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PRACTICE PARAMETERS FOR THE DIAGNOSIS AND TREATMENT OF ASTHMA

These parameters were developed by the
Joint Task Force on Practice Parameters, representing
the American Academy of Allergy Asthma and Immunology,
the American College of Allergy, Asthma and Immunology,
and the Joint Council of Allergy, Asthma and Immunology

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PRACTICE PARAMETERS FOR THE DIAGNOSIS AND TREATMENT OF ASTHMA

The American Academy of Allergy Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing asthma parameters to promote advancement and improvement in the care of patients with asthma and facilitate the education of physicians who care for such patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these Practice Parameters. Any request for information about or an interpretation of these Practice Parameters by the AAAAI or the ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology.

These Practice Parameters are endorsed by the Allergy-Immunology Subsection of the American Academy of Pediatrics.

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I. Preface

In 1987, as concern about increased asthma mortality in the United States escalated, plans were made to develop a strategy for establishing standards for the care of asthma by bringing together individuals who had already formulated approaches to this issue. (*Note*: Although originally conceived as "standards," development of boundaries for the field of allergy and immunology has evolved into the development of "parameters" as noted below.) More than 50 experts in the field of allergy and immunology were contacted and responded by drafting the sections that form the basis for the current "Parameters for the Diagnosis and Treatment of Asthma." These sections were subsequently edited by a working group from the American Academy of Allergy and Immunology.

At the same time the National Heart, Lung, and Blood Institute (NHLBI) was developing a National Asthma Program that would include "Guidelines for the Diagnosis and Treatment of Asthma," directed essentially at enhanced management of asthma by the primary care physician rather than asthma specialists (pulmonologists and allergists). In addition to supporting this initiative, it was logical that the Academy and the American College of Allergy and Immunology continue to support the effort of those involved in developing parameters for the specialty of allergy and clinical immunology.

To facilitate the process of establishing parameters, a Joint Task Force of the Academy and College with representation by the Joint Council of Allergy and Immunology was developed, chaired by Sheldon Spector and Arnold Gutman, and including Richard Nicklas, Joann Blessing-Moore, Rufus Lee, Stan Fineman, I. Leonard Bernstein, and David Pearlman.

It may naturally be asked, "Why did the major allergy professional organizations decide that a global medical perspective of asthma was appropriate?" Several brief historical tableaux illustrate how closely the specialty of allergy was associated with asthma from its nascent period during the early years of this century until the current renaissance era of molecular biology. Although asthma associated with environmental irritants was recognized as early as the mid-seventeenth century, the possibility that the disease was associated with an adaptive immune response emanated from the experimental observations of pioneers such as Richet, Von Pirquet, and Prausnitz. These seminal reports of allergic immune mechanisms were soon applied to clinical asthma by astute clinicians such as Cooke and Rachemann, who were among the early founders of the clinical subspecialty of allergy. In the ensuing half century, the concept of immunologically induced asthma was documented by allergists and immunologists and culminated in the isolation and elaboration of the allergic antibody, immunoglobulin E, and the recognition of the cardinal role of allergic mediators in the pathogenesis of asthma. This dramatic progress began to attract a new generation of pulmonologists into the asthma research arena, which now appears poised for a quantum leap into molecular mechanisms. Although it is eagerly anticipated that this expanded research horizon will provide many unforeseen benefits and perhaps cures for patients with asthma, the practical experience of allergists and immunologists in the detection of allergic factors, and the total management of asthma during the past 75 years should serve as the foundation on which

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future diagnostic, preventive, and treatment strategies are based. It is with these goals in mind that the "Parameters for the Diagnosis and Treatment of Asthma" was commissioned as a joint effort by the American Academy of Allergy Asthma and Immunology and the American College of Allergy Asthma and Immunology.

It is recognized that these Parameters will have a significant impact on our approach to the management of patients with asthma. They are published for the purpose of providing scientific information to the health care community and fostering improvement in the overall quality of the diagnosis and treatment of patients who suffer from asthma. Although individual physicians are not obligated to accept, follow or adhere to the boundaries established in this document, it should be noted that it has been constructed with much thought by and input from a substantial number of specialists concerned with asthma. Therefore the opinions contained herein, relating to the diagnosis and treatment of asthma merit review and consideration.

