000	4	0.18	64
Oral salbutamol	2	mg	50	176	4	8	4	0.38	139
Oral terbutaline	2.5	mg	50	161	4	10	4	0.39	143
Ipratropium	20	mcg	300	485	2	160	8	0.35	128
Oxitropium	100	mcg	300	588	2	800	8	0.42	154
Oral theophylline	125	mg	100	250	3	600	5	0.34	123

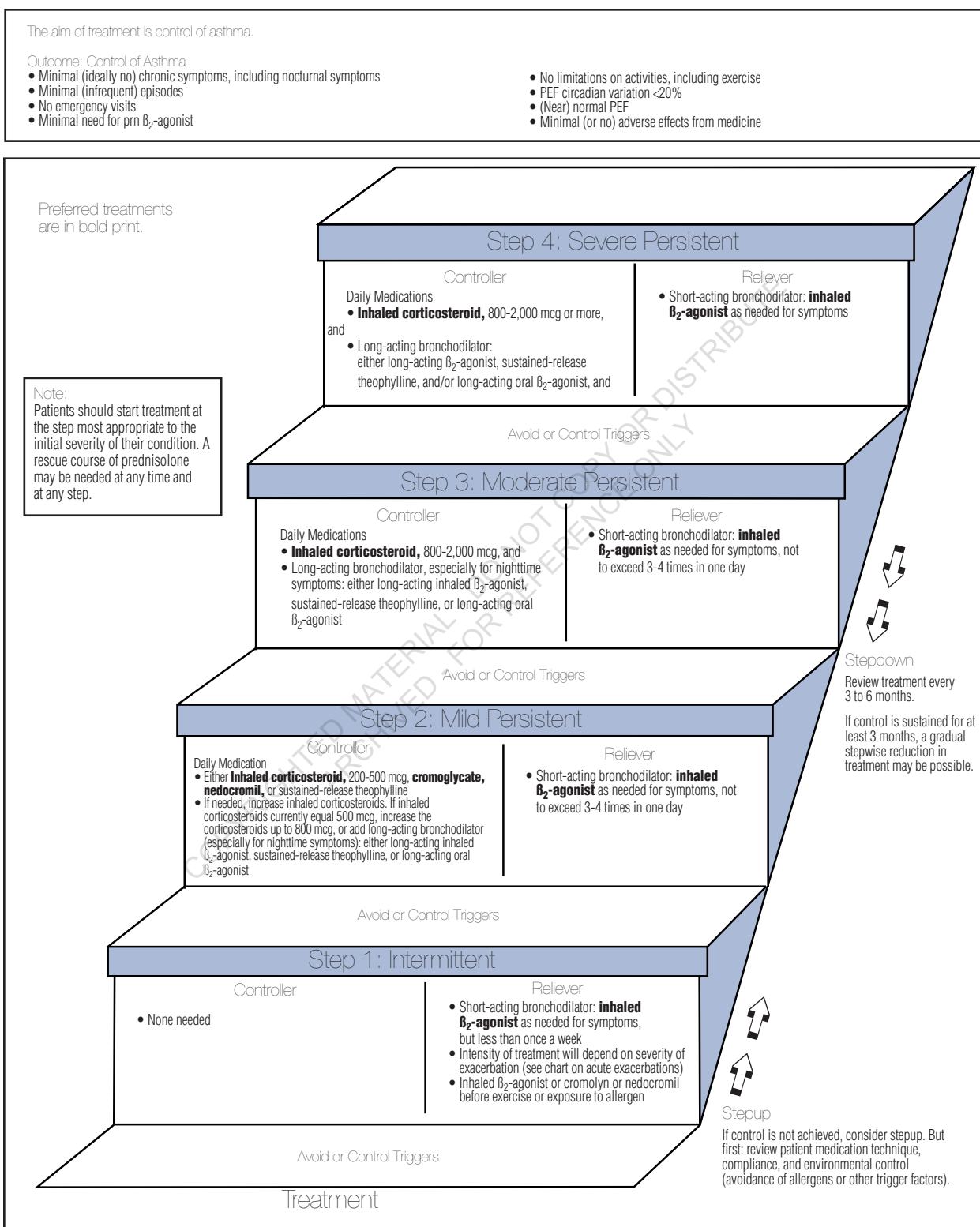
\*\* Reliever medications are not recommended for daily therapy. If symptoms require the use of reliever medications, the dose should not exceed the maximum indicated in this figure.

**Figure 7-3. The Long-Term Management of Asthma: Diagnose and Classify Severity**

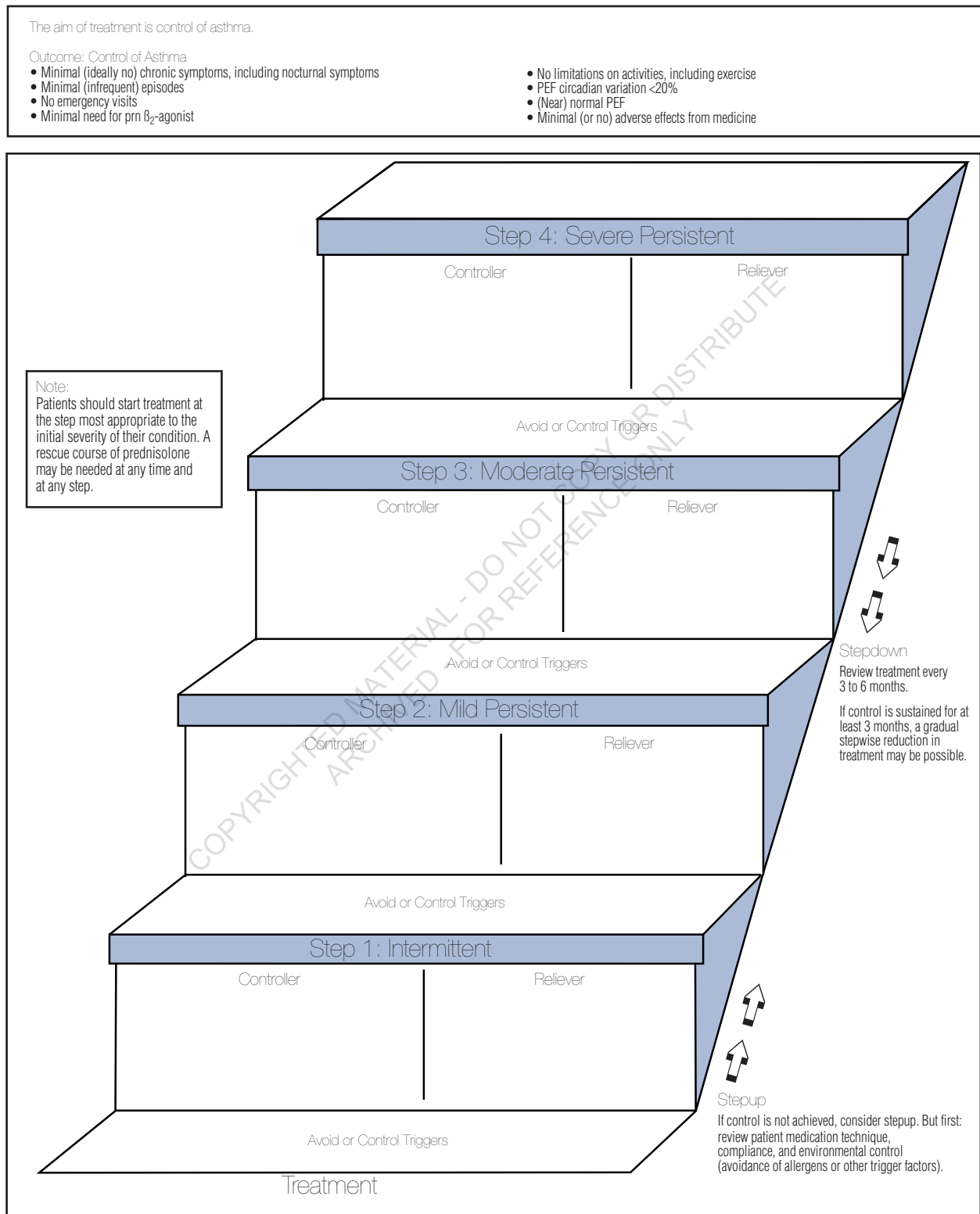




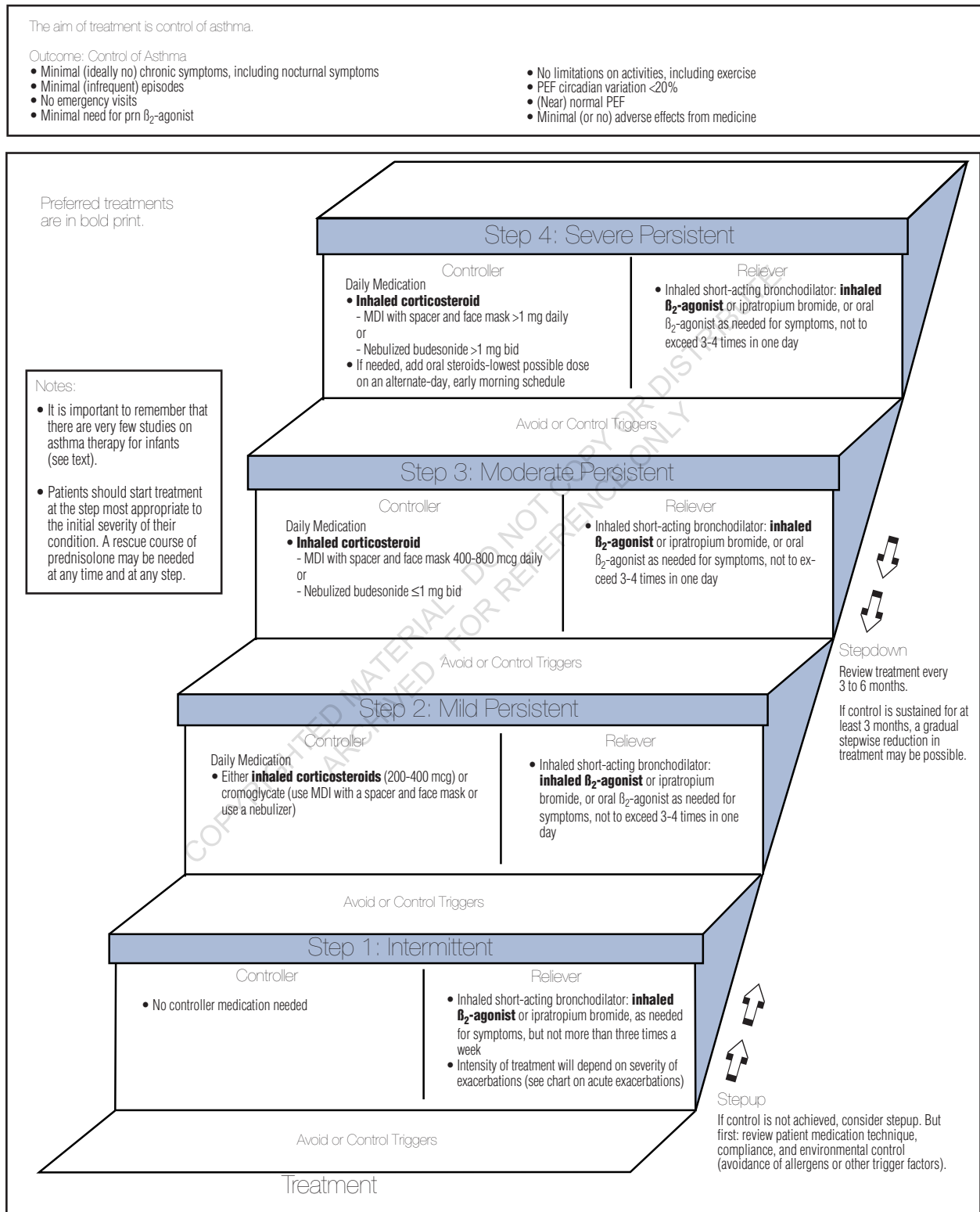
**Figure 7-4. The Long-Term Management of Asthma: Treatments in the Stepwise Approach**



**Figure 7-5. The Long-Term Management of Asthma: Develop a Stepwise Approach for Your Area**



**Figure 7-6. The Long-Term Management of Asthma: Treatments in the Stepwise Approach for Infants and Young Children**



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 classification of asthma severity permits this flexibility (45, 46, 116-120). As discussed previously and illustrated in figure 5-6 in the chapter on diagnosis and classification, the classification of asthma severity should include symptom and medical history evaluation, current treatment, clinical examination, and measurements of lung function where possible.

A stepwise approach to therapy recommends that the number (type) and 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 corticosteroids in order to achieve control of the patient's asthma as quickly as possible, and then decrease the medication, or to increase treatment in a gradual stepup manner. In either case, once control is sustained for about 3 months, a reduction in therapy, or stepdown, can be carefully considered. This stepdown is needed to identify the minimum therapy required to maintain control.

Few studies have as yet investigated the efficacy of various comprehensive therapeutic programs, including the stepwise approach to therapy, 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.

The figures included here illustrate the approach to stepwise therapy at each level of asthma severity. Guidance for selecting among available modalities for

treating the different levels of asthma severity is provided in the text.

Figure 7-1 lists the asthma treatment modalities with sufficiently proven clinical efficacy and refers also to the World Health Organization List of Essential Drugs. The figure compares treatment efficacy and risk for serious side effects. The cost of the medication is an obvious determining factor in the choice of the treatment and should be included in a table that will ultimately guide the choice of treatment. Costs of treatment vary from country to country and are only one of the factors that make up the total cost of a disorder such as asthma. This is further discussed in the chapter on socioeconomics. Figure 7-2 illustrates the calculation of medication costs in one country for mild persistent asthma; such calculations should be inserted in the "cost column" by each individual country in figure 7-1.

Figures 7-3 through 7-6 present illustrations of the stepwise approach to therapy to achieve and maintain control of asthma. Figure 7-3 presents steps for considering a diagnosis of asthma and classifying severity. Figure 7-4 presents all therapies that can be recommended for treating the different levels of severity of asthma. Those therapies that are in bold print are particularly recommended on the basis of what is now understood about the anti-inflammatory process in asthma. Figure 7-5 provides the opportunity for health care professionals to adapt the stepwise therapy to the needs and resources of their area. Figure 7-6 presents recommended treatments for the stepwise approach to therapy for infants and young children.

### **Steps To Achieve and Maintain Control of Asthma**

This section describes the steps of therapy appropriate for different levels of asthma severity. The presence of one or more features of clinical severity places a patient at the respective therapeutic step.

In the stepwise approach to therapy, progression to the next step is indicated when control is not achieved or lost at the current step, and there is assurance the patient is using medication correctly. The frequent (e.g., more than three times a week) presence of such symptoms as cough, wheezing, and dyspnea, and the increased use of short-acting bronchodilators may indicate inadequate control of asthma. The presence of symptoms at night or early in the morning is an especially useful indicator. Increasing variability in PEF indicates inadequately controlled asthma and is often observed before a change in symptoms. 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 stepdown in therapy.

**The steps suggested here are guidelines only.** 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.

**Step 1.** A patient has intermittent asthma if the patient experiences exacerbations (episodes of cough, wheezing, or dyspnea) less than once a week over a period of at least 3 months and the exacerbations are brief, generally lasting only a few hours to a few days. Nocturnal asthma symptoms do not occur more than two times a month. In between exacerbations the patient is asymptomatic and has a completely normal lung function, i.e., a pretreatment baseline FEV<sub>1</sub> or PEF greater than 80 percent of predicted or 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). Infants and children who occasionally wheeze during a period of viral upper respiratory tract infection are also in this category.

Intermittent asthma is not trivial. The severity of the asthma exacerbation may vary from patient to patient and from time to time. Such an exacerbation might even be life threatening, although this is extremely rare in patients with intermittent asthma.

The low frequency of the exacerbations and the fact that in between exacerbations the patient has a 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 when the patient only experiences occasional symptoms could be low. Rather, the exacerbations should be treated as such, depending on the severity of the exacerbation (see Part 5: Establish Plans for Managing Exacerbations). Treatment includes medication prior to exercise as needed (inhaled beta<sub>2</sub>-agonist or cromoglycate or nedocromil) or to allergen exposure (sodium cromoglycate or nedocromil). Treatment of the exacerbation includes an inhaled short-acting beta<sub>2</sub>-

agonist taken as needed to relieve the asthma symptoms. An inhaled anticholinergic, oral short-acting beta<sub>2</sub>-agonist, or short-acting theophylline may be considered as alternatives to inhaled short-acting beta<sub>2</sub>-agonists, although these alternatives have a slower onset of action and/or a higher risk for side effects. Occasionally, more severe or prolonged exacerbations may require a short course of oral corticosteroids.

If medication is required more than once a week over a 3-month period, the patient should be moved to the next step of care, regardless of PEF measurements. The same applies if the lung function in between exacerbations becomes abnormal.

**Step 2.** A patient has mild persistent asthma if he or she experiences exacerbations, persistent 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 exacerbations at least once a week but less than once a day over the last 3 months and some of the exacerbations 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 two times 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 can be started with either inhaled corticosteroids, sodium cromoglycate, or nedocromil sodium. A spacer device and mouth washing after inhalation are recommended when using inhaled corticosteroids to reduce oropharyngeal side effects. Children are usually given an initial trial (4 to 6 weeks) of sodium cromoglycate. The suggested introductory dose of inhaled corticosteroids is 200 to 500 mcg per day of beclomethasone dipropionate (BDP) or budesonide or equivalent. (Doses cited here are illustrative and refer to BDP or budesonide. In the absence of complete data, the same dosage—in mcg—guidelines may be applied to the other formulations such as flunisolide, fluticasone, and triamcinolone acetonide. However, the relative anti-inflammatory, suppressive effects of these formulations have not been established. Further studies are required before specific recommendations can be made about relative potencies with regard to their therapeutic efficacy or risk for systemic effects.)



Long-term treatment with sustained-release theophylline may be considered, but the need for monitoring of serum concentration levels may make this treatment less feasible.

Inhaled short-acting beta<sub>2</sub>-agonist should be available to take as needed to relieve symptoms, but should not be taken more than three to four times a day. Either an inhaled anticholinergic, oral short-acting beta<sub>2</sub>-agonist, or short-acting theophylline may be considered as an alternative to inhaled short-acting beta<sub>2</sub>-agonist, although they have a slower onset of action and/or a higher risk for 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.

If symptoms persist despite the initial dose of inhaled corticosteroids, and the health care professional is satisfied that the patient is using the medications correctly, the inhaled corticosteroids should be increased from 400 or 500 to 750 or 800 mcg per day BDP or equivalent. A possible alternative to increasing the dose of inhaled corticosteroids, especially to control nocturnal symptoms, is the addition of a long-acting bronchodilator to a dose of at least 500 mcg inhaled corticosteroids. The long-term efficacy of a combination of low-dose inhaled corticosteroids with a long-acting bronchodilator as compared to higher doses of inhaled corticosteroids remains to be studied.

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

**Step 3.** Moderate persistent asthma is characterized by daily symptoms over a prolonged time or nocturnal asthma more than once a week. The patient with moderate persistent asthma has 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.

Patients with moderate persistent asthma require controller medication every day to achieve and maintain control of their asthma.

The dose of inhaled corticosteroids should be 800 to 2,000 mcg beclomethasone dipropionate or equivalent a day. A spacer device with the inhaler is recommended to reduce oropharyngeal side effects and systemic absorption.

Long-acting bronchodilators in addition to the inhaled

corticosteroids may also be considered, particularly to control nocturnal symptoms. Sustained-release theophylline, an oral slow-release beta<sub>2</sub>-agonist, or a long-acting inhaled beta<sub>2</sub>-agonist may be used. Theophylline serum concentrations should be monitored, with a general therapeutic range of 5 to 15 mcg per mL.

A long-acting inhaled beta<sub>2</sub>-agonist may have a complementary effect to inhaled corticosteroids, although more data are necessary to establish the place of long-acting beta<sub>2</sub>-agonist in asthma therapy. The role of anticholinergics (ipratropium bromide) in long-term therapy is not well established, but an introduction of anticholinergics may be considered as an alternative for patients who experience such adverse effects as tachycardia or tremor from inhaled beta<sub>2</sub>-agonists.

Inhaled short-acting beta<sub>2</sub>-agonists should be available to take as needed to relieve symptoms, but should not be taken more than three to four times a day. Either an inhaled anticholinergic, oral beta<sub>2</sub>-agonist, or short-acting theophylline may be considered as an alternative to inhaled short-acting beta<sub>2</sub>-agonist, although they have slower onset of action and/or a higher risk for 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.** A patient has severe persistent asthma if the patient experiences highly variable, continuous symptoms, and frequent nocturnal symptoms; has limited activities; and experiences severe exacerbations in spite of medication. The patient with severe persistent asthma has a pretreatment baseline PEF of less than 60 percent of predicted or personal best and PEF variability greater than 30 percent. Control of asthma as defined earlier may not be possible. In severe persistent asthma, the goal of therapy becomes achieving best possible results: the least symptoms, the least need for short-acting beta<sub>2</sub>-agonist, the best flow rates, 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 corticosteroids at higher doses (more than 800 to 2,000 mcg per day of beclomethasone dipropionate or equivalent).