A document of this type must consider the complexity and heterogeneity of the condition, an extraordinary amount of conflicting data, incomplete understanding of the etiology, pathogenesis, and optimal treatment of the condition, and individual judgment required in the management of each patient. Indeed, each patient and his or her medical condition represent a unique diagnostic and therapeutic challenge. Nevertheless, at any given time medical knowledge and collective judgment dictate appropriate and inappropriate approaches to the management of any clinical condition. These "Parameters on the Diagnosis and Treatment of Asthma" have been formulated for the specialty of allergy and clinical immunology with recognition of these considerations. With this in mind, it is imperative that members of the Academy and College take the time to carefully read these Parameters.

The editors recognize that there are different approaches to the diagnosis and treatment of asthma and have attempted to reach a consensus, sometimes with great difficulty on various aspects of the management of asthma. Where there was a legitimate basis for different management techniques, recommendations are purposely flexible or there is discussion of different approaches that could be used. It is clearly in the best interest of everyone not to stifle innovative approaches to the diagnosis and treatment of asthma.

Where indicated, what was considered useful background information has been discussed, but an attempt was made to keep this document succinct and relevant to the diagnosis and treatment of asthma. Each section of the document is organized into a text with preceding summary statements. These summary statements reflect the editors' consensus on the key aspects of each section.

It is important to acknowledge the constantly changing nature of the field of allergy and immunology. It should be recognized therefore that the *Parameters* will need to be updated on a continuing basis to be consistent with the state-of-the-art.

Parameters "are a complicated refinement of many ideas, data, and value judgments." They are necessary to complement advances in technology and discard obsolete practices as long as such action is supported by biomedical research. Specialty organizations are in an ideal position to provide high-quality scientific direction for the health care community through the development and publication of practice parameters. This is based on the fact that specialty organizations are comprised of individuals who are directly involved in day-to-day management, education, and/or research related to the clinical condition for which the practice parameter is being developed.

The development of parameters is closely linked to quality of care for asthmatic patients. Is it possible to measure "quality of care?" Whatever the answer, patients are looking more and more to professional organizations to ensure quality of care. Quality of care has been said to be a multidimensional concept reflecting judgments that services rendered were: (1) those most likely to produce the best outcome that could be reasonably expected for the patient, (2) given with due attention to the ambience and aura of the patient-physician relationship, and (3) provided in a cost-efficient and cost-effective manner. Quality of care not only involves the technical aspects of care but also the "art of care" (i.e., the milieu, manner, and behavior of the provider in delivering care and communicating with patients; the interpersonal, humanistic dimension of medical practice, which reflects patients' and society's views, values, expectations, and demands). It is a dynamic and not a static concept. It has been argued that quality might best be assured by a continuing, formal, systemic program to identify problems, design activities to correct problems, and monitor corrective actions. The fundamental aim would be continual improvement in quality of care, recognizing that

important mechanisms are informational (i.e., education and feedback to individual practitioners and providers).

The Asthma Mortality Task Force in its summation stated, "There is an obvious need . . . to define optimal care in asthma. Such a definition must at least include optimal medication use, inclusion of objective measures of function, and appropriate techniques of asthma self-management." Although "asthma self-management" has been replaced by "cooperative management through education of patients by physicians," this challenge to improve the quality of care for asthma by the development of parameters for the diagnosis and management of this condition is the basis for this document.

The editors thank those within the Academy and College who have supported and encouraged this project as well as the individuals who have donated their time and energy to preparing the sections that form the foundation for this very important document.

II. Introduction

Asthma is a heterogenous disease process with multiple triggering factors. Irritants (e.g., indoor and outdoor pollutants, cigarette smoke, and odors), specific allergens (e.g., dust mites, animal proteins, mold spores, and pollens), and reactive chemicals are capable of eliciting an asthmatic response (see Section VI D, "Environmental Avoidance," Section VII I, "The Effects of Air Pollution in Asthmatic Patients," and Section VII K, "Occupational Asthma"). Patients with asthma can often identify precipitants, such as exercise or viral infections. Sometimes seasonal symptoms suggest the importance of airborne allergens, but perennial symptoms can also be caused by allergenic triggers. A careful history combined with selected diagnostic tests (see Section V, "Diagnosis and Evaluation") will identify many of the above precipitants, as well as food and additive hypersensitivity, occupational factors, sinusitis, and gastroesophageal reflux (see Sections VII, F through H and K). In addition, emotional factors, including anxiety and depression, can exacerbate asthma or influence the manner in which patients interpret symptoms and apply self-care techniques (see Section VII J). All of these are important in designing treatment regimens to minimize the impact of triggers by the use of avoidance, pharmacotherapy, and immunotherapy (see Sections VI, D through F).