A bronchodilator is recommended in addition to the inhaled corticosteroids, such as oral sustained-release theophylline or oral beta<sub>2</sub>-agonist and/or a long-acting inhaled beta<sub>2</sub>-agonist. An inhaled short-acting beta<sub>2</sub>-agonist regularly scheduled once a day, usually upon arising, may also be considered. A trial of inhaled

anticholinergic (ipratropium) may be considered, particularly for those patients who experience adverse effects from beta<sub>2</sub>-agonist.

Inhaled short-acting beta<sub>2</sub>-agonist should be available as needed up to three to four times a day to relieve symptoms.

Long-term oral corticosteroids should be used in the lowest possible dose (alternate or single daily dose after a 3- to 7-day burst). Persistent trials of high doses of inhaled corticosteroids administered with a spacer device should be made in an attempt to reduce oral corticosteroids. When patients are transferred from oral corticosteroids to high-dose inhaled corticosteroids, they should be monitored closely for evidence of adrenal insufficiency.

Access and adherence to moderate or high-dose inhaled corticosteroid therapy are sometimes difficult for patients, and their health care professionals should consider the alternative of frequent bursts of lower dose oral corticosteroids. There are not sufficient data to indicate whether this latter approach leads to similarly effective control of asthma. However, the data on side effects indicate that the therapeutic index (effect/side effect) of long-term inhaled corticosteroids is better than long-term oral or parenteral corticosteroid therapy.

Note that difficult-to-manage asthma may herald a life-threatening underlying disorder such as Churg Strauss syndrome or other forms of systemic vasculitis.

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

**Stepdown: Reduction of maintenance therapy.** Asthma is a variable disorder, and spontaneous and therapy-induced variations in severity occur. Especially anti-inflammatory therapy has been shown to reduce asthma severity over the long term (3). Once control of asthma is achieved and maintained for at least 3 months, a gradual stepwise 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 stepwise, following the reverse order of what has just been described with close monitoring of symptoms, clinical signs, and, as much as possible, lung function.

## ***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 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. The treatment will vary accordingly but should follow the recommendations for the treatment of persistent asthma. The treatment should ideally start just before the expected season or upon the first symptoms and be stopped at the end of the season and when no symptoms or lung function abnormalities are any longer present.

## ***Special Considerations for Children***

The pharmacologic management of children with asthma who require long-term medication to allow normal daily activity is difficult. The decision to place a child on daily medication is not taken lightly. Not fully understood are what long-term effects either medications or inadequately controlled asthma may have on the child's growth and development in general, or on the natural course of the asthma and the child's lung growth and development in specific. There is, however, some evidence that appropriate control of childhood asthma may prevent development of irreversible obstruction. In addition, there is considerable evidence that asthma can interfere substantially with a child's participation in age-appropriate activities and that pharmacologic treatment can reduce morbidity from asthma. The suggested criteria for initiating long-term controller medication are that daily controller medication is preferable to daily administration of short-acting beta<sub>2</sub>-agonists to relieve symptoms, and that daily controller medication should be initiated if the extent of asthma is associated with significant changes from normal lifestyle.

Underdiagnosis of asthma is a frequent problem, and it occurs most often in young children whose primary symptom is cough or who wheeze only when they have respiratory infections and are thus dismissed as having bronchitis or pneumonia even though the signs and symptoms are most compatible with a diagnosis of asthma (see the chapter on diagnosis and classification).

For children under 5 years of age, the PEF is either not attainable or too dependent on fluctuating levels of attention and effort to be reliable. For younger children, the history, which should include assessment of the child's

quality of life, and physical examination, although imperfect, are essential elements in decision making. Symptom reports kept by the parent on a patient diary card are also helpful.

Viral upper respiratory infections are a common asthma trigger among children. Although there is no specific therapy, patients and parents need to be vigilant in adhering to the regular asthma medication treatment plans and in being alert for early signs of an exacerbation so that asthma medication may be started or increased immediately. For those individuals who deteriorate rapidly every time they have a viral respiratory infection, it may be appropriate to increase the anti-inflammatory treatment or to institute a short course of oral corticosteroid therapy at the earliest sign of viral respiratory infection (121). The addition of antibiotics to treatment in the presence of viral upper respiratory infection does not have therapeutic benefit for asthma. However, antibiotics should be considered as additional therapy if signs of bacterial pulmonary respiratory infection (e.g., pneumonia) or sinusitis are present.

Systemic absorption of high doses (more than 400 mcg beclomethasone dipropionate or budesonide in children) of inhaled corticosteroids is a potential concern because of their possible effect on linear growth as discussed in the previous section. Thus when inhaled corticosteroids are substituted or added to treatment with sodium cromoglycate or nedocromil sodium in order to achieve control of asthma (see discussion in step 2), an appropriate stepdown to consider is gradually reducing the inhaled corticosteroids and maintaining control with the sodium cromoglycate or nedocromil sodium. The inhaled corticosteroid may need to be reinitiated for seasonal asthma.

### **A Stepwise Approach to Pharmacologic Therapy for Infants and Young Children**

Several studies have shown that as many as 50 to 80 percent of children with asthma develop symptoms prior to their fifth birthday. Diagnosis can be especially difficult in infants and young children (see the chapter on diagnosis and classification). Below the age of 5, the assessment and monitoring of severity with measurements of lung function, including PEF, are not feasible. Therefore, classifying asthma severity must, for the majority of children, be based on clinical criteria. The history is fundamental, and the symptoms, mainly in infants, should be described as cough and/or wheezing and/or dyspnea. Essential elements in decision making are evaluation of the child's quality of life and physical examination.

The requirement for long-term therapy may cause a significant alteration in the life of the child and the family. The goal of all concerned—parents, patients, and health care professionals—should be a happy child who can experience normal growth and development.

Given the uncertainty about outcome, the treatment of wheezy infants should be more circumspect than may be the case in older children with more established asthma and atopy. Figure 7-6 illustrates the recommended therapy. Many infants in the first year of life have very mild symptoms that do not affect their health in any way, and medications may be unnecessary. Those with troublesome symptoms can be treated with inhaled short-acting beta<sub>2</sub>-agonists, either from a metered-dose inhaler using a spacer and face mask or a nebulizer. However, many infants, particularly those with virus-associated wheeze, do not respond. Approximately 40 percent will improve with inhaled ipratropium bromide (122).

Infants requiring such treatment consistently more frequently than three times per week should be given more conventional long-term asthma therapy. This includes inhaled corticosteroids or sodium cromoglycate, although there is little evidence of efficacy for nebulized sodium cromoglycate under the age of 1 (123). Either nebulizers or spacers with facemasks and valve systems can be used; normally the dose used in the nebulizer is 2.5 times higher than the dose used in the spacer. Budesonide is recommended as the nebulized corticosteroid; other inhaled corticosteroids are not yet available in suitable form for nebulization.

Alternatively, infants with mild persistent symptoms could be commenced on ketotifen. Although there is some trial evidence of efficacy when used continuously for many months as prophylaxis (124), the majority of controlled studies on ketotifen in infants could not show significant benefit.

Note that at present inhaled corticosteroids are the only controller medications that have been convincingly shown to be effective in children under 3 years of age. Other medications have either not been studied thoroughly or have produced uncertain results. Therefore a therapeutic trial with alternative medications should be monitored very carefully, and the treatment stopped if a clear beneficial effect is not obvious. Sustained-release theophylline may have particular risks of adverse side effects in infants who frequently have febrile illness. Sustained-release theophylline should only be considered if there will also be careful monitoring of serum levels.



Nebulized budesonide in a high dose of 1 mg twice a day has been shown to be highly efficacious for more severe asthma (125). If nebulized budesonide is not available or not sufficiently effective, oral corticosteroid should be initiated for the infant with severe persistent asthma. Oral corticosteroid should be given at the lowest possible dose on an alternate-day, early morning schedule. The same stepup and stepdown approach should be employed as at any other age.

Bronchodilator therapy with inhaled beta<sub>2</sub>-agonist or ipratropium may be given as reliever medications. Oral beta<sub>2</sub>-agonist (syrup) may be considered, but it has a slower onset of action.

### An Asthma Management Zone System for Patients

An asthma management zone system helps patients understand the chronic and variable nature of asthma, monitor their condition, identify the earliest possible signs that the day-to-day control of asthma is deteriorating, and act quickly to regain control. The patient may initiate actions appropriate to each zone, according to a prearranged plan made with the health care professional.

Several different zone systems have been developed, using either numbered levels to note zones or adapting the zones to a traffic light system to make it easier for patients to use and remember (126-128). Asthma management zone systems have been used in a wide variety of settings, from large hospital-based clinics to small primary care offices. One study has also demonstrated the effectiveness of an asthma management zone system in a rural population (129). Sample asthma management zone system patient cards are included in the chapter on education and delivery of care.

The zones suggested here are guidelines only; specific zones should be tailored by the health care professional to individual patient circumstances because patterns of exacerbations vary markedly among patients, although exacerbations in a particular patient often follow a pattern. Early recognition of the symptoms indicating an exacerbation is very important because change in symptom pattern can be a sensitive indicator of an acute exacerbation. Measurements of lung function can help the patient to recognize the beginning of an acute exacerbation. Although the zones are presented as percentages of predicted PEF in order to accommodate variations in patient size and age, patient understanding of the zones will be improved if the patient's written treatment plan indicates the actual PEF values that correspond with the percent range.

- **Green Zone.** Green indicates all clear. Asthma is under control. In this zone, there is no interruption of activities or sleep, and there are minimal (ideally no) symptoms. PEF is usually 80 to 100 percent of predicted or personal best and has usually less than 20 percent variability. The specific medication to maintain this control of asthma in the Green Zone depends on the level of asthma severity. If the patient has stayed in the Green Zone for at least 3 months, a careful stepdown of the therapy should be considered.

- **Yellow Zone.** Yellow signals caution. Occurrence of asthma symptoms (nocturnal symptoms, decreased activity, coughing, wheezing, chest tightness with activity or at rest) and/or a PEF of 60 to 80 percent predicted or personal best and 20 to 30 percent variability while in the Yellow Zone indicates one of two things:

- An acute exacerbation may be present for which a temporary increase in medication, especially inhaled short-acting beta<sub>2</sub>-agonists and possibly oral corticosteroids, is indicated (see Part 5: Establish Plans for Managing Exacerbations). The patient should follow the medication plan developed with the health care professional.
- A deterioration of asthma may be characterized by a gradual reduction in PEF that fails to have a sustained response to inhaled beta<sub>2</sub>-agonist, greater intolerance of daily activities or exercise, or the development of nocturnal symptoms. Such a deterioration indicates the need for further treatment to be arranged with the health care professional. A short burst of oral corticosteroids (30 to 60 mg daily, in single or divided doses) until PEF returns to the Green Zone is recommended. Oral corticosteroids should then be ceased; often this is accomplished by gradually tapered doses. Alternatively, in selected cases (e.g., patients already on inhaled corticosteroids), the regular dose of inhaled corticosteroids may be doubled for 1 or 2 weeks or until PEF and symptoms improve.

Frequent fluctuations into the Yellow Zone may indicate that the asthma is not sufficiently under control, and that the Green Zone therapy needs to be increased.

- **Red Zone.** Red signals a medical alert. Asthma symptoms are present at rest or interfere with activity. PEF is below 60 percent of predicted or personal best. An inhaled short-acting beta<sub>2</sub>-agonist should be taken immediately. If PEF remains below 60 percent despite

the bronchodilator, immediate medical attention is required.

Therapy for the Red Zone emphasizes adequate dosage of inhaled short-acting beta<sub>2</sub>-agonist, which may require frequent administration, and the early introduction of corticosteroids. Oxygen is also administered if the patient is hypoxemic. Specific recommendations are presented in Part 5: Establish Plans for Managing Exacerbations.

If the PEF improves after initial bronchodilator treatment, the Yellow Zone actions should be followed. Entry into the Red Zone may reflect a failure of the Green Zone therapy. After the exacerbation is controlled, the Green Zone therapy and patient adherence (to the medication plan and environmental control measures) should be reviewed and adjusted accordingly.

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## PART 5: ESTABLISH PLANS FOR MANAGING EXACERBATIONS

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Exacerbations of asthma (asthma attacks) are episodes of progressively worsening 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<sub>1</sub>) (130), and as discussed earlier, these measurements are more reliable indicators of the severity of airflow limitation than the degree of symptoms.

Exacerbations usually reflect either a failure of long-term management or exposure to a trigger. 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. Morbidity and mortality are most often associated with underassessment of the exacerbation's severity, inadequate action at the onset of the exacerbation, and undertreatment of the exacerbation.

Treatment of exacerbations depends on the patient, on the health care professional's experience with what therapies are most effective for the particular patient, and on the availability of antiasthma medications and emergency facilities. 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. In addition, patients who live in rural settings, may, by necessity, have to manage an acute asthma exacerbation at home. Local health care offices or

dispensaries often have therapies available to provide temporary relief or amelioration of moderately severe exacerbations. Acutely severe exacerbations are potentially life threatening, and treatment requires close supervision. This may be accomplished most safely in a hospital or a hospital-based emergency department.

The primary therapies for exacerbations are the repetitive administration of inhaled short-acting beta<sub>2</sub>-agonist and the early introduction of oral or parenteral corticosteroids if needed. General guidelines applicable to most patients are discussed in this section.

The aims of treatment are to:

- Relieve airflow limitation as quickly as possible
- Relieve hypoxemia
- Restore lung function to normal as soon as possible
- Plan avoidance of future relapses
- Discuss and develop with the patient an action plan in case of a further exacerbation. Whenever possible, give the patient a written plan to take home.

Crucial to successful treatment is close monitoring of the patient's condition and response to treatment with serial measurement of lung function. Assessment of the patient's pulse, respiratory rate, and current symptoms also guides treatment decisions, but measurements of lung function are critical.

Patients at high risk of asthma-related death require particularly intensive patient education, close monitoring, and prompt care. These patients include those with a history of:

- Current use of or recent withdrawal from systemic corticosteroids
- Hospitalization or emergency care visit for asthma in the past year
- Psychiatric disease or psychosocial problems
- Noncompliance with 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



**Figure 7-7. Severity of Asthma Exacerbations\***

	Mild	Moderate	Severe	Respiratory arrest imminent
Breathless	Walking	Talking Infant—softer shorter cry; difficulty feeding	At rest Infant stops feeding	
	Can lie down	Prefers sitting	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: <div> <div>Age</div> <div>&lt; 2 months</div> <div>2-12 months</div> <div>1-5 years</div> <div>6-8 years</div> </div> <div> <div>Normal rate</div> <div>&lt;60/min</div> <div>&lt;50/min</div> <div>&lt;40/min</div> <div>&lt;30/min</div> </div>			
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: <div> <div>Infants</div> <div>2-12 months - Normal Rate</div> <div>Preschool</div> <div>1-2 years</div> <div>School age</div> <div>2-8 years</div> </div> <div> <div>&lt;160/min</div> <div>&lt;120/min</div> <div>&lt;110/min</div> </div>			
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 <sub>2</sub> (on air) <sup>†</sup>	Normal Test not usually necessary	>60 mm Hg	<60 mm Hg	
and/or PaCO <sub>2</sub> <sup>†</sup>	<45 mm Hg	<45 mm Hg	Possible cyanosis >45 mm Hg; Possible respiratory failure (see text)	
SaO <sub>2</sub> % (on air) <sup>†</sup>	>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, indicate the general classification of the exacerbation.

†Note: Kilopascals are also used internationally; conversion would be appropriate in this regard.

indicators of airflow limitation. The increased treatment should continue until measurements of lung function (PEF or FEV<sub>1</sub>) return close to normal, or the patient's personal best.

## As131

### Assessment of Severity of the Exacerbation

The severity of the exacerbation determines the treatment administered. Figure 7-7 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 (in patients over 5 years old), pulse, and respiratory rate—should be monitored during treatment. Any deterioration may require prompt intervention.

### Home Management of Exacerbations

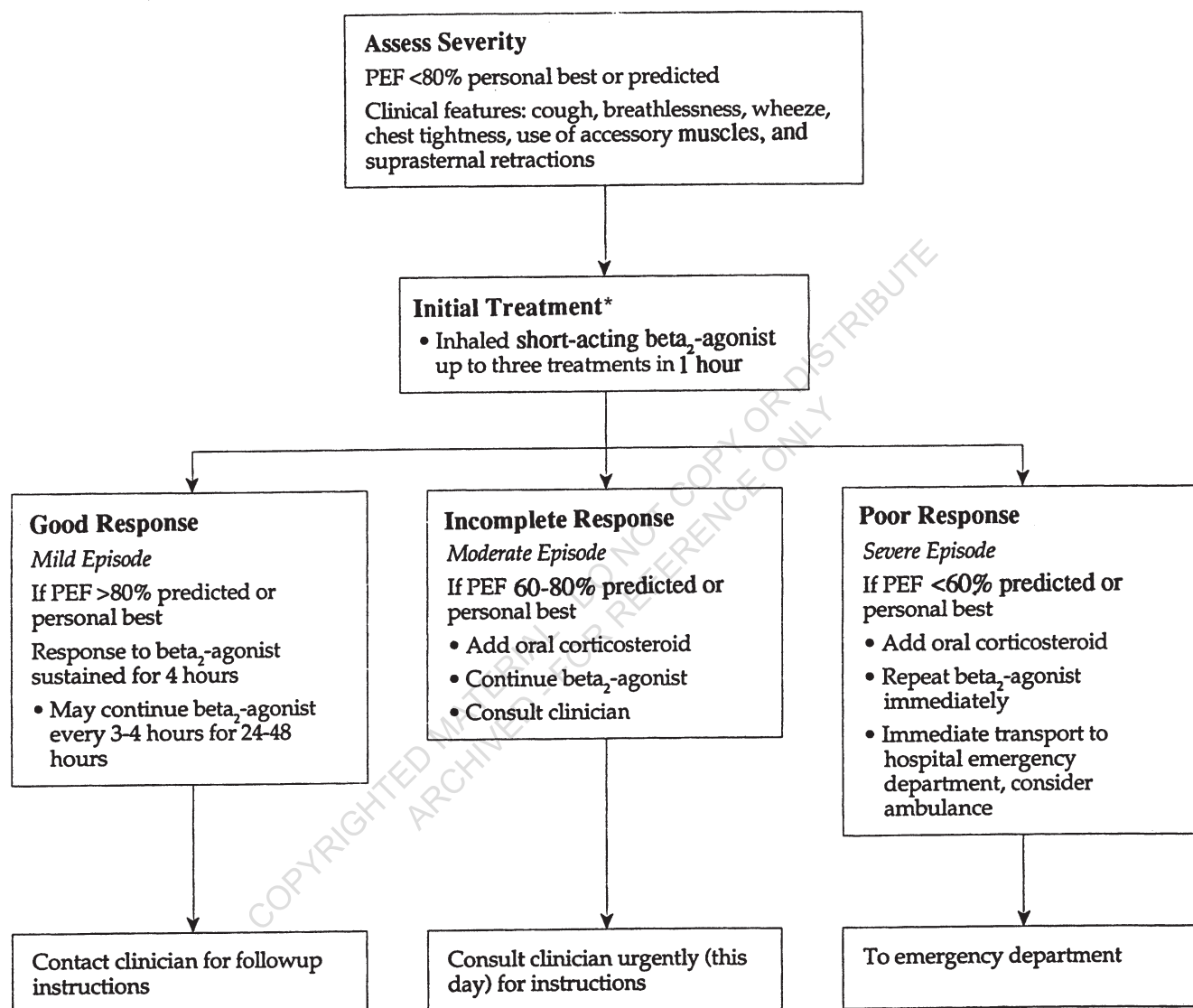
Initiation of appropriate therapy at the earliest possible signs of deteriorating control of asthma is important in the successful management of asthma exacerbations. When patients are able to begin treatment at home, they not only avoid delays in treatment but also add to their sense of control over 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 7-8 illustrates the approach to home treatment that is discussed here. Home peak expiratory flow rate determinations ideally should be an integral part of home management strategies. Ideally, all patients should have an action plan that outlines how and when to:

- Recognize signs of deterioration
- Start treatment
- Get medical care.

### Treatment

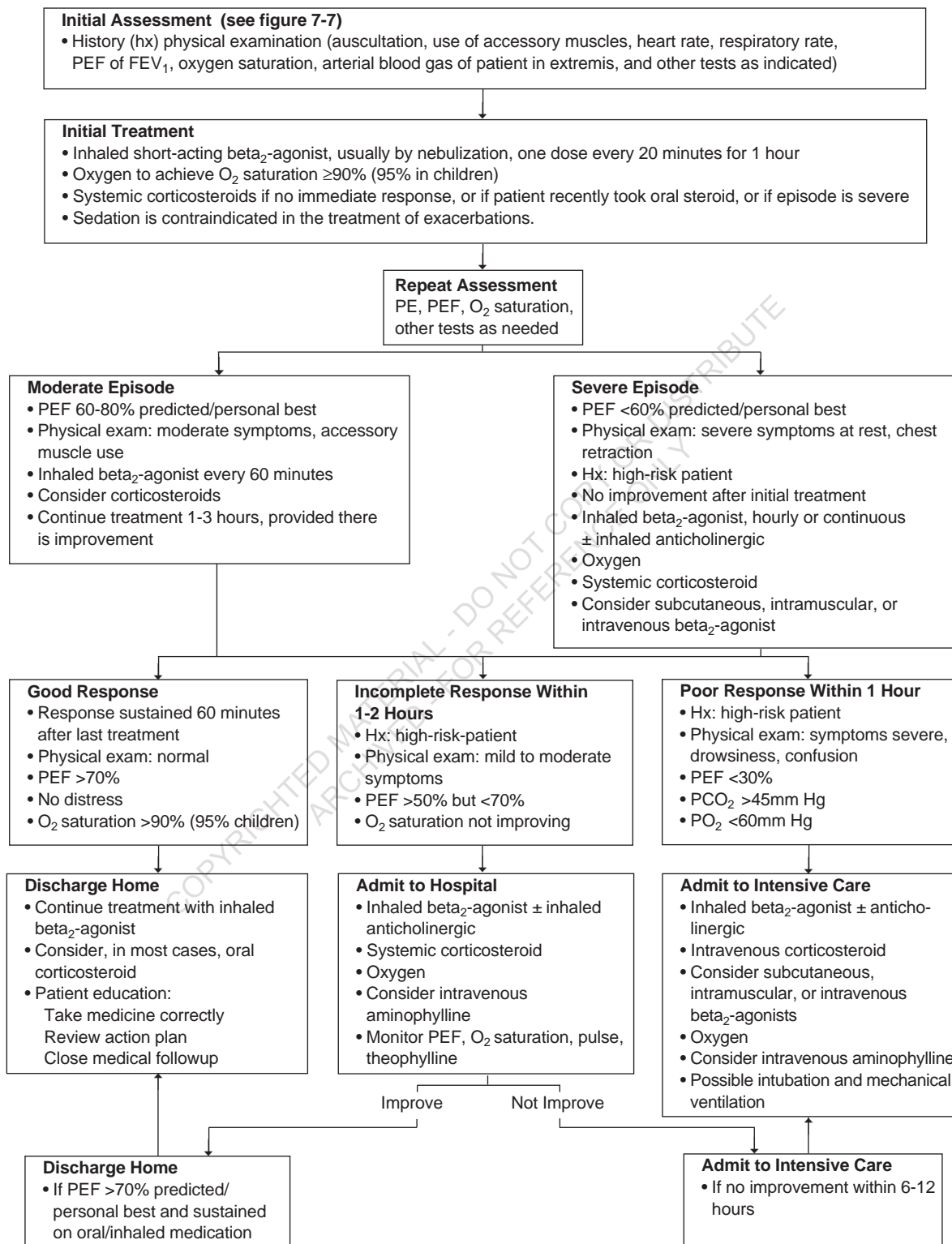
**Bronchodilators.** For mild to moderate exacerbations, repetitive administration of inhaled short-acting beta<sub>2</sub>-agonists (2 to 4 puffs every 20 minutes for the first hour) is usually the best method to achieve rapid reversal of airflow limitation. Either an inhaled anticholinergic, oral beta<sub>2</sub>-agonist, or short-acting theophylline may be considered as an alternative to inhaled short-acting beta<sub>2</sub>-agonist, although they have a slower onset of action and/or a higher risk for 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

**Figure 7-8. Management of Exacerbation of Asthma: Home Treatment**



\* Patients at high risk of asthma-related death (see text) should contact clinician promptly after initial treatment. Additional therapy may be required.

**Figure 7-9. Management of Exacerbation of Asthma: Hospital-Based Care**



\*Note: Preferred treatments are inhaled beta<sub>2</sub>-agonists in high doses and systemic corticosteroids. If inhaled beta<sub>2</sub>-agonists are not available, consider intravenous aminophylline; see text.

## Assessment

A brief history and physical examination pertinent to the exacerbation are appropriate prior to treatment.

The brief history will document:

- Severity of symptoms, including exercise limitation and sleep disturbance
- All current medication
- Time of onset and cause of present exacerbation
- Prior hospitalizations and emergency department visits for asthma.

The physical examination will:

- Assess severity of exacerbation (see figure 7-7)
- Identify complications (e.g., pneumonia, atelectasis, pneumothorax, or pneumomediastinum).

Functional assessments include:

- PEF or FEV<sub>1</sub> at least hourly, with initial measurements made before treatment if possible
- Arterial oxygen saturation by pulse oximetry, where available.

Laboratory studies should not be permitted to delay initiation of treatment. After initial treatment the following may be helpful:

- Chest x-ray if a complicating cardiopulmonary process is suspected
- Arterial blood gas measurement in patients with PEF 30 to 50 percent of predicted, or severe distress after initial treatment. A PaO<sub>2</sub> less than 60 mm Hg (8 kPa) and/or PaCO<sub>2</sub> greater than 45 mm Hg (6 kPa) indicate respiratory failure. Admission to an intensive care unit for continuous monitoring is indicated.

### Special considerations for infants and young children.

Several differences in lung anatomy and physiology place infants at greater risk than older children for respiratory failure. Close monitoring, using a combination of the parameters listed in figure 7-7 other than PEF, will permit a fairly accurate assessment.

Because of their ventilation/perfusion abnormalities, infants become hypoxemic earlier than adults. Oxygen saturation measurements should be performed on infants by pulse oximetry and should be greater than 95 percent. Arterial or arterialized blood gas measurement should be performed in infants with oxygen saturation less than 90 percent.

## Treatment

The following treatments are usually administered concurrently to achieve the most rapid resolution of the exacerbation.

**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, or by mask, or by a head box or oxygen tent in some infants). Supplemental oxygen should be administered to patients when arterial oxygen monitoring is not available.

**Beta<sub>2</sub>-agonists.** Inhaled short-acting beta<sub>2</sub>-agonists are generally administered by nebulization. The short-acting beta<sub>2</sub>-agonist may be nebulized with oxygen instead of air. The initial treatment is one dose every 20 minutes for 1 hour. Subsequently, hourly administration of short-acting beta<sub>2</sub>-agonist or even continuous nebulization increases rapidity of bronchodilation in children (133). Some studies suggest that high doses of short-acting beta<sub>2</sub>-agonist from a metered-dose inhaler with a spacer (4 to 8 puffs per treatment) may be equally effective (43, 134). Parenteral beta<sub>2</sub>-agonist may be added if there is no response to high-dose or continuous nebulized medication (135). Intramuscular or subcutaneous beta<sub>2</sub>-agonists may be used. Administration by intravenous bolus or infusion is preferred in some countries, although metabolic and cardiovascular consequences have been reported (136). Inhaled beta<sub>2</sub>-agonists are clearly preferred for children (137).

**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 acute severe exacerbations of asthma if inhaled or parenteral short-acting beta<sub>2</sub>-agonist is not available. However, the possibility for adverse effects, particularly among hypoxic patients, is greater. Epinephrine is sometimes considered if an acute severe exacerbation is not responsive to inhaled short-acting beta<sub>2</sub>-agonist.

**Additional bronchodilators.** Combining nebulized beta<sub>2</sub>-agonist with an anticholinergic (ipratropium bromide)



may produce better bronchodilation than either drug alone (90) and may be administered before aminophylline is considered. The role of theophylline/aminophylline in treating exacerbations remains controversial (91, 92, 138). Although theophylline may provide no additive bronchodilator effect over adequate doses of beta<sub>2</sub>-agonists, it may benefit respiratory drive or respiratory muscle function and prolong or sustain the response to beta<sub>2</sub>-agonist between doses. Intravenous aminophylline is not recommended in the emergency department within the first 4 hours of treatment; however, it may have a role in the treatment of patients hospitalized with severe acute asthma. A dose of 6 mg aminophylline/kg should be given slowly (over 10 minutes) intravenously in patients who have not received theophylline during the preceding 48 hours. In all other patients, serum concentration should be monitored and the dose adjusted accordingly, with consideration given to factors influencing metabolism of theophylline.

**Corticosteroids.** Systemic corticosteroids speed resolution of exacerbations refractory to bronchodilators (139, 140). Systemic corticosteroids administered by ingestion are usually as effective as those administered intravenously and are preferred because they are less invasive and less expensive. If vomiting has occurred shortly after administration of the oral dose of corticosteroids, then a similar dose should be readministered. Intravenous administration may be considered if intravenous access is desirable, or if there is possible impairment of gastrointestinal absorption (141). Corticosteroids require at least 4 hours to produce clinical improvement. Corticosteroids should be initiated if:

- The exacerbation is moderate to severe (see figure 7-7).
- The initial inhaled short-acting beta<sub>2</sub>-agonist dose has failed to achieve improvement.

Or:

- The exacerbation developed even though the patient was already taking long-term oral corticosteroids.
- Previous exacerbations required oral corticosteroids.

#### **Other treatment.**

- Antibiotics are not a direct part of treating exacerbations, but they are indicated for patients with signs of pneumonia or with fever and purulent sputum (due to polymorphs, not eosinophils), which suggest 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.
- Antihistamines have no established role in the treatment of exacerbations.
- Magnesium sulfate has not been established as an effective bronchodilator and is therefore not recommended.
- Chest physical therapy is not beneficial among patients with normal respiratory muscle strength and effective cough and may be unnecessarily stressful for the severely breathless patient.
- Hydration with large volumes of fluids does not play a role in the management of severe exacerbations in adults and older children.

#### **Special considerations for infants and young children.**

Rehydration may be necessary for infants and young children, who may become dehydrated as a result of increased respiratory rates and decreased oral intakes.

When treatments offer similar profiles for efficacy and safety, noninvasive procedures are preferred in order to avoid pain and anxiety. Thus inhaled or oral beta<sub>2</sub>-agonist and corticosteroid therapy is preferred over intravenous or subcutaneous therapy, and pulse oximetry is preferred over arterial blood gas measurements.

#### **Criteria for Continuous Supervision**

Factors indicating the need for close and continuous supervision that is provided either in a hospital or dispensary, depending on available facilities, include:

- Inadequate response to therapy within 1 to 2 hours of treatment
- Persisting severe airflow limitation (PEF less than 40 percent of predicted or personal best)
- Past history of severe asthma, particularly if hospitalization was required
- Presence of factors indicating high risk of asthma-related death

- 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 Admission to Intensive Care Unit***

Intensive care, generally in 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:

- A lack of response to initial therapy in the emergency department and/or rapidly worsening asthma
- Presence of confusion, drowsiness, other signs of impending respiratory arrest, or loss of consciousness
- Impending respiratory arrest: hypoxemia despite supplemental oxygen ( $PO_2$  less than 60 mm Hg [8 kPa] and/or  $PCO_2$  greater than 45 mm Hg [6 kPa]) (although respiratory failure may occur with either a high or low  $PCO_2$ ).

Intubation may be needed if there is continued deterioration in clinical features despite optimal therapy, if the patient is exhausted, and/or if the  $PCO_2$  is increasing. Intubation is extremely difficult and usually requires a specialist.

### ***Discharge From Emergency Department***

Patients with a good response to emergency department therapy (e.g., PEF returned to greater than or equal to 70 percent of predicted or personal best) require at least a 60-minute period of observation after the last dose of bronchodilator to ensure stability of response before discharge to home.

At discharge, the following actions are recommended:

- Identify and avoid the trigger factor that precipitated the exacerbation.
- Instruct the patient to contact the patient's family health care professional or asthma specialist within 24 hours of discharge. Emphasize the need for continuous, regular

care in an outpatient setting. A followup 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.

Further, the occurrence of a severe exacerbation indicates the need to review the regular, long-term medication plan and modify it if necessary:

- Prescribe at minimum a 3- to 5-day treatment regimen for the patient to continue after discharge. In most cases, this includes a course of oral corticosteroids and continuation of short-acting beta<sub>2</sub>-agonist therapy on a gradually reduced dose, based on the patient's status.
- Review the patient's inhaler technique and use of peak flow meter to monitor therapy at home.
- Review and, if necessary, modify the patient's (and family's) action plan for managing exacerbations so that the patient has a better understanding of how to:
  - Recognize signs that asthma is worsening
  - Start treatment
  - Reach medical care.

### ***Discharge From Continuous Supervision***

There are no absolute criteria for discharge; however, patients should be on discharge medications for at least 12 hours, 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:

- Short-acting inhaled beta<sub>2</sub>-agonist is needed no more frequently than every 4 hours.
- Patient is able to walk comfortably.
- Patient is not waking at night or in the early morning and needing a bronchodilator.
- Clinical examination is normal or near normal.
- PEF or  $FEV_1$  is more than 70 to 80 percent of predicted or personal best after short-acting inhaled beta<sub>2</sub>-agonist, and PEF variability is reduced, ideally to less than 20 percent variability. Note, however, that some patients' PEF may take several days to reach this desired level, and yet all other criteria indicate that discharge is warranted.

Discharge would then be appropriate, with continued PEF monitoring to be alert to any decreases in PEF indicating the need for additional treatment.

- Patient is able to use inhaler devices correctly.
- Patient's previous action plan is reviewed and modified if necessary.
- Patient understands the (written) plan for discharge medications.
- Arrangements are made for followup medical care.

Following discharge from continuous supervision, the patient should be reviewed by the patient's 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.

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## PART 6: PROVIDE REGULAR FOLLOWUP CARE

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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, and environmental triggers 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 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.

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## SPECIAL CONSIDERATIONS

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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

Retrospective 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. 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. 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 beta<sub>2</sub>-agonists are not associated with an increased incidence of fetal abnormalities. Acute exacerbations should be treated aggressively in order to avoid fetal hypoxia. Treatment should include nebulized short-acting beta<sub>2</sub>-agonists and oxygen; systemic corticosteroids 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 (142, 143).

### **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<sub>1</sub> values are less than 80 percent of the patient's personal best, a brief course of corticosteroids is required to reduce airflow limitation. Furthermore, patients who have received systemic corticosteroids 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 corticosteroid therapy may inhibit wound healing (144-146).

### **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. EIA may occur in any climatic condition, but it increases substantially in breathing dry cold air and is uncommon in hot, humid climates.

Exercise-induced asthma 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, 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 short-acting beta<sub>2</sub>-agonist before exercising is the most effective treatment for preventing asthma exacerbations. Many other compounds (sodium cromoglycate, nedocromil, anticholinergic agents, theophylline, inhaled corticosteroids, and antihistamine H<sub>1</sub>-antagonist) have been demonstrated to modulate EIA. Training and sufficient warming up also reduce the incidence and severity of exercise-induced asthma.

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 (147, 148).

### **Rhinitis, Sinusitis, and Nasal Polyps**

Upper airway diseases can influence lower airway function in some patients with asthma. For example, patients with active allergic rhinitis and sinusitis can have increased asthma symptoms. Although the mechanisms associated with these relationships have yet to be established, the clinical association should be considered in the treatment of asthma.

#### **Allergic Rhinitis**

During periods of active allergic rhinitis, some patients have airway hyperresponsiveness and may develop clinical features of asthma. In one study, treatment of allergic rhinitis with topical corticosteroids diminished the intensity of concomitant asthma symptoms (149). Whether similar control is achieved with antihistamines (H<sub>1</sub>-antagonist) or nasal sodium cromoglycate is not established (150-152).

**Figure 7-10. Tolerance of Nonsteroidal Anti-Inflammatory Drugs in Aspirin-Induced Asthma**

Precipitate asthma exacerbations	Well tolerated (cause no bronchoconstriction)
Salicylates	Sodium salicylate
Aspirin	Choline salicylate
Diffunisal	Choline magnesium trisalicylate
Salsalate (salicylsalicylic acid)	Salicylamide
	Dextropropoxyphene
Polycyclic acids	Azapropazone
Acetic acids	Benzydamine
Indomethacin	Chloroquine
Sulindac	*Paracetamol
Tolmetin	
Aryl aliphatic acids	
Naproxen	
Diclofanac	
Fenoprofen	
Ibuprofen	
Ketoprofen	
Tiaprofenic acid, Fluribiprofen	
Enolic acids	
Piroxicam	
Fenamates	
Mefenamic acid	
Flufenamic acid	
Meclofenamic acid	
Pyrazolones	
Aminopyrine	
Noramidopyrine	
Sulfinpyrazone	
Phenylbutazone	

\* When beginning therapy, give half a tablet of paracetamol and observe patient 2 to 3 hours for symptoms that occur in no more than 5 percent of patients.



## 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; furthermore, some investigators feel that persistent sinusitis is a major factor in chronic, unremitting asthma. Further studies are needed to confirm these suspicions (153). Diagnosis of sinusitis requires either x-ray or CT scan confirmation; clinical findings of sinusitis are often too subtle to make the diagnosis.

Antibiotic therapy of sinusitis has been associated with a reduction in asthma severity. Such therapy is more likely to be effective if antibiotics are given for at least 3 weeks. Treatment should also include medications (topical nasal decongestants or topical nasal corticosteroids) to reduce nasal congestion. However important these treatments are, they remain adjunct to primary asthma therapy (154, 155).

## Nasal Polyps

Nasal polyps associated with asthma and rhinitis, and often with aspirin sensitivity (29), are seen primarily in patients who are over 40 years old, and they are more prevalent in patients who have negative skin tests. Children with nasal polyps should be assessed for cystic fibrosis and immotile cilia syndrome. Nasal polyps are remarkably responsive to corticosteroids. Patients who have chronic nasal obstruction that persists in spite of treatment may benefit from surgery.

## Occupational Asthma

Occupational asthma is defined as asthma caused by exposure to an agent in the work environment. This may either cause a deterioration of preexisting asthma, or it may cause asthma to develop *de novo*. Sensitization may occur after a latent interval from months to years after exposure (25, 27). Figure 3-2 in the chapter on risk factors lists common agents known to cause occupational asthma.

The detection of asthma of occupational origin requires a systematic inquiry about the patient's occupation as part of the clinical history. Occupational asthma is suggested by symptoms of asthma during or shortly after exposure to certain fumes, gases, or dusts, or by periodicity of symptoms, with improvements during days away from work. A decline in PEF may be delayed: It may occur hours, or even a few days, after leaving the worksite (156). Confirmation of occupational asthma should ideally be made with measurements such as PEF monitoring at

home and at work or, in some cases, with supervised inhalation challenge (156).

Once the diagnosis is established, complete avoidance of exposure is mandatory to permit remission of asthma (25, 27, 156). However, once well established, occupational asthma may not be completely reversible (157). Continued exposure may cause greater sensitization to minute concentrations of the sensitizer(s), increasingly severe and potentially fatal asthma exacerbations (158) with less chance of subsequent remission, and, ultimately, permanently impaired lung function (159).

Pharmacologic therapy is identical to other forms of asthma, but it is not a substitute for adequate avoidance. Consultation with a specialist in asthma management or occupational medicine is advised.

Preexisting asthma or atopy as well as tobacco smoking may predispose some workers to higher risk in specific occupations, but screening measures are believed to be of limited value in most industries (25, 27). Prevention of sensitization by adequate occupational hygiene measures is most important. Advice may be given to atopic patients to avoid certain occupations.

## Respiratory Infections

Respiratory infections have an important relationship to asthma and provoke wheezing in many patients. Epidemiological studies have found the respiratory viruses, possibly chlamydia, but seldom bacteria, are the infectious microorganisms associated with increased asthma symptoms. In particular, respiratory syncytial virus, parainfluenza, rhinovirus, and influenza are the most frequently identified viruses associated with increased wheezing (160, 161). 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 (162). 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 (163). Treatment of exacerbations associated with a respiratory infection follows the same principles as in other asthma exacerbations; that is, inhaled short-acting beta<sub>2</sub>-agonist and the early introduction of oral corticosteroids or increase in inhaled corticosteroids 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. Furthermore, there is evidence that influenza immunization diminishes the

likelihood for this infection to cause asthma exacerbations to develop (32).

### Gastroesophageal Reflux

The relationship of increased asthma symptoms, particularly at night, to gastroesophageal reflux remains an issue of debate, although this condition is nearly three times as prevalent in all patients with asthma. Most of these patients also have a hiatal hernia; furthermore, the use of xanthines 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 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 beta<sub>2</sub>-agonists; using H-2 antagonists; 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 (164, 165).

### Aspirin-Induced Asthma

In 4 to 28 percent of adults with asthma, but rarely in children with asthma, aspirin and other nonsteroidal anti-inflammatory drugs (NSAID's) cause asthma exacerbations. The variability depends on the diagnostic criteria (166). Oral challenge tests to confirm a history of aspirin-induced asthma are hazardous and should be replaced by the safer inhalational challenge with lysine-aspirine (167).

The course of the disease and its clinical picture are characteristic. 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 (168, 169).

Tolerance to different nonsteroidal anti-inflammatory medications is noted in figure 7-10. 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 (170). Although a patient's clinical history may raise suspicion of aspirin-induced asthma, the diagnosis can be established with certainty only by aspirin challenge, conducted only where facilities for pulmonary resuscitation exist. There are no in vitro tests suitable for routine clinical diagnosis. If necessary for the diagnosis of aspirin-induced asthma, patients are challenged when their asthma is in remission and their FEV<sub>1</sub> is greater than 70 percent of personal or predicted best. Oral challenge tests are most commonly performed. All challenges are carried out in the morning with a highly trained experienced physician present and emergency treatment available. The reaction is considered positive if at least a 15 percent decrease in FEV<sub>1</sub> 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<sub>1</sub> or PEF greater than 20 percent occurs.