With regard to natural history, asthma commonly begins in early childhood and affects boys more frequently than girls. When children with asthma mature to adults, about one fourth will have persistent symptoms of asthma, one fourth will be free of symptoms, and one half will experience infrequent or episodic symptoms.[1] Children with severe asthma are more likely to experience persistent asthma as adults.[2]

Many conditions are easily misinterpreted as asthma, and appropriate identification can lead to a dramatic reorganization of the treatment plan. Conditions such as chronic bronchitis, vocal cord dysfunction, cystic fibrosis, congestive heart failure, extrapulmonic obstructive lesions, foreign bodies, immunodeficiency resulting in recurrent pneumonia, bronchopulmonary dysplasia, bronchiolitis obliterans, and allergic bronchopulmonary aspergillosis may present with asthmatic symptoms or complicate the course of asthma (see Sections V C 2, and C 4 and Section VII A).

The hallmark of asthma has always been the concept of reversible airway obstruction. However, with the recognition that asthma is an inflammatory process, the importance of one or more pathologic features, including epithelial damage, increased vascular permeability, mucosal edema, mucus production, and the infiltration of a heterogenous cellular infiltrate, are now more fully appreciated. Inflammation can result from immunologic or nonimmunologic causes. The IgE-mediated allergic process is the basis not only for the immediate clinical presentation of asthmatic symptoms but is also directly responsible for the late response, which is associated with a smoldering inflammation. It is also recognized that nonallergic stimuli may be responsible for similar inflammatory mechanisms.

Much attention has been focused on the mast cell and basophil as the pivotal cells in the immediate allergic reaction, associated with the release of preformed factors (e.g., histamine), as well as newly generated mediators (e.g., prostaglandin D_2). Basic research has demonstrated that recruitment of eosinophils, neutrophils, and other inflammatory cells by chemotactic factors (eosinophilic chemotactic factor, neutrophilic chemotactic factor, and leukotriene B_4) and cytokines (e.g. IL4) appears to be directly responsible for the long-term inflammatory changes in the airways. Late-phase bronchoconstriction will develop in many patients with allergen-induced asthma. The bronchial lavage fluid and bronchial tissue in patients during late responses are characterized by the presence of eosinophils, neutrophils, monocytes, and T-lymphocytes. The ability of corticosteroid pretreatment to inhibit late-phase responses suggests that the cellular exudate plays a direct role in late-phase reactions. The role of inflammation in the pathogenesis of asthma should be considered when a treatment regimen for an individual patient is recommended.

The variable clinical pattern and natural history of asthma impose the need to individualize treatment with regard to choice of medication, avoidance of allergenic and nonallergenic triggers and immunotherapy, when adequate avoidance is not possible. Treatment should also be tailored to the patient's age, concomitant medical conditions, complications, other medications being taken by the patient, and exposure conditions (e.g., work-

place, school, urban, and rural) (see Sections VII, K through M). This requires an initial definition of realistically attainable goals of therapy (treatment objectives) for each patient. The relative safety of the therapeutic alternatives influences the therapeutic decisions that are made in striving for these goals. In some patients, the probability of greater morbidity from the disease may justify greater therapeutic risk, as long as sufficient benefit can be obtained.

Asthma is a capricious disease. It is not surprising therefore that the perception of asthma is changing from a condition that is easily controlled and highly predictable to one that is multifaceted, individualistic, and subject to sudden unexpected changes. In part this perception has been fostered by the recognition that during the past 15 years there has been a gradual increase in asthma mortality in the United States.[3] This increase has occurred at a time when mortality rates from most other chronic diseases are on the decline. A substantial increase in hospitalization for asthma has also been seen, not only in the United States but elsewhere during a period when emphasis has been put on the outpatient management of patients with chronic disease.[4] In fact asthma is the most prevalent nonsurgical indication for hospitalization in the pediatric age group and makes up 10% to 15% of medical admissions.[5] These trends are inconsistent with improved treatment regimens and better understanding of asthma pathophysiology over the same time period.