Once aspirin or NSAID intolerance develops, it is present for life. Patients with aspirin-induced asthma should avoid aspirin, all products containing it, and other analgesics that inhibit cyclooxygenase and hydrocortisone hemisuccinate (171). For NSAID-sensitive patients with asthma who require NSAID's for other medical conditions, a desensitization may be conducted in the hospital under the care of a specialist (172).

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## RESEARCH RECOMMENDATIONS

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Priorities for future investigations related to management of asthma include:

- Determining the risk for side effects of inhaled corticosteroids in malnourished children.
- Studying the effect of inhaled corticosteroids on the clinical course of generalized herpes infections.
- Studying further the therapeutic efficacy of antiallergic drugs.
- Studying the long-term effects of asthma therapy on the natural history of asthma and on lung function.

- Comparing the long-term therapeutic effect in persistent moderate asthma of a high dose of inhaled corticosteroids versus a combination of a moderate dose of inhaled corticosteroids with a long-acting bronchodilator.
- Determining the long-term safety of inhaled corticosteroids, especially in children and older people.
- Investigating the therapeutic efficacy of traditional methods of healing in controlled studies.
- Comparing the effects and side effects of pharmacological treatment and immunotherapy in the long-term management of asthma.
- Studying the efficacy of the stepwise treatment of asthma as recommended in this document on large populations of patients with asthma using a variety of outcome measures, including quality of life.
- Evaluating the efficacy and applicability of the recommendations for the management of acute asthma exacerbations in different health care systems.

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# CHAPTER

8

# ***SOCIOECONOMICS***

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## KEY POINTS:

- Considering the social and economic impacts of asthma on the affected individual and his or her community is an important component of planning and evaluating effective management and prevention programs.
- Asthma is a chronic condition with a substantial degree of social burden on both children and adults worldwide.
- For any country currently caring for persons with asthma, the economic burden may be substantial, but it is likely to be reduced with improvements in prevention and management strategies.
- Improving the social and economic impacts of new asthma control programs will require careful consideration of local health care resources as well as the social/cultural preferences of each community.
- The use of health economic methods such as cost-of-illness and cost-effective studies can provide insights into the most efficient design and implementation of asthma control programs, with potential reductions in cost to the individual and society.

Asthma prevalence, as discussed in the chapter on epidemiology, varies considerably among countries. It is difficult to establish how many persons are affected worldwide. One study suggests that about 100 million persons in the world have asthma (1). But the social and economic impact of asthma goes far beyond the bare numbers of affected individuals. A long-term disorder such as asthma creates a burden for individuals and for society that must be measured in terms of reduced quality of life or general well-being, ongoing disability, and premature death as well as reduced productivity and increased medical care expenditures. Thus asthma is a major public health issue with cumulative costs to individuals and countries that deserves the attention of governments and public health systems. The implementation of effective treatment strategies for asthma is likely to reduce both morbidity and excess health care expenditures.

This chapter first describes the social impact of asthma on both children and adults, looks at the possible social impact of asthma interventions on society, and explores

the current economic impact of asthma on countries and individuals. The focus then turns to health economics and health care planning for asthma, a discussion of health care financing for asthma, an illustrative cost-of-illness study, and recommendations for addressing the socioeconomic burdens of asthma.

## THE SOCIAL IMPACT OF ASTHMA

The basic epidemiology of asthma provides insight into the millions of persons affected with asthma worldwide. Because of the social disabilities that relate both directly and indirectly to persons affected, improving health status and thereby improving quality of life are principal goals in asthma care. A reasonably complete characterization of health status recognizes the multidimensional nature of health. This concept of health includes concern for the physical, physiological, psychological, and socioeconomic aspects of an individual's ability to function in society. Thus asthma, which has been well characterized as a disorder that affects physical and physiological function by its impact on respiration, equally affects psychological and socioeconomic function.

### The Impact on Child Health and Development

The most useful measurement of the social burden of asthma on children may be loss of school attendance. In the United States, for example, asthma in children accounted for 7.3 million days restricted to bed and 10.1 million days missed from school per annum (2). The impact is similar in England and Australia. In London, school loss because of wheezy illness was reported by 12 percent of children and amounted to more than 30 days missed per person for the academic year (3). In Australia, school loss caused by asthma accounted for approximately 965,000 days annually (4). The social burden goes beyond lost schooling: Data suggest that 35 percent of children with asthma experience a great deal of pain or bother as a result of their asthma, that 17 percent have symptoms often, and that nearly 5 percent experience symptoms all the time (2).

Measurements of actual days lost from school provide only a one-dimensional view of asthma's impact on child development, however. To help understand the long-term consequences, other important measurements include scholastic achievement and the attainment of age-appropriate social functioning. Children with asthma may be at higher risk of learning disability as compared with children without asthma, and among families with low incomes, children with asthma have twice the odds of grade failure compared with well children (5). For

example, in a study of children attending primary school in New Zealand, data indicated that 19.4 percent had experienced asthma or recurrent wheezing (6). When these data were related to school performance, those absent more than 4 weeks demonstrated poor academic performance. Interestingly, those who were labeled “wheezy” rather than “asthma” were shown to have lost school time disproportionately and suffered more academically. Thus even in a country that pays attention to asthma, it appears that children are not yet receiving accurate diagnoses and thus effective treatment, and as a result their academic performance is at risk.

Asthma also can affect psychological development, including self-esteem. In one study, nearly 41 percent of parents of children with asthma said that asthma caused their children to feel self-pity. These children also were found to have poor self-opinion as well as poor relationships with their peers (7).

To date, nearly all of what is known about the social impact of asthma has come from data gathered in developed countries. However, there is every reason to suspect the same patterns of social impact in other countries according to a survey of 100 asthma patients and their families and coworkers or schoolmates in a rural and urban area of Andhra Pradesh, India, that was conducted by a member of the NHLBI/WHO Global Strategy for Asthma Project from April to June 1993 (8). The survey revealed that 51 percent of children under 14 years of age missed 2 to 15 days of school during the 2-month recall period. The average was 2.66 days absence from school due to asthma. Schoolmates reported they noticed some restriction of activity in 60 percent of the children with asthma.

The impact of asthma on the children of any country, therefore, is likely to be both large and underestimated, at least in monetary terms. Data from developed countries clearly demonstrate this burden of asthma on children and suggest that the burden is even greater on a per-person basis in developing countries.

### **The Impact on Adults**

For many adults, active asthma-related symptoms are likely to lead to loss of work and decreased productivity that can have substantial impact on the work force. For example, asthma is reported to account for more than 1.5 million days' loss of production per year in New South Wales (9). Data from Britain have indicated 5.73 million days of certified incapacity for work in 1987-88 as a consequence of asthma (10). Similarly, asthma has

contributed to nearly 1.9 million days of sick leave in Sweden annually (11). In addition, one study found that 25 percent of a sample of patients with asthma had experienced at least one period of 4 or more consecutive days off work during a 6-month period due to their asthma (12). Similarly, the Andhra Pradesh survey reported that 34 percent of the adult respondents with asthma had absences from work due to asthma. During the 1-month recall period (April to June 1993), adults with asthma averaged 1.65 work days lost due to asthma. Coworkers reported they noticed some restriction of activity in 68 percent of the adults with asthma.

Many occupations involve exposure to agents in the workplace that can sensitize the airways and cause asthma (see the chapter on risk factors). With the introduction of new materials into industry, the number of exposures (currently more than 200 substances relate to occupational asthma—see figure 3-2 in the chapter on risk factors) will continue to grow. Occupational asthma must therefore be considered an important source of asthma's excessive social burden. For example, in Japan it has been estimated that 15 percent of asthma in men is caused by occupational exposure (13). Developing countries that have increasing industrialization are at particular risk for introducing new cases of asthma through unregulated occupational hazards. Further, preexisting asthma or atopy as well as tobacco smoking may predispose some workers to a higher risk in specific occupations (especially those with exposure to certain high molecular weight sensitizers). Although screening measures are believed to be of limited value in most industries, screening or counseling of work forces prior to exposure or potential exposure to high molecular weight sensitizers could be beneficial. Prevention of sensitization by adequate occupational hygiene measures is most important. If a worker develops asthma after exposure, total avoidance of future contact with the sensitizing agent is essential, and employee reassignment may need to be considered. Industries and governments may be able to assist by encouraging adequate occupational hygiene measures and by providing appropriate counseling and placement services for workers who develop occupational asthma.

Some impacts of asthma on adults are intangible. Persons with asthma may be burdened with social stigmas. Chronic symptoms of cough and wheeze may lead family members and friends to believe mistakenly that asthma is a grave or communicable illness rather than a condition that is fully treatable.

Loss of days of work because of asthma may lead to a person's progression from steady employment to marginal

or lost employment. Asthma symptoms that are exacerbated by work exposure may wrongly lead to multiple work days lost and subsequent dismissal from the job. Dismissal or job changes that occur because of asthma may result in permanent and unnecessary loss of lifetime earnings.

### **The Impact on Family**

From the moment that a child develops asthma symptoms, a change in the way the child functions within the family and larger social structure is likely. Because children with inadequately treated asthma are estimated to have higher levels of sick days in bed as compared to children without asthma, and nearly 30 percent report some restriction in activities of daily living (2), a child with asthma may impede other family members' work and nonwork. In most countries, caring for a sick child is associated with the need to divert family resources to the care of that child. On days the child has symptoms, the mother or other caregiver must devote extra time to the child with asthma at the expense of other family or household responsibilities or work duties. Nights with a child experiencing asthma symptoms can result in significant sleep loss for both child and family. Even when the child with asthma receives good health care, the normal patterns of family life may be affected because trips (sometimes a substantial number) to the health care provider are required, and the caregiver takes time away from family or work. Some of this burden on the child and his or her family is measurable in economic terms; much of it is not. For example, a study in the United States estimated that in 1 year, school days lost due to asthma cost \$726 million in caretakers' time lost from work, including outside employment and housekeeping (14).

The impact on family functioning can be similar for both adults and children. Family members in the Andhra Pradesh survey reported a range of impacts on daily family life, including not expecting the person with asthma to contribute to such instrumental activities as shopping, housework, or cooking; having to help the person with asthma with basic activities of daily living; having to help the person with his or her work; and having to take time to be with the asthma sufferer when he or she had symptoms. Family support was the most important contributor to a patient's ability to cope with the morbidity experienced with asthma. A majority of the survey respondents (88 percent) reported that they received very good cooperation, help, and encouragement from their family. The respondents acknowledged the family effort this support involved. Most frequently cited gestures of support were taking the patient to the doctor, buying or fetching medicine, arranging money for treatment,

reminding the patient to take medicine, helping to avoid exposure to allergens (and, in some cases, relocating the family), giving relief from work, and showing concern.

Thus when asthma is not well controlled, it is likely to affect the social functioning of a country, impairing not only child development and education but also causing disruption in job training or ongoing employment for millions of adults worldwide.

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## **THE SOCIAL IMPACT OF ASTHMA MANAGEMENT INTERVENTIONS**

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Asthma management interventions are likely to affect society at large in important ways. For example, many strategies for primary prevention (see the chapter on prevention) are heavily dependent on lifestyle changes and therefore have the potential for substantial—yet immeasurable—social impact. This potential may translate into subtle impediments to the implementation of improvements, however. For example, domestic animals such as dogs and cats are a likely source of allergens that aggravate asthma and lead to severe respiratory difficulty. Removal of these and other animals from the indoor environment is crucial for patients with asthma, and it may be an important way to prevent the development of asthma in people at high risk. Yet for many societies, these animals may play an important role in the family as either companions or means of security. Societies heavily dependent on pets may have to advocate at least temporary avoidance for a period of 6 months to more than 1 year from the time of childbirth in the household. For another example, control of domestic mites, which are also asthma risk factors, may require changes in both the type and hygiene of bedding as well as a redesign of housing. Exposure reduction strategies could take advantage of the fact that change in household routine after childbirth is a widely accepted cultural phenomenon. Even though using plastic wrappings on the mattress and boiling bed sheets frequently might be difficult on a permanent basis, families could adopt such practices for at least 6 months to 1 year after childbirth.

Other aspects of existing culture within a country may make achieving optimal asthma control difficult. Cultural beliefs and customs may be either a support or a hindrance. For example, in some cultures, the people generally prefer to use orally administered medications rather than inhaled medications. In addition, standard practices in housing construction or maintenance (grass roofs, indoor fires, inadequate ventilation systems) may lead to hidden exposures to allergens or respiratory irritants. Cigarette smoking habits may be deeply

embedded within a culture and therefore extremely difficult to change.

The organization of a health care delivery system in a country is likely to be affected by asthma. As outlined in the chapter on management of asthma, asthma must be considered a chronic disorder, and long-term relationships between the individual with asthma and the primary care team must be developed to achieve optimal asthma control. Yet access to such care is often difficult. In some cases, many miles separate the person with asthma from the health center, clinic, or primary care office. In other cases, clinics or primary care offices have large staffs that change frequently. Effective control strategies should be designed for each country in a way to serve the needs of both the affected individual and the health care delivery system.

## THE ECONOMIC IMPACT OF ASTHMA

In addition to the clear and impressive social impacts of asthma, there also are substantial economic costs. The economic burden is reflected in:

- **Direct medical care costs** of health services used for prevention and treatment of asthma
- **Indirect costs** expressed in terms of the value of asthma-related morbidity, premature mortality, and productivity loss
- **Intangible costs** associated with the value of psychosocial impacts of asthma.

Standard methods exist for conducting cost-of-illness studies and for placing an economic value on incremental direct medical care costs and indirect nonmedical costs as well as for adjusting these costs to account for differences in timing. Costs can be associated with undertreatment as well as overtreatment of asthma. To date, methods that value the intangible costs of illness have not been fully developed. One study (15) has provided a primer on the conduct of cost-of-illness studies. The costs of illness can be viewed from the perspective of the society, of the health care system (organizations within a community that provide or finance care), or of the individual with asthma.

### Costs of Asthma From the Societal Perspective

Figure 8-1 summarizes available studies on the economic costs of asthma in different countries. It reveals that the societal costs of asthma are substantial, for both direct medical expenditures and indirect costs of lost productivity

(from absenteeism or reduced effectiveness at work). The figure shows that a preponderance of economic costs associated with asthma is used for medical management. On average, 58 percent of total asthma costs (from 26 to 80 percent) are for direct medical care expenditures. In the United Kingdom, approximately 21 percent of the total direct costs were expended on hospital-based care at a per-case rate of 620 pounds as compared to an estimated 153 pounds per case year for treating asthma in the community setting. In the United States, of the total dollars spent on medical care, about 60 percent are for hospital and emergency department expenditures, 30 percent for medication costs, and 10 percent for physician services. The distribution of resources is thus highly skewed toward hospitalization and emergency care.

Figure 8-2 demonstrates the economic burden of asthma using both cost-per-capita and cost-per-affected-individual approaches. The cost data were inflated to 1991 U.S. dollars using two inflators: the country-specific all-item price index for direct medical care costs and the labor compensation index for the costs associated with worker productivity loss. For developed countries where information on asthma costs is generally available, the 1991 per capita costs of asthma ranged between \$25 and \$40 (U.S.) per year. The 1991 costs of asthma per affected individual ranged between \$326 and \$1,315 (U.S.) per year.

As seen from figures 8-1 and 8-2, there is large variation in the costs of asthma among countries. Yet such a comparison does provide several insights. Principally, the direct medical expenditures for asthma are notable for each country studied. Hospitalization and emergency care are consistently disproportionately high. The costs of medication also constitute a key element of the costs of care. Finally, even in a cross-comparison between an industrialized area such as the United States and an agricultural area such as Transkei, South Africa, the total costs of asthma as a single condition currently comprise up to 1 to 2 percent of health care expenditures.

### Costs of Asthma From the Health Care System Perspective

Both the direct and indirect costs of asthma contribute to the global economic burden of asthma. Yet within any community, the most apparent economic burden of asthma results from the direct use of the health care system.

In New South Wales, for example, asthma is one of the top 10 reasons for visits with general practitioners and accounted for approximately 55,000 emergency visits to



Figure 8-1. Summary of Studies on the Economic Costs of Asthma\*

Author/country	Year of data	Study design	Economic costs			
			Direct costs	Indirect costs	Total costs	Per person
National Asthma Campaign (35) Australia	1991	PA,AC	\$320 million	\$260-400 million	\$580-720 million	-----
Mellis et al. (9) New South Wales, Australia	1989	S,PA,AC	\$142 million	\$67 million	\$209 million	\$769
Thompson (11) Sweden	1975	S,PA,MC	218 million (Kronor)	618 million (Kronor)	836 million (Kronor)	-----
Action Asthma (10) United Kingdom	1988	Pay,PA,AC	£344 million	£499 million	£843 million	-----
Vance & Taylor (17) United States	1967-69	F,PA,MC(?)	-----	-----	-----	\$1,245 per family
NHLI (36) United States	1967	S,PA,AC	\$243 million	\$272 million	\$515 million	-----
Marion et al. (16) United States	1977-80	F,PA,MC	\$940 per family	\$147 per family	-----	\$1,087 per family
Ross (37) United States	1988	S,PA,AC	\$8.7 billion	\$2.2 billion	\$10.9 billion	-----
Weiss et al. (14) United States	1990†	S,PA,AC	\$3.6 billion	\$2.6 billion	\$6.4 billion	-----

Notes: \* Direct costs are those direct medical expenditures associated with treatments for asthma; indirect costs are those that relate to lost productivity due to illness, including absence from work. Cost information reported in denomination of corresponding country. S, societal perspective; Pay, National Health Service payer perspective; F, family perspective; PA, prevalence approach; MC, marginal cost analysis; AC, average cost analysis. †Projected from 1985 data.



Figure 8-2. Comparison of Five Studies on Direct and Indirect Costs of Asthma, Adjusted to 1991 U.S. Dollars\*

Country and year of data	Monetary conversion in 1991	Population in 1990	Asthma prevalence in 1990	Direct medical costs	Indirect costs	Total costs	Per capita cost	Per asthma patient cost
Australia 1991	1.28A\$/1£	16.5 million	8.5%	\$250.0 million	\$207.0 million	\$457.0 million	\$27.70 per person	\$326 per asthmatic
New South Wales, Australia 1989	1.28A\$/1£	5.3 million	6.0%	\$125.8 million	\$37.5 million	\$163.3 million	\$30.81 per person	\$513 per asthmatic
Sweden 1975	68Kr/1£	8.6 million	3.0%	\$90.8 million	\$257.5 million	\$348.3 million	\$40.50 per person	\$1,315 per asthmatic
United Kingdom 1988	.562£/1£	57.2 million	6.0%	\$722.5 million	\$1.07 billion	\$1.79 billion	\$31.26 per person	\$522 per asthmatic
United States 1990	-----	249 million	4.0%	\$3.6 billion	\$2.6 billion	\$6.4 billion	\$25.70 per person	\$640 per asthmatic

\* Direct medical care costs, which are direct medical expenditures associated with treatments for asthma, were adjusted using the all-item price index. Indirect medical care cost, which relate to lost productivity due to illness, including absence from work, were adjusted using the labor compensation index for each country. The price and labor indices, the monetary conversion factor, and population estimates were derived from the following three sources: *Australia Country Report*, 1989-91, vols 1-4, London, U.K., The Economist Intelligence Unit Limited; *Sweden Country Report*, 1985-91, vols 1-4, London, U.K., The Economist Intelligence Unit Limited; *United Kingdom Country Report*, 1988-91, vols 1-4, London, U.K., The Economist Intelligence Unit Limited.

public hospitals (9). In the United Kingdom, 1.5 to 2 million persons may consult or obtain treatment from a general practitioner annually for asthma (10). In Sweden, persons with asthma accounted for nearly 23,000 hospital admissions, or 240,000 hospitalization days annually (11). In the United States, asthma accounted for substantial health care utilization, including more than 460,000 hospitalizations, 1.8 million emergency department visits, and 8 million doctor visits annually (14). Asthma is a leading condition for hospital admissions for children in the United States.

Little is known about the costs of asthma in developing countries. However, an example can be seen in a study of Transkei, South Africa. Transkei has a population of 4.5 million. Its economy is predominantly agricultural. The population is served by a public health care system with an annual budget of 380 million rand. Based on an estimated 1.0 percent prevalence, direct medical expenditure for asthma care (1.4 million rand) accounts for 0.38 percent of the total health care budget. As with other countries, a large part of the expense is spent on hospital or emergency care, and the relatively low proportion of health expenditures probably represents a low diagnosis and treatment rate in rural areas.

### **Costs of Asthma From the Individual Perspective**

To the individual with asthma or his or her family, the costs of asthma can be immense. For example, studies have demonstrated that the average amount spent by a family on medical treatments for children with asthma in the United States ranged between 5.5 and 14.5 percent of family income (16, 17). The Andhra Pradesh study demonstrated similar financial impact for families from both urban and rural areas. Eighty-four percent of the respondents with asthma spent personal money on their treatment regardless of whether their health care was financed publicly or privately. The average expenditure for asthma treatment was about 9 percent of per capita income. Although the amount was highly variable among respondents, approximately 70 percent of the household expenditures for asthma treatment were spent on medications. Twenty-one percent of the respondents with asthma and 15 percent of their family members perceived asthma as a financial burden to the family. The direct costs of the treatment of asthma were reported to take away a considerable amount of family income or livestock capital, especially for the families from the rural area. The indirect cost of one family member missing work in order to care for a person suffering from asthma symptoms was also cited as a major factor in the financial burden.

## **HEALTH ECONOMICS AND HEALTH CARE PLANNING FOR ASTHMA**

Establishing priorities for the allocation of limited resources to the health sector in general, and to health services for noncommunicable disease in particular, is a major problem for health planners, especially in developing countries. To argue the case for asthma health care convincingly, health planners need to evaluate and compare available or proposed intervention strategies.

### **Evaluating Costs**

The evaluations and comparisons of available or proposed intervention strategies have often been undertaken on the basis of the direct and indirect economic costs of asthma, with the potential economic benefits of a program of prevention, control, and treatment generally related to estimates of cost savings resulting from optimal asthma care. But it is difficult to estimate economic costs and benefits even for a program solely concerned with asthma, and it is even more difficult when asthma care is part of an integrated community health program. Easier to compute are the direct expenditures on health services, essential hospital care, pharmacotherapy, and health care professionals. However, neither health education and other public health programs designed to prevent diseases sharing common risk factors (such as asthma, bronchitis, and other respiratory illnesses) nor community control programs aimed at promoting positive health (through improvements in physical efficiency, performance, and quality of life) can be evaluated by conventional cost-of-illness methods. Furthermore, the indirect costs of morbidity and mortality caused by asthma or its complications, which are calculated in terms of lost person hours and consequent loss of production, may be particularly difficult to compute in developing countries.

The most effective way to make evaluations and comparisons and ensure efficient allocation of societal resources for the medical care needs of any community or population is to use economic analysis techniques (18, 19). One of these techniques is cost-benefit analysis. Because benefits and costs are calculated in terms of productivity and earning capacity, cost-benefit analysis evaluates both expenditures and health improvements in monetary terms. A more important technique for health planners is cost-effectiveness analysis, in which alternative intervention strategies are compared based on a ratio of cost to effectiveness (for example, cost per improvement in days without symptoms [20, 21]). This means that cost-effectiveness analysis enables health planners to evaluate and rank alternative strategies in terms of the cost of

producing similar outcomes, and these outcomes do not have to be computed only in monetary terms but must use similarly measured outcomes. Thus it is cost-effectiveness analysis that best assists health planners in rationally selecting the most efficient alternative intervention strategies for asthma control in a particular country given the desired outcome and available health care resources.

A few review studies have been made of cost-effective interventions for asthma care (22, 23). These begin to provide health planners with data on how health care resources for asthma can be most efficiently allocated.

An illustrative cost-of-illness study is presented later in this chapter.

### Evaluating Appropriateness

One of the most important aspects of implementation of any new asthma intervention program is related to the attention paid to its appropriateness within each country. The guidelines for the management of asthma care (outlined in the chapter on management of asthma) represent the state of the art in high-quality asthma care. Yet for each country, adoption of these management strategies is likely to have both an economic and a social impact.

Many of the primary and secondary prevention strategies (as noted in the chapters on prevention and on management of asthma)—such as removal of animals from the home or changes in mattress, bed linen, and pillow care—require acceptance by the general public. In addition, many of the primary control strategies require expenditures of new public health funds or, at least, reallocation of funds away from existing programs.

### Evaluating Economic Impact

In introducing new asthma management strategies into the existing health care economy for any country, health planners must be concerned with economic impact as well as cultural appropriateness. For example, both the health care financing community and patients with asthma must be made aware of the benefits of the proposed changes in pharmacotherapy (such as changing from tablets to aerosols for beta<sub>2</sub>-agonists or corticosteroids), which may have an impact on the availability and distribution of existing health resources. (See the discussion in the chapter on management of asthma, and figures 7-1 and 7-2 on cost calculations.) The costs and benefits of new asthma management programs must be weighed not only relative to cultural appropriateness but also relative to the existing resources of each community and relative to

what these existing resources can purchase by way of other nonmedical goods.

Health planners should note that although the costs of new asthma management strategies may seem high, an analysis of the current medical expenditures in a country may reveal that substantial savings could be recovered from more efficient use of resources in program implementation. To demonstrate such an analysis, an illustrative study that examined the current direct medical expenditures for Transkei is presented later in the chapter. The analysis indicated that most of the costs of care (52 percent) are with hospitalizations and emergency care, that current treatment depends on the administration of oral tablets and the use of unscheduled as-needed beta<sub>2</sub>-agonist, and that use of both oral and inhaled steroids is low. Nonetheless, 21 percent of asthma expenses were on medications. If it were shown that inhaled corticosteroid therapy prevented asthma-related hospitalization, it could be practical to make these medications available to those at greatest risk for hospitalization. Indeed, in Transkei the cost of inhaled corticosteroid for 1 year is equivalent to one-fourth of the average hospitalization. Thus an investment in high-cost inhaled corticosteroid therapy could result in substantial savings if the therapy were targeted at patients with high hospital and emergency care use. Such savings have been shown in a study in Sweden in which the introduction of inhaled corticosteroids substantially reduced costs by improving control of asthma and thus reducing hospital admissions (24). A further study in the Netherlands found similar results (25, 26).

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## HEALTH CARE FINANCING FOR ASTHMA

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Appropriate treatment of asthma can result in a dramatic reduction in symptoms and suffering and improvements in functional capacity for the individual. Thus families and society also benefit from appropriate management of asthma. It seems logical to provide private and public funding for medical services to help patients with asthma prevent most asthma symptoms and exacerbations as well as to treat promptly those exacerbations that do occur. Particularly those from lower income and social strata and children may benefit from social financing of care. As noted earlier, children with asthma are at risk for poor scholastic achievement and possibly poor social development when their asthma is uncontrolled. In addition, public financing for a few Centers of Excellence in Asthma Management may be worthwhile because these centers could act as resource centers for educational and preventive programs and materials, referral centers for

difficult-to-manage cases, and multidisciplinary centers for collaborative clinical and health services research, including cost-effectiveness analyses for health planning.

In many countries, health care and the costs associated with asthma care are fully financed by national programs. Where they are not, special considerations, perhaps involving government agencies, should be given to providing full coverage for asthma care. In particular, the provision of necessary primary and secondary prevention programs should be given priority consideration. Effective primary prevention programs have the potential—which needs to be researched—to effect substantial reductions in the total social costs of asthma especially when targeted to at-risk individuals and families. Financing for prevention should include an allotment for education of health professionals about the nature and implementation of effective strategies. Secondary prevention of asthma exacerbations also should be appropriately financed, especially when delivered in the ambulatory setting, perhaps starting with appropriate resources being made available for pharmacotherapy that adequately controls the asthma. Asthma care is most expensive when patients are treated in hospitals or emergency departments. If an appropriate level of funding is made available by private and public sources, access to primary care services may reduce the need for more costly hospital-based care.

Private and public funding of primary and secondary prevention strategies should include investment in research to determine the costs and benefits of individual programs and therapies for the patients with asthma targeted by these strategies. For example, before substantial redistribution of resources is made for a new intervention, at least one cost-effectiveness study should be undertaken to determine the incremental value to the patient and society of the new intervention relative to the existing programs.

In determining the financing of asthma care and allocation of resources within any country, many factors must be considered. These include the prevalence of asthma in the community, the existing costs of asthma (both direct and indirect), the effectiveness of alternative interventions, and the relative value of the externalities associated with asthma as compared with other chronic and acute illnesses pertinent to that country.

It is expected that in time the use of the concept of disability-adjusted life years (27) will allow for cross comparison of the burden of illness. Use of this measurement will allow for the comparison of cost effectiveness for asthma care interventions with interventions for other illnesses.

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## EXPLORING THE COSTS OF ASTHMA: AN ILLUSTRATIVE CASE STUDY IN TRANSKEI

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Planning and establishing a public health program for asthma requires information about the cost of the intervention and the cost of the illness. Published cost-of-illness studies are mostly from developed countries. Because it cannot be assumed that developing countries have similar cost experiences, a case study in Transkei was undertaken in 1993 specifically for this report. The case study, described in this section, provides the opportunity to look at illness costs in one developing country and illustrates how routinely collected information can be used to conduct a cost-of-illness evaluation of asthma.

### Setting

The Republic of Transkei is one of the black homelands in South Africa. It has a total land area of 43,653 square kilometers with a population of 4.5 million people, of whom 95 percent live in rural areas. It is situated between latitudes 30 and 33 south and longitude 27 and 30 east in the drought-prone area of southern Africa. Transkei borders on Lesotho and the Republic of South Africa, and on the Indian Ocean to the southeast. The climate is subtropical, with temperatures in general ranging from between 18 to 22°C in summer and 7 to 14°C in winter.

Transkei, essentially a developing country, has an as-yet poorly developed health and social services system. Health services are provided by the government through 30 hospitals, with a total bed capacity of 7,600. Promotive, preventive, and some curative services are provided in 280 rural day clinics spread all over the country and managed principally by nurses. These clinics also provide long-term treatment for such conditions as tuberculosis, hypertension, mental health, and asthma. Nursing staff at these clinics do not make diagnosis or initiate definitive treatment; they administer maintenance care following the treatment protocols of health care professionals initiated at the government-sponsored hospitals.

Umtata General Hospital, a tertiary-care hospital located in the capital city, is the main teaching center for the medical school of the University of Transkei. Because of facility shortages and a low doctor/patient ratio, adequate specialist services and emergency department care are not provided in this center.



Medical care use information is routinely collected on all patients attending all government health units. This information includes time of attendance, demographic characteristics, diagnosis, treatment given, and, where applicable, the period of hospitalization. Problems of completeness and accuracy of data related to collection of routine health data apply here as elsewhere in the developing world.

### Methods of Data Collection and Analysis

The case study used available medical care utilization and cost data and, where possible, provided estimates of the indirect burden of asthma. Evaluation was made from the perspective of the government, which pays for the medical care services in Transkei. Reported on in the study were the following elements of asthma's cost:

- Asthma-related medical care utilization and associated costs
- Estimates of the indirect burden of asthma to the individual and his or her family
- The share of country resources allocated to asthma treatments
- The societal and individual asthma burden.

The case study used the cost-of-illness method, which has been comprehensively discussed by Hodgson and Meiners (28) and more recently by Hodgson (15). The method is based on the link between disease morbidity and social opportunity costs (21). In a chronic illness such as asthma, the sustained chronicity and frequent periods of acute exacerbation define morbidity. Persistent fluctuations in morbidity determine, in part, the social and economic impact of the illness on the individual and family. The cost-of-illness method empirically describes the economic consequences of illness on individuals or populations.

The analytic components of the method include characterization of direct medical care utilization and costs; indirect, nonmedical care consequences; and economic ramifications of the social illness burden borne by the individual or society. The results of such an inquiry can be expressed as annual or lifetime illness costs for the population of affected individuals and compared to similar costs derived from other diseases.

Data exist on asthma costs in several developed countries,

including the United States, Australia, the United Kingdom, and Sweden (21). Published reports from developing countries are lacking, in part because of few available data. Information on medical care use is often incomplete, especially on treatment for chronic diseases managed out of hospital. In most countries, specific data on indirect costs are usually nonexistent, although these costs can be estimated either from small surveys of affected individuals or by extrapolating from available data (29). The valuation methods for the social impacts of illness are not well defined (30) and have generated significant debate among health services researchers. Methodologists continue to make advances in refining utility estimation and scales of quality of life or general well-being without much agreement about how to estimate the associated economic consequences.

It is against this background that the Transkei study collected available medical and nonmedical utilization and cost data on a sample of patients with diagnosed asthma requiring treatment for their asthma. Individuals with undiagnosed asthma, or those not receiving medical treatments for asthma, were not represented, although the investigators suspected that the number of such individuals in Transkei was significant.

Using the cost-of-illness method (described by Hodgson and Meiners [28]), information was gathered on medical care use and costs of patients with diagnosed asthma from an approximate 10 percent sample of hospitals and rural clinics in Transkei during the 12-month period January to December 1992. The sampling scheme resulted in selection of 2,302 asthma-related medical care events from four hospitals and 26 rural clinics.

Data on the following utilization variables were collected:

- **Hospital care.** Defined as asthma-related admissions requiring more than 24 hours of observation in the hospital.
- **Observation stays (hospital emergency care).** Defined as receiving emergency care were patient visits requiring aminophylline, epinephrine, or hydrocortisone injection or nebulization with oxygen or ventolin and requiring observation in a hospital for less than a 24-hour period. No emergency care departments exist in the country except at the tertiary-care hospital.
- **Rural clinic visits.** Defined as the number of asthma-related routine maintenance or primary care visits to the rural clinics for patients either previously or newly diagnosed with asthma during the year. Asthma care at the clinics is delivered primarily by registered nurses.



- **Medication and other treatment costs.** Defined as the total number of prescription medications dispensed to patients with asthma whether as part of inpatient or outpatient care. Prescriptions for coexisting conditions and antibiotics are not included in the cost estimates.

Medical care service unit costs were provided by the Transkei study investigators. These data reflected actual costs incurred by the health care system in the country and therefore represented the social opportunity cost of medical resources consumed. Hospital and observation stay costs were estimated to be 80 rand per patient day; rural clinic visit costs were estimated to be 20 rand per visit; and the actual cost of each medication was provided.

The completeness and validity of data were of some concern, but they are nonetheless consistent with what is possible for such a study given data available, collection methods, cost, and the short timeframe for conducting the study. The unit of analysis was the visit and not the patient. The data collectors were unable to acquire patient identifiers; therefore how many patients are represented by the total number of visits is unknown. The prevalence of asthma has been estimated for Transkei at approximately 1 percent, or roughly 45,000 individuals.

In two of the four hospitals selected, not all information on medical care utilization was recorded. In addition, a fair amount of the data did not contain patient demographic information. Within these limitations, figures 8-3 and 8-4 illustrate the distribution of visits by age, sex, and month of visit. The somewhat lower figures reported in April and May are likely due to omission or loss of data (records).

## Findings

Figures 8-5 through 8-7 show that there were a total of 2,302 asthma-related medical care events during the year. Of these, 108 were for inpatient hospital care; 44 were for emergency observation stays; and the remaining 2,150 were for clinic visits. For the 108 hospitalizations, the average length of stay was estimated to be 9 days. The figures further display the age and sex variation of these visits. It is noteworthy that in the four study hospitals, 21 out of 2,600 deaths were patients with asthma. Note that travel delays usually mean late arrival to the hospital in worse condition.

Of those patients for whom demographic data were available, a large proportion of the hospitalized patients were age 60 and above. Upon discharge, this group of individuals generally requires more organized family or social support within the community. Such support is

frequently lacking because family members must tend to work activities.

Figure 8-8 depicts the type, frequency, and annual cost of asthma-related medications. No data existed on the extent of compliance with long-term therapy, although it was known to be problematic. In Transkei the use of potentially cost-effective medications such as inhaled corticosteroids is hampered by the cost. Individuals who would benefit from inhaled anti-inflammatory therapy rarely receive this medication. As a result, the condition of these patients may become worse, which often leads to more costly hospital or emergency care.

Figure 8-9 presents a summary of medical utilization and costs for asthma-related treatments during the 1-year study period. The total direct medical care costs were 157,760 rand. Fifty-two percent of total costs were hospital-based expenditures. Even if it is assumed that each hospital visit and hospital observation stay represented a different patient (and it is more common for patients to have multiple visits), then it is striking to see that 52 percent of direct medical care costs were borne by relatively few patients.

The case study examined the estimated medical care utilization and associated costs for asthma in Transkei. Although specific measurements were beyond the scope of this study, there are substantial indirect costs of asthma in this community that can be broadly estimated. For example, individuals with prolonged severe bronchospasm requiring acute medical attention can only be managed in the hospital setting. Most patients live far from the hospital and are frequently unable to arrange expedient transportation. Travel itself to the hospital or clinic usually means a day's income lost, or in the case of family farms, arrangements must be made to tend to the work either through other family members or by hiring assistance. The average annual per capita income for Transkeians was 1,428 rand (1990). For an individual with an average hospital stay of 9 days and 1 day travel time and cost each way, lost productivity can amount to a significant cost. Using current income, such a person would lose about 43 rand in wages per hospitalization, assuming no posthospital convalescence. Although not calculated, the indirect cost of premature death due to asthma may also be significant in Transkei, considering the 21 deaths in the four study hospitals.

Indirect costs also take into consideration the fact that suboptimally treated asthma may lead to frequent days of disability due to shortness of breath, wheezing, coughing, and loss of sleep. For the children of Transkei, this may mean they are unable to go to school, to perform in all

**Figure 8-3. 1992 Annual Distribution of All Asthma-Related Attendances (Rural Clinic Visits, Observation Stays, and Hospitalizations) by Age and Sex --An Illustrative Case Study in Transkei**

Age (years)	Female	Male	Unspecified	Total	Percent of total
0-19	77	83	2	162	7.0
20-59	754	351	5	1,110	48.2
60 +	472	278	2	752	33.7
Unspecified	182	92	4	278	12.1
Total	1,485	804	13	2,302	100.0

**Figure 8-4. Distribution of Visits by Month --An Illustrative Case Study in Transkei**

Month (1992)	Total	Percent of total
January	106	4.6
February	135	5.9
March	115	5.0
April*	83	3.6
May*	67	2.9
June	176	7.6
July	283	12.3
August	500	21.7
September	179	7.8
October	105	4.6
November	106	4.6
December	216	9.4
Unspecified	231	10.0
Total	2,302	100.0

\* The lower figures recorded in April and May are more likely due to omission or loss of data than the expected pattern.

**Figure 8-5. Asthma Hospital Admissions (More Than 24 Hours) by Age, Sex, and Length of Stay**  
**--An Illustrative Case Study in Transkei**

<b>Age (years)</b>	<b>Total</b>	<b>Percent of total</b>
0-19	12	11.1
20-59	27	25.0
60 +	42	38.9
Unspecified	27	25.0
<b>Sex</b>		
Female	61	56.5
Male	47	43.5
<b>Length of Stay</b>		
2-7 days	49	45.3
8-14 days	37	34.3
Over 14 days	14	13.0
Unspecified	8	7.4
<b>Total</b>	<b>108</b>	<b>100.0</b>

**Figure 8-6. Asthma Emergency Observation Stays (More Than 24 Hours) by Age and Sex**  
**--An Illustrative Case Study in Transkei**

<b>Age (years)</b>	<b>Female</b>	<b>Male</b>	<b>Total</b>
0-19	2	3	5
20-59	6	2	8
60 +	14	7	21
Unspecified	5	5	10
<b>Total</b>	<b>27</b>	<b>17</b>	<b>44</b>

Figure 8-7. Asthma Clinic Visits by Age and Sex--An Illustrative Case Study in Transkei

Age (years)	Female	Male	Unspecified	Total	Percent of total
0-19	70	73	2	145	6.7
20-59	729	341	5	1,075	50.0
60 +	434	253	2	689	32.1
Unspecified	164	73	4	241	11.2
<b>Total</b>	<b>1,397</b>	<b>740</b>	<b>13</b>	<b>2,150</b>	<b>100.0</b>

Figure 8-8. Type, Frequency, and Annual Expenditures for Inpatient and Ambulatory Prescribed Drugs (in 1992 Rand) --An Illustrative Case Study in Transkei

Drug	Number of prescriptions	Annual cost (rand)
<b>Xanthines</b>		
Aminophylline (Inj)	119 *	5,205.72 **
Aminophylline (Syr)	8	1.04
Aminophylline (Tab)	1,455	5,238.00
Theophylline (Tab)	276	4,857.60
<b>Steroids</b>		
Hydrocortisone (Inj)	77 <sup>a</sup>	3,390.12
Prednisone (Tab)	99	297.00
<b>Beta<sub>2</sub>-adrenergic stimulants</b>		
Ventolin (Inh)	798	7,581.00
Ventolin (Tab)	1,286	4,629.60
Ventolin (Syr)	8	1.60
Berotec (Inh)	134	1,541.00
Ipradol (Inh)	4	92.40
<b>Prophylactic drugs</b>		
Becotide (Inh)	43	645.00
<b>Total<sup>†</sup></b>	<b>4,307</b>	<b>33,480.08</b>

\* Number of hospitalized patients receiving drug.

\*\* Includes the cost of normal saline solution.

† Excludes antibiotics and other drugs.

**Figure 8-9. Direct Medical Care Expenditures on Asthma Treatments (in 1992 Rand)**  
**--An Illustrative Case Study in Transkei**

Medical care service	Number of units	Price per unit	Expenditures (rand)	Percent of total
Inpatient hospitalization	108 admissions 9 days ALOS	80 rand per day	77,760.00	49.3
Emergency observation	44 visits	80 rand per visit	3,520.00	2.2
Clinic visits	2,150 visits	20 rand per visit	43,000.00	27.3
Medications	4,307 prescriptions	Variable	33,480.08	21.2
<b>Total</b>			<b>157,760.08</b>	<b>100.00</b>

**Figure 8-10. Direct Medical Care Costs for Asthma (in 1992 Rand)**  
**--An Illustrative Case Study in Transkei**

Medical care service	Expenditure in sample	Multiplier*	Total costs (rand)
Inpatient hospitalization	77,760.00	7.5	583,200.00
Emergency observation	3,520.00	7.5	26,400.00
Clinic visits	43,000.00	10.8	464,400.00
Medications	33,480.08	10.8	361,584.86
<b>Total</b>			<b>1,435,584.86</b>

\* Four of 30 hospitals and 26 of 280 clinics were included in the sample.



school activities, and to help with family chores and thus contribute to the family's economic productivity. For adults, disability due to asthma clearly leads to loss of productivity. These types of indirect costs relating to illness can significantly impact a community's economic health. Estimating these costs for developing countries can be done by using a formula designed for one chronic illness (schistosomiasis) in a developing country or by using a generally accepted ratio for developing countries. Indirect costs may range from 50 to 100 percent of direct costs.