Although the reason for these changes is unknown, several possibilities have been suggested.[6-8] Authoritative reviews of epidemics of asthma deaths in other countries have focused on patient management, particularly in the failure of patients and physicians to recognize the severity of the patient's asthma. Of great concern therefore has been the possibility that increases in asthma mortality and possibly also morbidity may be a reflection of the way that physicians diagnose and treat patients with asthma.

It is essential that features that distinguish the fatality-prone asthmatic patient be characterized as distinctly as possible (see Section VI C). Those features that have been most clearly documented are the severity of the patient's asthma and psychological factors.

In addition, such high-risk patients may have asthma that is not well defined, sometimes in terms of the establishment of the diagnosis, but more often in terms of the way in which patients use and physicians prescribe medications. Poorly defined asthma may be associated with a failure to use and to interpret serial pulmonary function tests properly (see Section V B 1), and may result in the lack of a long-term prophylactic plan of action for exacerbation of asthma. Such a plan is more likely to be effective when it is based on cooperative management between the patient and the physician (see Section VI G 2).

Communication of the assessment plan and therapeutic objectives directly by health care providers to the patient helps obtain mutual agreement for the treatment plan. This, in turn, enhances the likelihood of compliance on the part of the patient, who then has the same perceived goals as the physician and understands the rationale for treatment, follow-up, and appropriate alterations in the therapeutic plan, such as more effective use of corticosteroids (see Section VI E 7). In addition, the patient will have a better understanding of the need to recognize and avoid external/internal precipitants and the potential for medication-induced adverse effects.

The responsibility of those involved in the treatment of asthma is not only the prevention of morbidity and mortality but also improvement in quality of life for the asthmatic patient. To accomplish this, specific goals of diagnosis and treatment should be considered. Appropriate selection of therapeutic measures for asthma requires not only definition of outcome goals but also systematic assessment of the patient, a reasonable sequential selection procedure for therapeutic agents (see Section VI A), and cooperative management through education of patients by physicians and other health care professionals (see Section VI G 2).

One of the most important outcome goals is prevention of the long-term effects of airway inflammation. Prevention encompasses two major components: (1) eliminating exposure or minimizing the effects of exposure to allergens and irritants and (2) a prophylactic therapeutic plan. Recent epidemiologic studies of naturally occurring and occupational asthma have documented the growing importance of allergic factors in the pathogenesis of asthma. The list of possible allergens is increasing and the number of so-called cases of intrinsic asthma is decreasing. Therefore the investigation of possible allergic causes of asthma should be coordinated by well-trained allergists/immunologists, who have the requisite training and experience to conduct and interpret in vivo diagnostic tests such as skin and provocation tests. The allergist/immunologist is well prepared to offer

reliable advice on avoidance measures. Finally, a decision regarding the relative benefit/risk ratio of immunomodulatory therapy should also be under the guidance of an allergist/immunologist. However, avoidance and immunotherapy regimens almost always require supplementary pharmacologic treatment, at least during the initial phase of the patient's care.

Because of the need for individuality of treatment, outcome goals might include the following: (1) reduction in emergency care, (2) reduction in hospitalization, (3) prevention of nocturnal symptoms, (4) tolerance of physical activity appropriate for the patient's age, (5) improvement in pulmonary function, (6) minimization of time lost from work, school, and daily activities, (7) improved self-image based on a full understanding of the disease and confidence in outlined approaches to treatment, (8) optimal control of asthma with use of the least medication possible, administered in a manner that permits the most normal lifestyle and is associated with minimal side effects, and/or (9) general improvement in the quality of life of the patient (see Section VI G 4).

When long-term medication is required, adequate monitoring is necessary to assess the continued efficacy, safety, and need for such treatment. The medication regimen should be reviewed for compliance, appropriate technique for medication administration, drug interactions, and potential anomalies in drug absorption or elimination. For example, theophylline is susceptible to certain changes in absorption such that the lowest serum theophylline concentration during a 24-hour period might occur during the night. For patients with a predominant pattern of nocturnal asthma, improved response may be obtained by providing doses that will produce therapeutic theophylline concentrations during this time period.

Sequential selection of further medication when initial measures are suboptimal should proceed in an orderly manner that is understandable to the patient. It should also be based on objectives mutually agreed on by the patient and physician. The process of assessment can be divided into the following components: (1) history of the frequency and duration of asthmatic symptoms, especially in regard to nocturnal symptoms, (2) activity restriction, (3) requirements for unscheduled medical care, (4) details of intervention measures required, and (5) physiologic status (pulmonary function).