Generalizing these costs to the entire country and then comparing these to the overall health care budget illustrates the level of resources devoted to management of this condition. Figure 8-10 depicts the total direct medical care costs for asthma for the entire country. In Transkei, the government health budget exceeded 380,800,000 rand per year. Thus, direct medical expenditures for asthma represented only 0.38 percent of total annual medical expenditures, suggesting the relative priority of this disease. Using an estimate of 45,000 people with asthma in the country, expenditures per person with asthma were about 31.91 rand, or about \$10 (U.S.).

Compared with asthma care expenditures in developed countries (see figure 8-1), this amount per person with asthma might at first seem trivial. However, for a developing country's economy, such as that of the Transkei community, this expenditure may still be notable given the possibility that alternative treatments for more people with asthma may cost less, and given the sizable indirect costs of asthma such as the lost productivity reflected in the 9-day average length of hospital stays.

Within a developing country such as Transkei, implementation of health services is hampered by the lack of infrastructure and capital. Resource constraints are tremendous, necessitating the use of data that can be used for planning. Cost-of-illness studies should be viewed as a means to an end. Knowledge of the use and cost of medical care services can frame important cost-effectiveness questions about alternative treatment strategies and the potential efficiencies to society for allocating resources or the possible inefficiencies from restricting expensive treatment, such as inhaled anti-inflammatory agents. The cost-of-illness method presents a process that health planners can use to focus on important resource allocation questions in the context of all diseases and the total health care budget.

Knowledge of these costs of illness provokes the next set of health policy questions for this community: Are there

adequate health care services for patients with asthma within Transkei? Relative to other health care needs, are persons with asthma receiving proportionate services? How does the Transkei community spend its asthma-related dollars across categorical services such as hospital care versus ambulatory care? Are medication expenditures for asthma adequate and appropriate? These basic questions help focus on the difficult issues relative to cost effectiveness of care for this condition.

## Applications

From a strictly economic perspective, the burden of asthma is substantial to governments that pay for care and lose the benefits of productivity as well as to individuals or families that are affected by the condition. Patients with asthma in developed countries consume about \$350 to \$500 (U.S.) per year in direct medical care expenditures. This contrasts with data from the country of Transkei, where patients with asthma consume only about \$10 (U.S.). When the indirect costs of disease such as lost wages from missing work or the cost of paying for expensive child care are added, the cost of asthma per patient increases to over \$600 to \$800 (U.S.). Comparable figures for developing countries such as Transkei are lacking because there are few data on indirect costs.

Based on descriptive data from cost-of-illness studies alone, it is not possible to evaluate definitively the efficiency of the use of medical care resources and the equity or social justice implications of resource allocation. However, by applying the tools of economic evaluation—including cost-effectiveness and cost-benefit analyses—efficiency can be evaluated, the current allocation of existing resources can be assessed, and decisions on whether or not to purchase new medical technology can be effectively made. An illustration is the case of inhaled corticosteroids. In 1992 in Transkei, only 43 prescriptions were written for beclomethasone. The annual cost of providing beclomethasone to a patient in Transkei is equivalent to the cost of 2.25 days in the hospital, or roughly one-fourth of a typical asthma-related hospitalization. Thus making these agents available to those at greatest risk of hospitalization seems sensible. In addition, such simple public health measures as domestic mite control and education about asthma (as outlined in the chapter on management of asthma) could lead to significant total reduction in asthma-related expenditures.

From a prevention point of view, it may be important to assess whether inhaled corticosteroids given early in life prevent or significantly reduce the long-term morbidity of asthma. Some research has indicated that delaying the

introduction of inhaled corticosteroids may result in irreversible lung changes (31-33). Inhaled corticosteroids may prevent or slow irreversible changes to the airways that may then reduce the long-term consequences of asthma. Because lifetime illness costs may thus be reduced (34), the economic implications are profound for those who finance asthma care.

Asthma represents a substantial social and economic burden in developing as well as developed countries. Although there are some useful studies in developed countries on socioeconomic burden, similar studies such as those described in this chapter—on social impact in Andhra Pradesh and economic impact in Transkei—demonstrate how important the impacts of asthma are on developing countries. Cost-of-illness and economic evaluation studies can highlight where resources could potentially be used more effectively.

## RESEARCH RECOMMENDATIONS

- Studies examining the quality of life of individuals with asthma need to be considered for many countries in which asthma is not as yet perceived to be contributing to the overall burden of illness. These studies should follow those studies discussed in the chapter on epidemiology.
- Cost-of-illness studies need to be conducted for a number of developing countries to provide the basis for health program planning. These studies should examine both direct medical expenditures and indirect costs.
- Each country may design county or region-specific asthma control programs based on methods outlined in the chapters on prevention and on education and the delivery of care. These intervention programs should include cost-effectiveness approaches specific to national health resources and based on cultural acceptance.
- Each community should examine a range of alternatives, including public health strategies aimed at reducing exposure to respiratory allergens and pollutants as well as primary care strategies based on education and pharmacotherapy.
- As asthma control programs are developed, there is a concomitant need to develop and implement a monitoring process to evaluate success of the interventions. Communities should not only evaluate the success of interventions but also be prepared to remove (not fund) those interventions that prove to be cost ineffective.

- Additional research is needed to examine the optimal cost-effective strategies and, in particular, to examine how best to balance resource expenditures for prevention versus pharmacologic control.

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# CHAPTER

9

## ***EDUCATION AND THE DELIVERY OF CARE***

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## KEY POINTS:

- National and international guidelines may be helpful, but to be effective they need adaption for local use and should be incorporated into district protocols and formularies. Such adaption should be undertaken by local asthma planning teams to ensure relevance and ownership.
- 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.
- Clear communication is the key to good compliance.

How can we ensure that the effective treatments now available for asthma benefit each and every patient? Treatment must reach the patients—and be used. A successful outcome depends upon a health system in which the value of clear communication and education is recognized. Thus the following are essential:

- 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 finance should be available to governments or individuals to ensure that asthma treatments are available.
- Patients should use the asthma treatments correctly.

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.

Research has shown that currently there are deficiencies in most of these four essentials. For example, delays in diagnosis are common (1) and lead to inappropriate (nonasthma) treatments being given. In other cases, severity is underestimated with the result that preventive

therapy is underused (2, 3). One study showed that 74 percent of those admitted to the hospital with severe asthma could have had the admission prevented by different prior care (4). Surveys of deaths from asthma have shown that nearly 90 percent of cases involve avoidable factors (5). Care in hospitals has also been shown to be associated with different outcomes depending upon whether care was by a respiratory specialist, by a generalist, or by a physician with an interest in another specialty. This may mean up to a tenfold difference in the chances of a patient being readmitted with a further exacerbation within a short time (6). Other 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 (7-9).

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 9-1. Education includes education about primary prevention, secondary prevention, and management of asthma. This chapter thus considers the organization and education of health professionals, patient education, and the education of others whose actions may impinge upon those with 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. Likely members of such a team are shown in figure 9-2. Countries will vary so much for reasons of economics, culture, and environment that the priorities and problems presented to each planning team will vary considerably. Some of the issues that need to be considered are shown in figure 9-3.

### Guidelines

It may be useful for these planning teams to establish and use guidelines. Guidelines on the management of asthma not only help set standards of clinical care and may serve as a basis for audit, but they also act as a starting point for the education of health professionals. Guidelines may therefore be used to ensure that all members of the health care team are aware of the goals of treatment and of the different ways of achieving these goals. Sections on referral patterns may be used as a basis for deciding how different patients are cared for and as a basis for working out shared care protocols. However, whether national guidelines (10, 11) or international guidelines (12), it is



**Figure 9-1. 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).

### **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, coaches
- Patients (and their families and loved ones).

### **What to educate?**

- Information about the guidelines
- Information about the diagnosis
- Information about prevention
- Training in (guided) self-care
- 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.
- Recognize that patient education involves:
  - the giving of information and the acquisition of skills
  - the altering of behavior by the patient.
- Good communication and the development of a partnership between patients and health care professionals are essential if barriers to education are to be overcome.
- Monitoring, auditing, and the 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.

**Figure 9-2. 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
- Medical sociologists
- Health economists

**Figure 9-3. Checklist of Issues for National or District Asthma Planning Teams**

- What is the size of the problem of asthma in this country or district?
- Who will provide the bulk of care in the area (primary care or hospital, doctor or nurse, self-help groups)?
- 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?
- Which 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 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)?

unlikely that their production alone will reduce morbidity. The only national audit undertaken before and after the introduction of national asthma guidelines looked at their impact on the hospital care of acute severe asthma. This audit showed that specialist care was better than generalist care in both years but that, with one minor exception, there was no specific improvement in the measured parameters after the introduction of the guidelines (13).

It is therefore likely that such guidelines have to be taken to a local level so that there may be a greater feeling of ownership and relevance. Where this has been done, for example, in an accident and emergency department (14) or within one health district (15), serial audit can be shown to demonstrate improved care and a reduction in morbidity following the introduction of guidelines.

Guidelines are often most useful when they include summary charts of the key recommendations for diagnosis and management because the charts can be easily copied so that all grades of health care professionals may have them near to hand when advising patients. The International Consensus Report (12), for example, includes summary charts of the stepwise approach to asthma therapy for long-term management of asthma, of the severity of asthma exacerbations, and of the management of exacerbations at home and in the hospital. For another example, the British guidelines were published both as part of the whole report and separately (10).

Such guideline documents, however, often take asthma as their starting point, and it may be helpful to see the condition within the whole context of respiratory medicine. Therefore, this chapter first provides summary figures that place asthma in context: Figure 9-4 displays an overview of lung diseases; figure 9-5 looks at differential diagnosis; and figure 9-6 provides patient history key questions. These are followed by figures 7-4 and 7-6 (repeated from the chapter on management of asthma), which summarize the long-term management of asthma in adults and children. Any or all of these figures may easily be reproduced for use by health care professionals.

### 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 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. To do this effectively

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 inhaler technique?
- 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?

To audit **outcome**, ask:

- Has there been any sleep disturbance due to asthma?
- Has asthma led to time off from work or school?
- Has use of reliever medication increased?
- Has urgent medical attention/treatment been needed?

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## PATIENT EDUCATION

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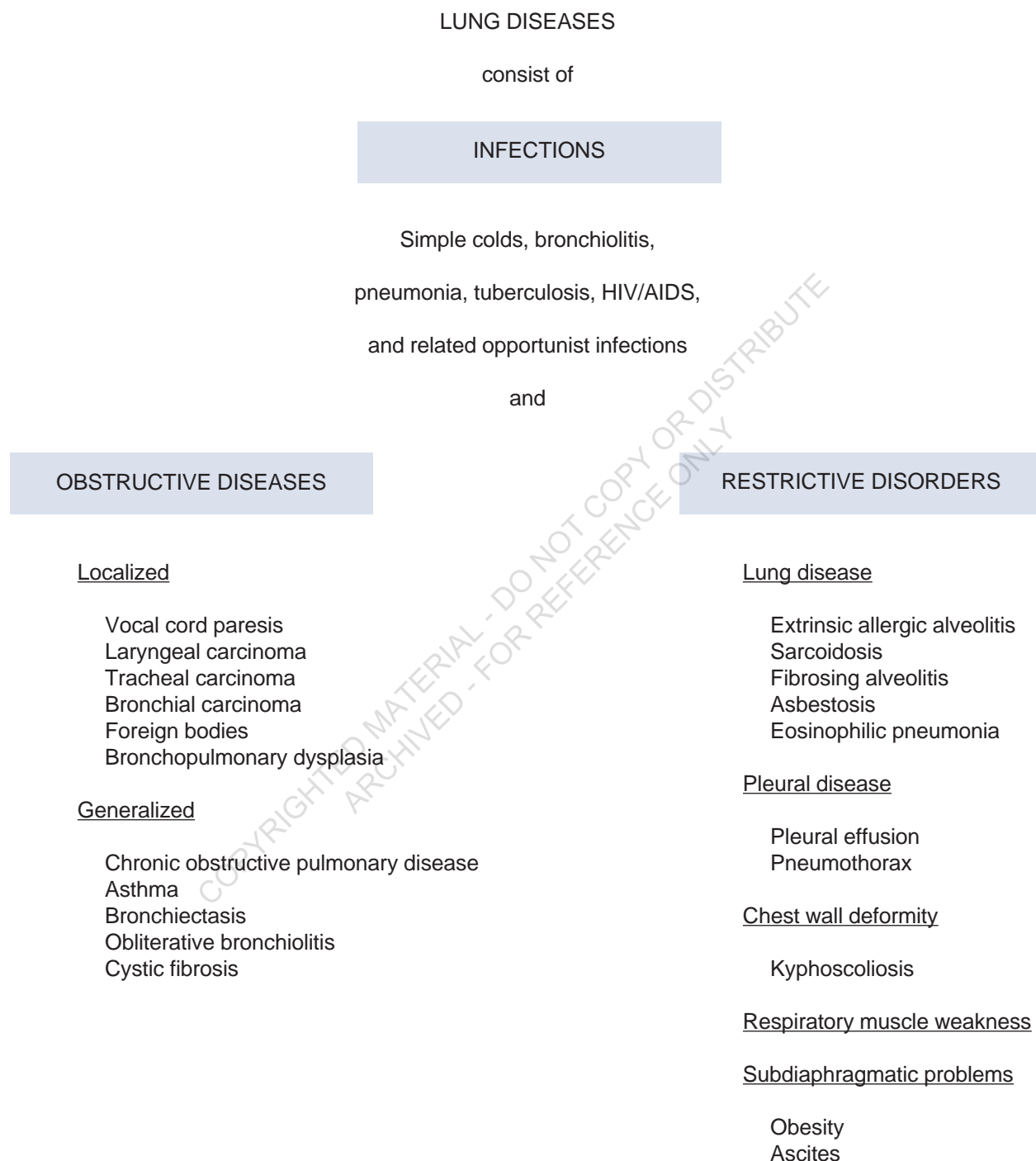
The aim of patient education, which is a continual process, is to provide the patient with asthma and the patient's family with suitable information and training so that the patient can keep well and adjust treatment according to a medication plan developed with the health care professional. The emphasis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

### Improving Compliance

As better education of health care professionals ensures that patients are prescribed the most appropriate treatments, how can we ensure that the treatments will be taken? How can we measure or elicit noncompliance? How can we improve compliance?

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. Studies of adults and children (16) have shown noncompliance rates of around 50 percent with the taking of regular preventive therapies. Noncompliance may be elicited by prescription monitoring, pill counting, or drug assay, but at a clinical level it is best detected by asking about therapy in a way

**Figure 9-4. Overview of Lung Diseases**

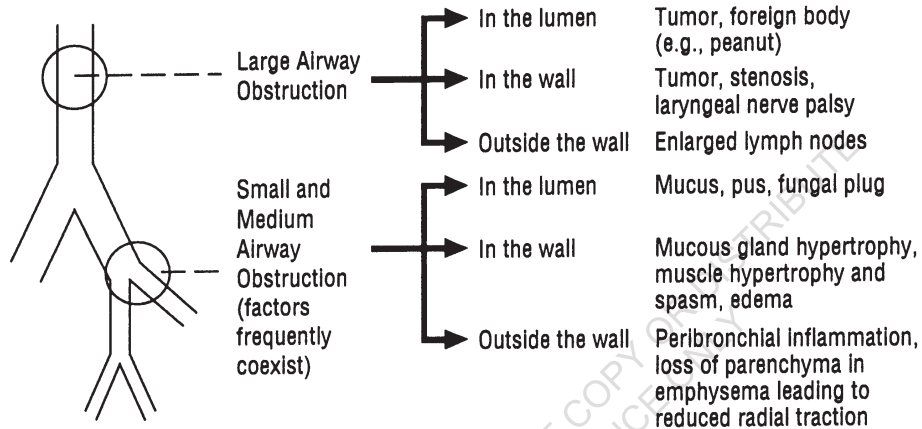




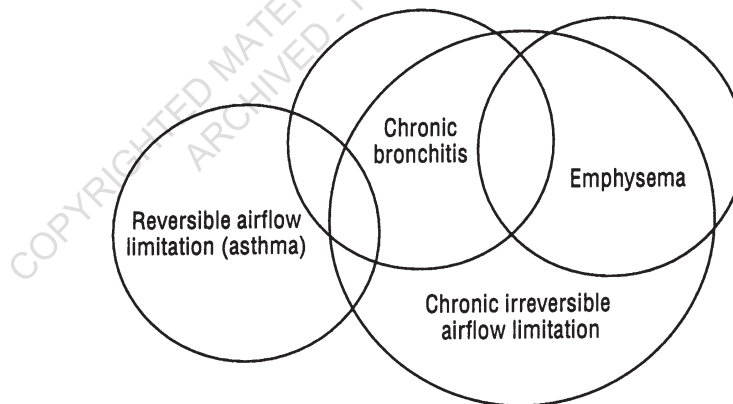
**Figure 9-5. Differential Diagnosis of Obstructive Airway Diseases**

**WITH AIRWAY-TYPE SYMPTOMS  
OF COUGH, WHEEZING, BREATHLESSNESS, AND  
AIRWAY NARROWING (OBSTRUCTIVE SPIROMETRY, PEF)**

**ALWAYS THINK: IS OBSTRUCTION  
LOCALIZED OR GENERALIZED?**



If generalized be sure to differentiate



Venn diagram showing the interrelationship among chronic bronchitis, airflow limitation, emphysema, and asthma. An overlap is shown because with time and under treatment some of the airflow limitation associated with asthma may become fixed, and in "irreversible" airflow limitation a small degree of response to bronchodilators is often shown.

A steroid may be necessary to place an individual in the left- or right-hand side of the Venn diagram.

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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 9-7. In general, however, compliance can be increased:

- 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.

Thus the aims of patient education are to:

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

But patient education involves more than providing information and patient acquisition of skills in inhaler technique and peak expiratory flow rate monitoring. Patient education also involves an alteration in behavior. This will occur only if the patient is given adequate opportunity as part of the educational process to express his or her fears and concerns, and if the patient is able to discuss with the health care professional his or her expectations of the condition and its treatment and to hear how realistic those expectations are. It is important to remember that when, for example, a patient fears possible side effects from the medication, or a mother wants to know if her child will grow out of asthma, such concerns must be discussed or they will act as barriers to subsequent educational efforts. Furthermore, listening to the patients' concerns about treatment or their ability to follow the recommended treatment plan may help the health care professional adjust the plan so that it is more practical or acceptable to patients. This effort to develop a plan in partnership with patients may improve compliance.

## Effective Methods

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
- 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
- Other innovative methods such as through drama.

In evaluations of these methods, patients have shown preference for learning about the condition by listening to the health care professional or by watching a video (17). However, effectiveness does not always equate with preference. One study showed patients preferring a book to an audiotape, but the latter was actually more effective in terms of knowledge gained (18). Further, although studies may demonstrate that patient knowledge can be improved, interventions involving the giving of material alone do not necessarily lead to reduction in morbidity (19). What can lead to improved control of asthma, according to recent studies (20, 21), are more interactive educational interventions coupled with personalization of advice. For example, three educational sessions on asthma conducted by a specially trained nurse may be sufficient to reduce significantly 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 (22). 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 adherence/compliance, with the benefit shown to extend over a 12-month period (23).

Discerning which component of an intervention (giving information, closer medical care, or followup and enhanced supervision) has been most effective is not always easy. What is probably most effective is to give

**Figure 9-6. 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 antiasthma 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 for respiratory symptoms.

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

**Figure 9-7. 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 followup
- Anger about condition or its treatment
- Underestimation of severity
- Cultural issues
- Stigmatization
- Forgetfulness or complacency
- Attitudes toward ill health
- Religion issues

**Figure 7-4. The Long-Term Management of Asthma: Treatments in the Stepwise Approach**

The aim of treatment is control of asthma.

Outcome: Control of Asthma

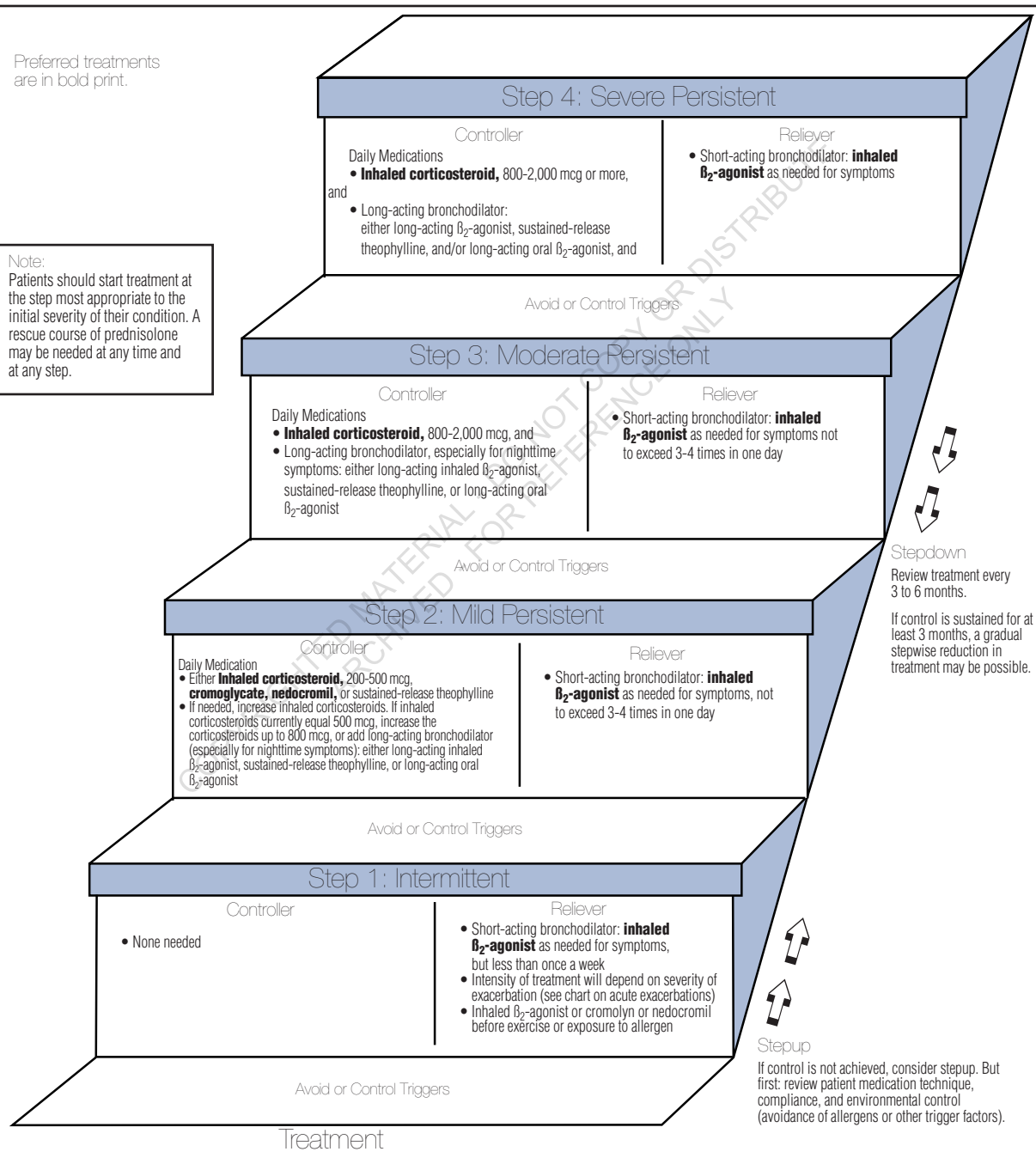
- Minimal (ideally no) chronic symptoms, including nocturnal symptoms
- Minimal (infrequent) episodes
- No emergency visits
- Minimal need for prn  $\beta_2$ -agonist

- No limitations on activities, including exercise
- PEF circadian variation <20%
- (Near) normal PEF
- Minimal (or no) adverse effects from medicine

Preferred treatments are in bold print.

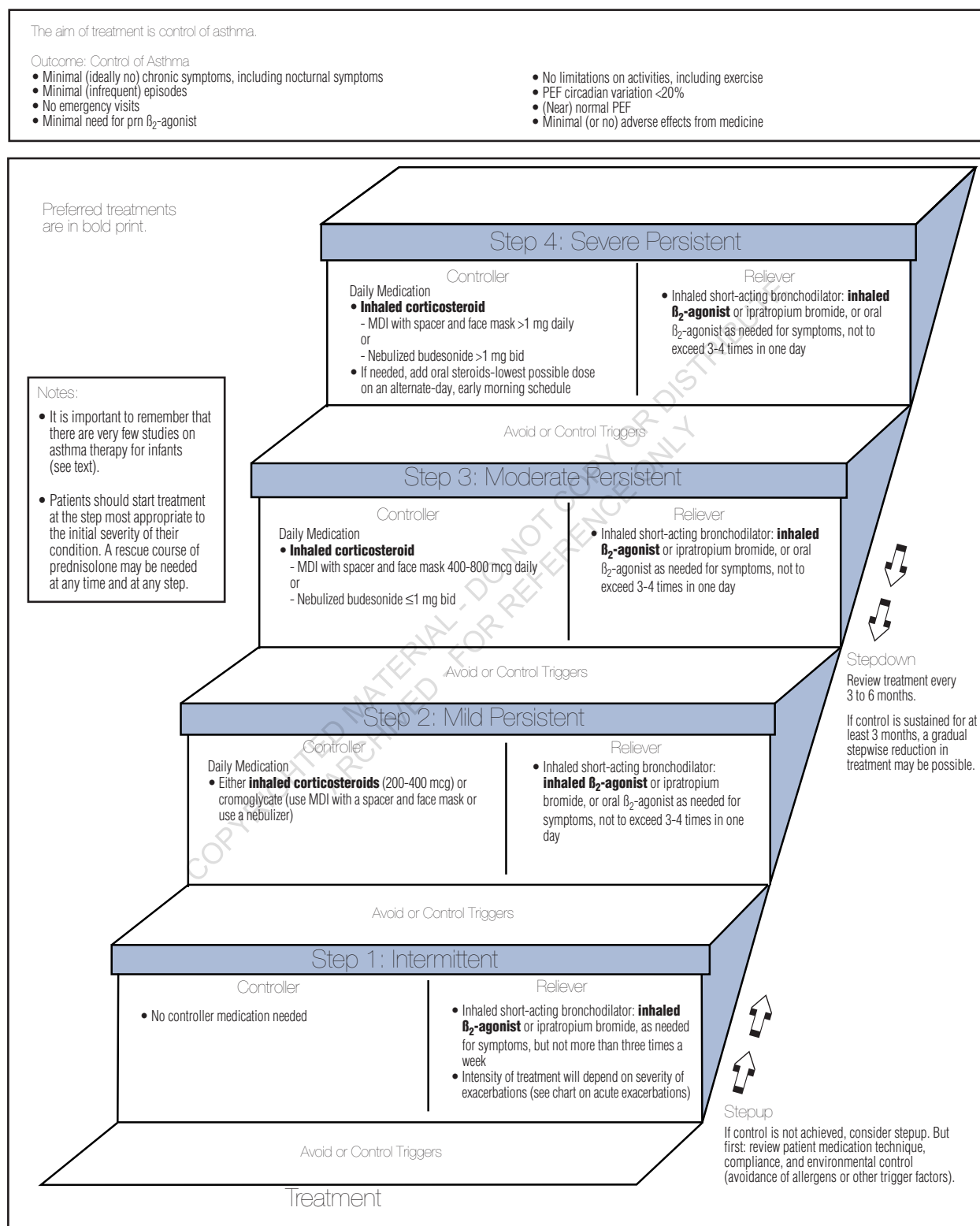
Note:

Patients should start treatment at the step most appropriate to the initial severity of their condition. A rescue course of prednisolone may be needed at any time and at any step.





**Figure 7-6. The Long-Term Management of Asthma: Treatments in the Stepwise Approach for Infants and Young Children**



information verbally and then by several other routes—with those routes selected on the basis of patient education status and literacy level. (Instruction via videos or drama may be for many more appropriate than leaflets.) Health professionals must not only provide information, teach inhaler skills, and promote an understanding of asthma triggers and the signs that indicate asthma is worsening. They must also assure good communication between the health care professionals and patients, thus giving patients adequate opportunities to express their fears and concerns and discuss their expectations and treatments. This is essential if satisfaction and compliance are to be increased (24, 25).

### **Individualizing Education in a Stepwise Manner**

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 9-8 outlines the basic features of a patient education program, and figure 9-9 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.

### **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. Figure 9-10 illustrates some of these devices; more 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 (10).

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 the patients' level of expectations. For most patients it is reasonable for them 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) 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 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. The patient should receive training in how to measure and record PEF (see figure 9-11). 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.

### **Figure 9-8. 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 (see figure 9-9)
- Signs that suggest asthma is worsening
- 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 9-9. Prevention: A Patient Checklist**

**What should I avoid?**

- Active smoking
- Passive smoking
- Beta blockers (tablets and eye drops)
- Aspirin (and NSAID's) 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?**

- Domestic mites
- Other common allergens
- Adverse occupational environments
- Foods and additives
- Certain types of exercise in certain climatic conditions
- Adverse indoor environments

**What should I always undertake, if necessary by adjusting treatment?**

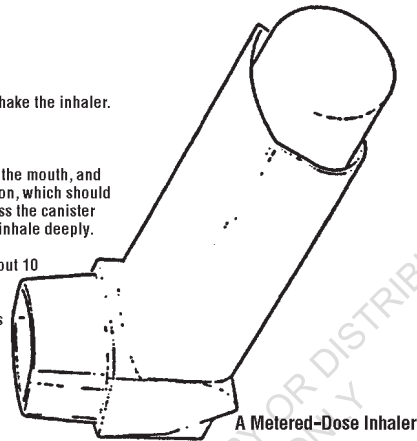
- Normal social activities
- Exercise
- Sports

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

**Figure 9-10. How To Use Inhalers\***

## HOW TO USE A METERED-DOSE INHALER

1. Remove the cap and shake the inhaler.
2. Breathe out gently.
3. Put the mouthpiece in the mouth, and at the start of inspiration, which should be slow and deep, press the canister down and continue to inhale deeply.
4. Hold the breath for about 10 seconds.
5. Wait about 30 seconds before taking another inhalation.

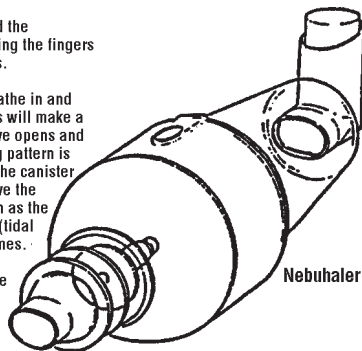


ALWAYS DEMONSTRATE TO THE PATIENT HOW TO USE THE METERED-DOSE INHALER

## HOW TO USE A SPACER DEVICE e.g., NEBUHALER

Method particularly useful for young children

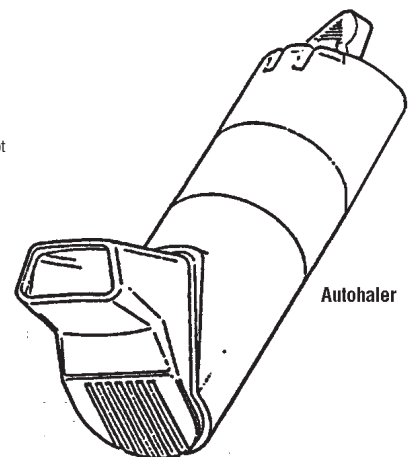
1. Remove the cap, shake the inhaler, and insert into the device.
2. Place the mouthpiece in the child's mouth (if using the Nebuhaler be careful the child's lips are behind the ring).
3. Seal the child's lips around the mouthpiece by gently placing the fingers of one hand around the lips.
4. Encourage the child to breathe in and out slowly and gently. (This will make a "clicking" sound as the valve opens and closes.) Once the breathing pattern is well established, depress the canister with the free hand and leave the device in the same position as the child continues to breathe (tidal breathing) several more times.
5. Remove the device from the child's mouth.



ALWAYS DEMONSTRATE TO THE PATIENT HOW TO USE THE NEBUHALER

## HOW TO USE THE AUTOHALER

1. Remove protective mouthpiece by pulling down lip on back of cover.
  2. Hold the inhaler upright and push the lever up; then shake the inhaler.
  3. Breathe out gently. Keep the inhaler upright and put the mouthpiece in the mouth and close lips around it. (Do not block air vents at bottom of the Autohaler.)
  4. Breathe in steadily through the mouth. DON'T stop breathing when the inhaler "clicks," and continue taking a really deep breath.
  5. Hold the breath for about 10 seconds.
  6. While holding Autohaler upright, lower the lever. Wait at least 60 seconds before taking another inhalation.
- N.B. The lever must be pushed up ("on") before each dose, and pushed down again ("off") afterwards. Otherwise it will not operate.



ALWAYS DEMONSTRATE TO THE PATIENT HOW TO USE THE AUTOHALER

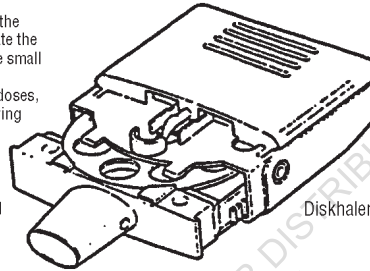
\*Other inhalers are becoming available in addition to those included in this figure. Clinicians should demonstrate the use of any device prescribed to patients, and should have the patient demonstrate back to the clinician.



Figure 9-10 (continued)

## HOW TO USE THE DISKHALER

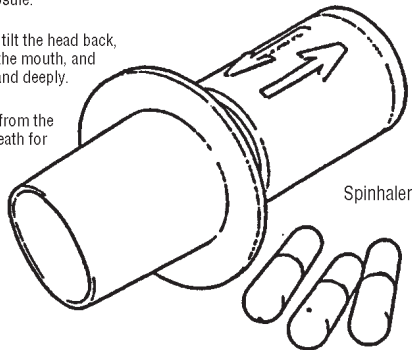
1. Remove mouthpiece cover. Then remove the white tray by pulling it out gently and then squeezing the white ridges either side until it slides out.
2. Put foil disk - numbers uppermost - on the wheel and slide tray back.
3. Slide tray in and out by holding the corners of the tray. This will rotate the disk. A number will appear in the small window. Rotate until number 8 appears. As the disk contains 8 doses, this is a convenient way of knowing how many doses remain.
4. Keeping the Diskhaler level, lift the rear of the lid and pull it up as far as it will go. This will pierce the top and bottom of the blister. Close the lid.
5. Hold the Diskhaler level, breathe out gently, and put the mouthpiece in the mouth. (Do not cover the small air holes on either side of the mouthpiece.) Breathe in through the mouth as quickly and deeply as possible.
6. Remove the Diskhaler from the mouth and hold the breath for about 10 seconds.



ALWAYS DEMONSTRATE TO THE PATIENT HOW TO USE THE DISKHALER

## HOW TO USE THE SPINHALER

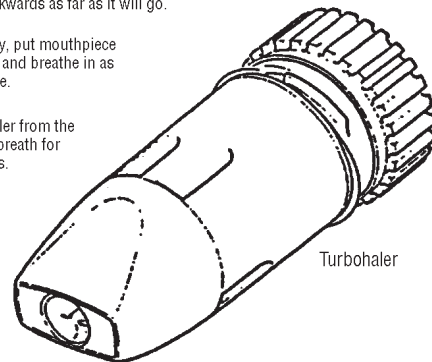
1. Hold Spinhaler upright and unscrew the body.
2. Put colored end of spincap into cup of propeller.
3. Screw the two parts together and move grey sleeves up and down at least twice. This will pierce capsule.
4. Breathe out gently, tilt the head back, put Spinhaler into the mouth, and breathe in quickly and deeply.
5. Remove Spinhaler from the mouth and hold breath for about 10 seconds.



ALWAYS DEMONSTRATE TO THE PATIENT HOW TO USE THE SPINHALER

## HOW TO USE THE TURBOHALER

1. Unscrew and lift off white cover. Hold Turbohaler upright and twist blue grip forwards and backwards as far as it will go.
2. Breathe out gently, put mouthpiece between the lips, and breathe in as deeply as possible.
3. Remove Turbohaler from the mouth and hold breath for about 10 seconds.



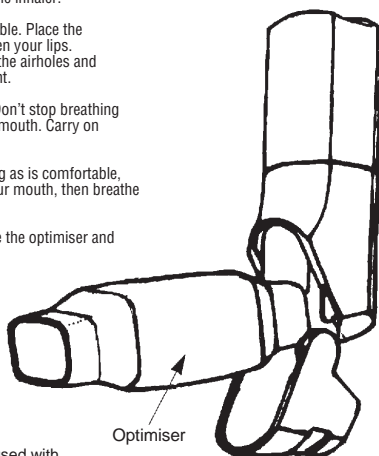
ALWAYS DEMONSTRATE TO THE PATIENT HOW TO USE THE TURBOHALER

Figure 9-10 (continued)

## HOW TO USE THE *Easi-Breathe* INHALER

With Optimiser (Small Volume Spacer)

1. Shake the inhaler vigorously.
2. Then, holding the inhaler upright, open the cap and slot the optimiser firmly onto the mouthpiece of the inhaler.
3. Breathe out normally as far as is comfortable. Place the mouthpiece of the optimiser firmly between your lips. Make sure that your hand is not blocking the airholes and that you are still holding the inhaler upright.
4. Breathe in slowly through the optimiser. Don't stop breathing when the inhaler puffs the dose into your mouth. Carry on until you have taken a deep breath.
5. Hold your breath for 10 seconds or as long as is comfortable, remove the inhaler and optimiser from your mouth, then breathe out slowly.
6. After use, hold the inhaler upright, remove the optimiser and close the cap.
7. If you need to take more than one puff, close the cap, wait at least one minute between doses and then repeat the process from Step 1.



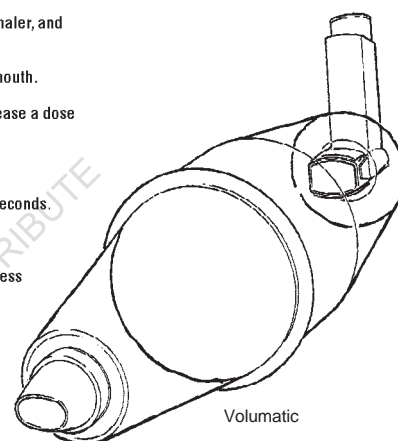
NOTE: The *Easi-Breathe* Inhaler can be used with or without an Optimiser as recommended by your physician.

ALWAYS DEMONSTRATE TO THE PATIENT HOW TO USE THE *EASI-BREATHE* INHALER.

## HOW TO USE A SPACER DEVICE e.g., VOLUMATIC

Method for patients who can use the device  
without help

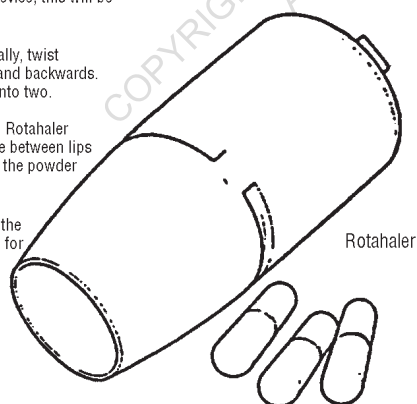
1. Remove the cap, shake the inhaler, and insert into the device.
2. Place the mouthpiece in the mouth.
3. Press the canister once to release a dose of the drug.
4. Take a deep, slow breath in.
5. Hold the breath for about 10 seconds. Then breathe out through the mouthpiece.
6. Breathe in again but do not press the canister.
7. Remove the device from the mouth.
8. Wait about 30 seconds before a second dose is taken.



ALWAYS DEMONSTRATE TO THE PATIENT HOW TO USE THE VOLUMATIC

## HOW TO USE THE ROTAHALER

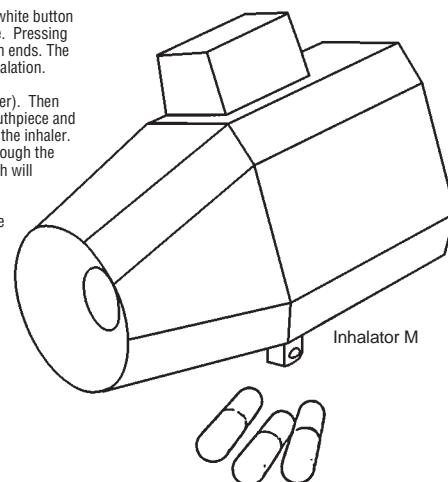
1. Hold Rotahaler vertically and put capsule colored end uppermost into "square" hole. Make sure top of Rotacap is level with top of hole. (If there is a Rotacap already in the device, this will be pushed into the shell.)
2. Hold Rotahaler horizontally, twist barrel sharply forwards and backwards. This splits the capsule into two.
3. Breathe out gently. Keep Rotahaler level and put mouthpiece between lips and teeth and breathe in the powder quickly and deeply.
4. Remove Rotahaler from the mouth and hold breathe for about 10 seconds.



ALWAYS DEMONSTRATE TO THE PATIENT HOW TO USE THE ROTAHALER

## HOW TO USE THE INHALATOR M

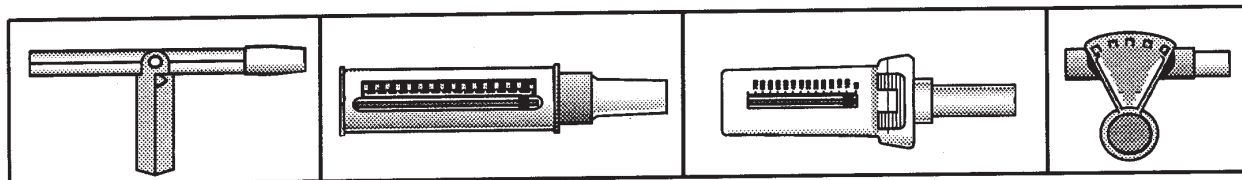
1. Open the mouthpiece (white part) of the inhaler. Insert the capsule into the hole provided and close the inhaler again completely.
2. Hold the mouthpiece upwards. The white button must be pressed in as far as possible. Pressing the button pierces the capsule at both ends. The active ingredient is now ready for inhalation.
3. Breathe out deeply (without the inhaler). Then close your lips firmly around the mouthpiece and breathe in slowly but deeply through the inhaler. Repeat twice. Do not breathe out through the inhaler, as the moisture in your breath will condense inside it.
4. Open the mouthpiece again. Hold the inhaler so that the capsule hole is pointing downwards and shake out the empty capsule. Close the inhaler again.