Our understanding of asthma will change, newer pharmacologic agents will certainly appear, and fads and enthusiasm for specific therapeutic approaches will come and go. Nonetheless, systematic assessment of the pattern of disease and physiologic abnormality in the individual patient will remain the cornerstone of rational selection of therapy. When combined with appropriate avoidance, allergen immunotherapy, and a sequential selection scheme for pharmacologic agents, the pharmacologic potential of specific agents can be matched to the physiologic abnormality in a manner that minimizes the amount of medication use. Cooperative management through education permits reliable application of therapeutic measures by those with the greatest opportunity and potential motivation, the patient or family.

It is important to obtain a comprehensive assessment of the patient's response to the treatment plan. This should include an evaluation of the number of wheezing episodes, circumstances surrounding these episodes, exercise tolerance, requirements for modifying treatment, quality of sleep, school or work absence, performance of normal daily activities, medical office calls, emergency room visits, and hospitalizations. Home monitoring devices, such as the peak flow meter, serve as important indicators of day-to-day and within-day variability of pulmonary function. More complete pulmonary function tests should be performed at periodic intervals. Assessment of airway hyperresponsiveness may also be used at times to determine effects of treatment (see Section V B 2).

Effective use of therapeutic measures by the patient or family member at home provides earlier intervention, and earlier intervention during an acute exacerbation increases the likelihood that emergency medical requirements will be unnecessary. Asthma can be a dangerous disease. Recent increases in asthma morbidity and mortality in this country have been a sobering reminder of this fact. The severity of asthma is frequently misunderstood, and it is not infrequently misdiagnosed. Resourceful and knowledgeable physicians are required to distinguish the multiple precipitating factors of asthmatic symptoms and make appropriate individualized treatment decisions based on proper stepwise assessment of the patient's clinical status. It is now clear that quality care for asthma also requires a motivated and knowledgeable patient who understands the specific outcome goals of treatment. Cooperative management through continuing education and communication with patients is the responsibility of every physician who treats asthmatic patients. For this to be effective,

the practicing physician must be able to optimally diagnose and treat patients with asthma. This can best be accomplished by asthma specialists because of their specialized training and orientation. Early referral to asthma specialists (allergists and pulmonologists) (see Section IV) should be considered in all asthmatic patients, and in particular, those with asthma that is difficult to control.

REFERENCES

1. Martin AJ, McLennan LA, Landau LI. The natural history of childhood asthma to adult life. Br Med J 1980;280:1397-400.
2. Pearlman DS. Bronchial asthma: a perspective from childhood to adulthood. Am J Dis Child 1984;138:459-66.
3. Sly RM. Changing asthma mortality and sales of inhaled bronchodilators and anti-asthmatic drugs. Ann Allergy 1994; 73:439-43.
4. Evans R III, Mullally DI, Wilson RW, et al. National trends in the morbidity and mortality of asthma in the U.S.: prevalence, hospitalization, and death from asthma over two decades 1965-1984. Chest 1987;91(suppl):65S-74S.
5. Gergen PJ, Weiss K. Changing patterns of asthma hospitalization among children. JAMA 1990;264:1688-92.
6. Miller TP, Greenberger PA, Patterson R. The diagnsosis of potentially fatal asthma in hospitalized adults: patient characteristics and increased severity of asthma. Chest 1992;102: 515-8.
7. Rea HH, Scragg R, Jackson R, et al. A case-control study of deaths from asthma. Thorax 1986;41:833-9.
8. Malveaux FJ, Houliha D, Diamond EI. Characteristics of asthma mortality and morbidity in African-Americans. J Asthma 1993;30:431-7.
9. Strunk RC, Mrazek DA, Fuhrmann GSW, La Brecque JF. Physiologic and psychological characteristics associated with deaths due to asthma in childhood. JAMA 1985;254: 1193-8.