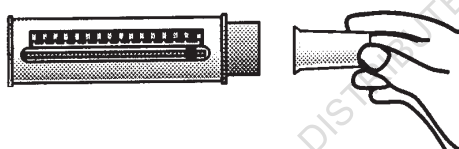
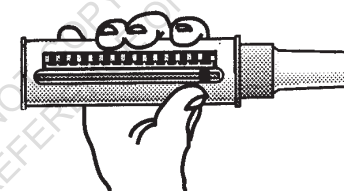
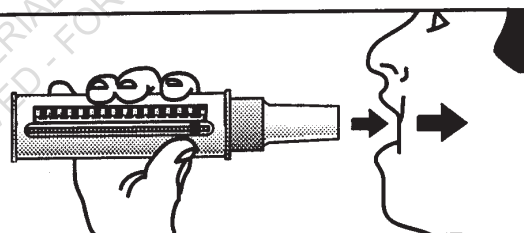
ALWAYS DEMONSTRATE TO THE PATIENT HOW TO USE THE INHALATOR M

**Figure 9-11. How To Teach and Check Peak Flow**

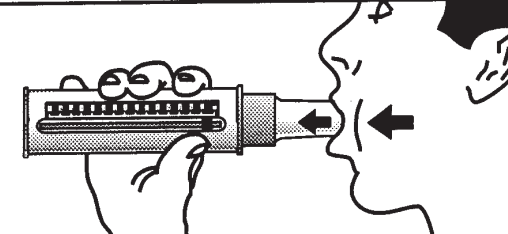

There are several types of peak flow meters. Four different types are illustrated here, and they all meet established standards.



The steps for using a peak flow meter are the same for all peak flow meters. Each patient should select one type and use it for his or her peak flow monitoring, as the patient in this illustration is doing.

1. Fit disposable mouthpiece to peak flow meter.
 
2. Ensure patient stands up and holds peak flow meter horizontally without restricting movement of the marker. Ensure the marker is at the bottom of the scale.
 
3. Ask patient to breathe in deeply, seal lips around mouthpiece, and breathe out as quickly as possible.
 
4. Record the result.
 

Repeat steps 2 to 4 twice more. Choose the highest of the three readings and compare with predicted values.


5. Remind children to blow out through the meter rather like blowing out candles on a birthday cake.
 

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It may be helpful to stress that PEF monitoring is not done merely for the health care professional's record, but rather it provides critical information for making decisions about treatment, and thus PEF monitoring is a tool for patients to help themselves.

### **Guided Self-Management**

All patients self-manage their own asthma to some extent, as, for example, when they decide to use their bronchodilator for the relief of symptoms. However, there is now increasing evidence of the benefits of giving many patients with asthma a specific guided self-management plan. Such a plan permits the patient to adjust treatment in response to a variety of circumstances, according to a medication plan previously agreed upon with the health care professional. Patients (or parents) should appreciate from the outset that a self-management plan is designed to enable them to look after themselves (or their child) without constantly having to consult the health care professional (26). Whether to use a simple plan or a more complicated scheme varies from patient to patient. Simple plans include:

- The daily dose of preventive therapy (controller medication)
- The name and dose of bronchodilator that should be taken to relieve symptoms (reliever medication)
- Advice on how to recognize signs that suggest deteriorating control, including symptoms and, if appropriate, PEF
- Advice on how to treat worsening asthma, including advice about how and when to seek medical attention
- Advice on increasing treatment at the first sign of a cold.

More detailed plans may be based on symptoms alone, but it is often preferable to couple them with objective monitoring of PEF. Studies have shown that 20 to 60 percent of patients cannot 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 rate (27, 28).

Working out a detailed self-management plan may be time consuming and needs to be done with care if it is to contain realistic, effective advice. It should be a joint exercise between patient and health care professional and cannot be undertaken until a reasonable period of preliminary monitoring of PEF at home has been

undertaken. In some cases it is necessary to give maximum therapy initially or to give a course of corticosteroid tablets so that the best attainable PEF can be determined for the individual patient (see the chapter on management of asthma). The subsequent action plan is then based upon this “individual best” PEF.

More detailed plans include:

- Levels of symptoms and levels of PEF at which the patient or parent increases preventive treatments
- Levels at which a course of corticosteroid tablets is started
- Levels at which urgent medical attention is sought
- Identification of specific asthma triggers to be avoided.

Such plans may be individually written, filled in on preprinted cards, or based on a series of colored lines affixed directly onto the peak flow meter. Examples of such plans are shown in figure 9-12.

Trials now confirm that giving patients a detailed, written, guided self-management plan leads to better overall control of asthma and improved compliance (29-31).

Although it is usually best to base such self-management plans upon objective monitoring of the condition by the recording of peak expiratory flow rate, such plans can be based on symptoms alone where peak expiratory flow rate monitoring is either unavailable or inappropriate (32).

### **Followup Consultation**

At the followup consultation, the patient's questions are first 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.

Home PEF recordings and symptoms, as revealed in the patient diary, are also reviewed regularly. From such discussion will evolve the individualization of the guided self-management plan (e.g., the green-yellow-red asthma management zone system described in the chapter on management of asthma) whereby the patient adjusts therapy or seeks medical attention in a predetermined manner in response to particular signs, symptoms, or PEF measurements (29, 32). Furthermore, review of home PEF and symptom monitoring is necessary to assure that the goals for therapy are met. Appropriate adjustments in therapy can then be considered.

Figure 9-12. Sample Patient Action Cards

**SEE ORIGINAL MECHANICAL**

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## Support Groups

Many patients 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 at the end of this chapter.

## 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 their health care professional during which they 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. Although more research is needed, evidence suggests that 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 (see the chapter on prevention).

Research is needed to establish whether public education campaigns to prevent the development of asthma might be effective (see the chapter on prevention). Evidence suggests that prevention strategies to reduce infants' exposure to indoor allergens, particularly domestic mites, and to maternal smoking may be the most promising measures.

## RESEARCH RECOMMENDATIONS

Priorities for future investigations related to prevention of asthma include:

- Determining the impact of the introduction of asthma guidelines at national, district, and local levels. Guidelines are useful as a basis for audit, for setting standards, and for education. Given the correct outcome measures, results of research on the effects of guidelines could provide insights into the most effective kinds of patient and professional education.
- Examining further the efficacy of asthma self-management plans. The use of guided self-management plans and the giving of greater control to patients and parents are laudable on the basis of common sense, of our current understanding of factors involved in compliance, and of initial largely uncontrolled trials. Further controlled trials could clarify the thresholds at which different therapeutic interventions should be initiated and whether these thresholds should be based primarily on PEF.
- Clarifying the relative effectiveness of interventions delivered by different health care professionals (for example, nurses, primary care physicians, outreach workers) and the specific positive advantages of asthma support groups. The impact of the interventions on patients' quality of life should be included in measuring program effectiveness.

## SOURCES OF FURTHER EDUCATIONAL MATERIALS

Materials are produced in the national languages of the following asthma associations and support groups.



**AUSTRALIA**

Asthma Australia  
Australia Association of Asthma Foundations Inc.  
Unit 3  
46 Geils Court  
Deakin, ACT, 2600, Australia

National Asthma Campaign  
5th Floor  
615 St. Kilda Road  
Melbourne, Victoria 3004  
Australia

**BARBADOS**

Asthma Association of Barbados  
c/o Barbados Drug Service  
Jemmotts Lane  
St. Michael  
Tel. 427-8309

**BELGIUM**

Astma Fonds  
Eendrachtstraat 56  
1050 Brussels, Belgium  
Tel. 32.2.512 54 55.

**CZEC REPUBLIC**

Association in Aid of Children With Chronic Diseases  
Zelena 14, 160 00 Prague 6  
Tel./Fax 0042 2 311 42 13.

**DENMARK**

Astma-Allergi-forbundet  
Hovedvejen 9 C  
2600 Glostrup  
Denmark  
Tel. 43.43.59.11. Fax 43.43.54.33.

**FINLAND**

National Foreningen Lurgesygdonne  
Herlufsholnvej 37  
2720 Vanlose  
Tel. 31.74.55.44.

**FRANCE**

'ASTHME'  
Programme National de Recherche et d'Education  
10 Rue du Commandant Schloesing  
75116, Paris, France  
Tel. 47.55.03.56. Fax 44.05.91.06.

Comité de Lutte contre les Maladies Respiratoires et la  
Tuberculose (CNMRT)  
75006 Paris, France  
Tel. 33-1-46345880  
Fax 33-1-42290658

**GERMANY**

Allergiker-und Asthmatikerbund in Mönchengladbach  
Hindenburgstrasse .110  
41061 Mönchengladbach, Germany

**HONG KONG**

Hong Kong Asthma Society  
Tsat Tse Mui  
P.O. Box 60397  
Hong Kong  
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Fax 852 769458

**ICELAND**

Samtok Gegn astma og ofnaemi  
Box 936  
121 Reykjavik, Iceland  
Tel. 91.22 153.

**INDIA**

Asthma and Bronchitis Association of India  
c/o Pulmonary Function Laboratory  
St. Georges' Hospital  
Bombay 400 001

**IRELAND**

The Asthma Society of Ireland  
24 Anglesea Street  
Dublin 2

**JAPAN**

Japanese Society of Allergology  
1-35-26 Hongo, Bunkyo-ku  
Tokyo 113, Japan  
Tel. 81-3-3816-0280  
Fax 81-3-3816-0219

**NETHERLANDS**

Nederlands Astma fonds  
Postbus 5, 3830 AA Leusden  
The Netherlands  
Tel. 033.94 18 14. Fax 033.95 03 30.

**NEW ZEALAND**

The Asthma Foundation of New Zealand  
P.O. Box 1459  
7th Floor, Rossmore House  
123 Molesworth Street  
Wellington, New Zealand  
Tel. 011 64 4 499 4592. Fax 011 64 4 499 4594.

**NORWAY**

Norges Astma - og Allergiforbund  
Industrig, 36, 0357  
Oslo 3

**POLAND**

Towarzystwo Przyjaciół Chorych na Astmę  
Klinika Pneumonologii  
ul. Banacha 1a  
02-097 Warszawa, Poland  
Tel. 22.23.59.73. Fax 22.658.36.29.

The Asthma Suffering Children's Relief Association  
Clinic of Children's Allergic Diseases  
National Research Institute of Mother and Child Rabka  
Branch  
ul. Polna - Pawilon 11  
34-410 Rabka, Poland

**SAUDI ARABIA**

Saudi Society of Allergy and Immunology  
(Society of Friends of Patients)  
c/o Harb Harfi, M.D.  
King Faisal Specialist Hospital  
P.O. Box 3354, Riyadh 11211  
Saudi Arabia  
Tel. 464-7272. Fax 442-7784

**SLOVENIA**

Pulmonary Patients Association of Slovenia  
Pljučni dispanzer Vic  
Postojnska 24  
61000 Ljubljana

**SOUTH AFRICA**

Allergy Society of South Africa  
Dept. of Clinical Science  
U.C.T. Medical School, Observatory  
Cape Town 7925  
Tel. 021.471250. Fax 021.478955.

**SWEDEN**

Riksförbundet mot Astma-Allergi  
Box 8273  
163 08 Spanga, Sweden  
Tel. 08.760.40.10. Fax 08.760.16.86.

**SWITZERLAND**

Schweizerische Elternvereinigung, Asthma - und  
Allergiekranke Kinder Zentralsekretariat  
Mia Isler Schaufelgrabenweg 28  
3033 Wohlen

**U.K.**

National Asthma Campaign  
Providence House  
Providence Place  
London, NI ONT  
Tel. 44.71.226.2260. Fax 44.71.704.0740.  
(Materials in English, Welsh, Urdu, Bengali, Gujarati,  
Punjabi, Hindi.)

**U.S.A.**

National Asthma Education and Prevention Program  
National Heart, Lung, and Blood Institute  
9000 Rockville Pike  
Building 31, Rm. 4A-18  
Bethesda, MD 20892  
Tel. (301) 496-1051

AAFA/Asthma and Allergy Foundation of America  
1125 15th Street, NW, Suite 502  
Washington, DC 20005  
Tel. (202) 466-7643

American Academy of Allergy and Immunology  
611 East Wells Street  
Milwaukee, WI 53202  
Tel. (414) 272-6071

Allergy and Asthma Network/Mothers of Asthmatics, Inc.  
3554 Chain Bridge Road, Suite 200  
Fairfax, VA 22030  
Tel. (703) 385-4403

American Lung Association  
1740 Broadway, 14th Floor  
New York, NY 10019-4374  
Tel. (212) 315-8700

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# CHAPTER

**10**

# ***RECOMMENDATIONS***

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The study group on the Global Strategy for Asthma Management and Prevention recommends that the WHO consider actions that encourage the development and dissemination of training programs, health care services, prevention activities, and research described in this chapter. The study group further recommends that WHO, through its education and technical assistance programs, encourage national governments to consider these actions as well.

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## TRAINING

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- Training programs for health care workers and public health officials should emphasize that:
  - Asthma is a serious chronic disorder, which, if left untreated, can cause absences from work or school, emergency department and hospital visits, and, in some cases, death.
  - Asthma is a controllable disorder; most people with asthma can lead normal, productive lives if their asthma is managed effectively.
- Training programs and resource materials for primary care health workers should include instruction on the diagnosis and management of asthma and on asthma patient education. This is essential because most asthma patients should be treated at the primary care level.
- Training programs and resource materials on any respiratory disease should incorporate information about the differential diagnosis of asthma as well as appropriate asthma management recommendations. It will be particularly useful to integrate discussion of asthma with materials on acute respiratory infections.

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## HEALTH CARE SERVICES

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- Asthma management programs should incorporate patient education, measurements to assess and monitor severity, pharmacologic therapy, and nonpharmacologic secondary prevention measures (e.g., avoidance of asthma triggers).
- Asthma management programs should promote the appreciation of asthma as a chronic inflammatory disorder. Treatment programs should emphasize that control of asthma requires daily and long-term therapy with controller medications. Priorities for long-term treatment should include medications for controlling airway inflammation.

- Asthma management medications should be made widely available and accessible. Most of the recommended pharmacologic therapies for asthma management are included in the WHO List of Essential Drugs; efforts should be made for timely revisions to the list to acknowledge new therapies as appropriate.
- Asthma management programs should consistently provide education to enable patients to perform “guided self-management” of their asthma. Patients must be skilled in the day-to-day self-management of asthma in order to stay well and adjust treatment according to a medication plan developed in partnership with a health care professional. Sufficient resources should be specifically allocated to support educational programs.
- Health services planning should improve home management of exacerbations, early communication with health care workers, and access to facilities that treat asthma exacerbations. Asthma can be a life-threatening disorder. Survival from severe exacerbations of asthma can depend on prompt and appropriate treatment.
- National and regional health planning efforts should be encouraged, and technical assistance offered, to conduct health economic studies. These studies will provide insights for setting priorities for management and prevention programs that are appropriate for the resources and needs of that region.
- Activities should be undertaken in relevant WHO programs to encourage national and regional programs to develop specific strategies for adapting and implementing the recommendations for asthma management and prevention made in this report. Specific targets could be established that are appropriate to that region for reducing hospitalizations, increasing patient education, improving diagnosis, increasing use of appropriate therapies, and improving monitoring of asthma through objective measurements.

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## PREVENTION

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- Collaboration between countries should be fostered to prevent occupational asthma. Information on known occupational sensitizers and the programs to prevent or minimize exposure to them should be communicated clearly to public health officials.
- Consideration of primary prevention efforts should be promoted that include adjustment of the environment to reduce exposure to indoor allergens (particularly domestic mites), avoidance of passive smoking



(especially for infants), and reduction of exposure to occupational sensitizers. This may be a particularly important public health program measure in those populations that have not yet adopted lifestyles believed to cause increasing rates of asthma prevalence and morbidity.

- Determine the relative effectiveness of different interventions for asthma management on the various outcome measures, including the patient's quality of life.

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## RESEARCH RECOMMENDATIONS

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Research programs are needed that will:

- Encourage national programs to participate in large-scale epidemiological studies of prevalence and social impact of asthma.
- Determine the causes for the increasing prevalence and morbidity of asthma in developing countries.
- Develop reliable, preferably noninvasive tests to reflect the asthmatic airway inflammation for use in diagnosis, monitoring the activity of the disorder, and evaluation of treatments.
- Investigate the relationship of pathological changes to indices of lung function, especially in patients with life-threatening, highly unstable disease.
- Determine to what extent the guidelines for the management of asthma are followed as well as determine the means by which they can best be implemented.
- Determine if there is sufficient evidence on the causes of asthma to initiate prevention programs and evaluate selected efforts.
- Identify the role of contributing factors (e.g., viral infections, pollutants) in the development of asthma.
- Identify the mechanisms of the chronicity of asthma.
- Develop methodology for the early detection of asthma (preclinical asthma), especially in infants.
- Study the long-term effects of pharmacologic and nonpharmacologic asthma therapy on the natural history of asthma and on lung function.
- Examine the optimal cost-effective strategies in asthma, and in particular, examine how best to balance resource expenditures for prevention versus control of asthma.

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# ***GLOSSARY***

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ULASTER  
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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. Over 100 million people worldwide have asthma, and the prevalence is increasing among children.

The Global Strategy for Asthma Management and Prevention project has three aspects:

- The National Heart, Lung, and Blood Institute (NHLBI, National Institutes of Health, United States) and the World Health Organization (WHO) collaborated in a Global Initiative for Asthma effort to extend the relevance and impact of the "International Consensus Report on Diagnosis and Management of Asthma" published in 1992 by the NHLBI. This report presented an approach to asthma therapy that translated scientific advances into recommendations for clinical management of asthma. The recommendations represented a remarkable consensus among medical and scientific leaders in 11 countries who had previously developed national clinical practice guidelines on asthma. Response to the NHLBI International Consensus Report was significant—within a year, professional and medical societies in many countries had translated and disseminated the report. The diversity of national health care service systems and variations in the availability of asthma therapies required, however, that the recommendations be adapted to ensure their appropriateness throughout the global community. In addition, public health officials needed information about the costs of asthma, prevention activities, and education methods in order to develop asthma care services and programs responsive to the particular needs and circumstances of their countries.

To meet these needs, the NHLBI and WHO jointly convened two Global Strategy for Asthma Management and Prevention Workshops with participants from every region in the world. The objective was to develop information, recommendations and tools to assist health care professionals and public health officials in designing and delivering effective asthma management and prevention programs in their communities. Another objective of the workshops was to identify areas for future research investigations.

- The World Health Organization then convened the workshop members into a study group to document information on the nature and extent of asthma worldwide and to recommend appropriate approaches to its prevention and control, including research.

- The study group hopes that, through its role in coordinating international efforts, the WHO will encourage regional and national health care planners and health authorities to develop specific strategies for implementing the recommendations in this report.

The findings and recommendations of the study group are presented in this report.

The increasing prevalence of asthma in all regions of the world has concerned scientists and health care professionals internationally. The World Health Organization's Assistant Director-General, Dr. N.P. Napalkov, opened the study group meeting on behalf of Dr. Hiroshi Nakajima, Director-General. Dr. Napalkov noted that asthma prevalence is extremely variable among populations in the Western Pacific regions, ranging from over 50 percent of the children in the Caroline Islands to virtually none in Papua New Guinea. Data from Australia, New Zealand, and Singapore show increasing prevalence among children and high mortality rates. Asthma and chronic bronchitis are the most common and most important chronic airway diseases in Africa, where data from 10 African countries have shown asthma prevalence ranging between 2 and 5 percent among schoolchildren.

As with all chronic diseases, rising prevalence is only part of the concern. Mortality due to asthma rose in the last decade and has not changed in recent years. Morbidity due to exacerbations and persistent symptoms presents a huge burden to individuals and their communities. For example, in the United States over 10 million school days were lost in 1 year by children with asthma, and the consequent lost productivity of their parents was almost \$1 billion (U.S.). Unlike many chronic diseases, asthma often appears very early in childhood. The lifelong consequences of inadequately treated asthma can be substantial. A major burden of asthma falls on the developing world, especially in terms of disability-adjusted life years. The extent of the burden of asthma is related to its severity. Although patients with severe asthma are fewer in number than those with milder asthma, patients with inadequately controlled severe asthma have high expenditures in health care costs, especially in terms of hospitalizations.

The social and economic burdens of asthma can be alleviated through appropriate asthma prevention and management strategies. Although asthma cannot be cured, it can be controlled. There are several major advances in our understanding of asthma:

- **A new appreciation for the significant role of airway inflammation in the pathogenesis of asthma.** Asthma