III. Summary statements

CONSULTATION WITH AN ASTHMA SPECIALIST

- The cooperative interaction between the patient and/or the patient's representative(s), the primary care physician/provider, and the asthma specialist is necessary to maximize the possibility of meeting the goals of asthma therapy, as stated in this document.
- It is important that the primary care physician/provider recognize the contribution that can be made by the asthma specialist in the management of asthma.
- The asthma specialist should recognize the importance of the primary care physician/provider in the continuing care of patients with asthma, which enhances the possibility of a successful outcome for the patient.
- Active participation of an asthma specialist in the continuing care of patients with asthma is associated with lower asthma morbidity, including fewer emergency room visits, decreased hospitalizations, reduced length of stay in the hospital, reduced number of days lost from school and work, and a reduction in the global cost of asthma care.
- There are a number of compelling reasons for recommending that a patient consult an asthma specialist, such as instability of the patient's asthma, the need for identification of possible allergenic or nonallergenic triggers, patient education and when the diagnosis of asthma is in doubt. For patients who meet these criteria, consultation with an asthma specialist should be obtained early during the treatment program.

DIAGNOSIS AND EVALUATION

A. Clinical evaluation of asthma

- Evaluation of asthma should include a detailed medical and environmental history and focus on potential allergic and nonallergic triggers.
- Other illnesses and medications may impact on the safety and effectiveness of treatment.
- Asthma may present only with chronic cough or dyspnea.
- Illnesses other than asthma may also present with cough, wheezing, dyspnea, and tightness in the chest.
- Asthma severity should be accurately determined on the basis of the history, physical examination, and some measure of pulmonary function.
- Known or suspected "triggers" of asthma can often be identified in the home, work, school, and recreational environments.
- An appropriate physical examination is essential.
- Clinical symptoms should be categorized according to intensity, duration, frequency, environmental or geographic changes, diurnal or circadian variation, and seasonal or nonseasonal occurrence.
- A careful assessment of the effectiveness and adverse effects of past medications is necessary.
- Treatment of patients with asthma must be individualized.

B. Physiologic evaluation

1. Pulmonary function testing

- The patient's perception and the physician's assessment of asthma severity may correlate poorly with the degree of airway obstruction.
- The degree of physiologic impairment of asthma can be significantly underestimated in some patients unless appropriate pulmonary function studies are obtained.
- A new patient evaluation for asthma generally should include spirometric determinations.
- Asthmatic patients may require some measurement of pulmonary function at each follow-up visit.
- Spirometry and peak expiratory flow rates are useful measures of airway function; spirometry provides more detailed information than does a peak flow rate.
- Spirometry helps differentiate obstructive from restrictive airway disease. However, other tests, such as lung volume and diffusing capacity, may be required.
- During treatment, lung function may remain significantly abnormal long after symptoms have abated and physical findings have returned to normal. Some patients may have complete resolution of symptoms despite little or no improvement in pulmonary function.

- A direct correlation exists between the amount of improvement in pulmonary function measurements after 4 to 6 hours of treatment for acute asthma, the rate of overall recovery, and the likelihood of relapse.
- High-dose systemic corticosteroid therapy should be continued for acute asthma until the patient has sufficiently improved as measured by the clinical response and/or pulmonary function tests.

2. Bronchoprovocation

- A positive inhalation challenge to "nonspecific" bronchoconstrictive substances, such as methacholine or histamine, demonstrates the presence of bronchial hyperresponsiveness and is highly associated with asthma but may also be seen in patients with other pulmonary diseases and even some normal individuals.
- A positive "nonspecific" challenge can help identify patients with atypical asthma, patients who have cough, chest tightness, or dyspnea alone, or patients with asthma who are in relative remission.
- A negative "nonspecific" bronchoconstrictive challenge can also alert the clinician to the possibility that the patient's "asthmatic" symptoms could be caused by other respiratory disorders such as endobronchial disease (e.g., tumor) or vocal cord adduction.
- Viral infections, viral vaccines, certain occupational exposures, and pollutants may produce bronchial hyperresponsiveness and thus a positive response to methacholine or other "nonspecific" challenge.
- A relationship may exist between the degree of bronchial hyperresponsiveness and the extent of treatment required to control symptoms in a certain subset of patients.
- Methacholine or other "nonspecific" forms of challenge need not be carried out in those with well-established asthma and should not be carried out in those with compromised pulmonary function.

C. Specific diagnostic techniques

1. Skin testing in the asthmatic patient

- Allergen skin testing, as performed by percutaneous and intracutaneous techniques, is the most sensitive method for detecting specific IgE antibody. However, the presence of specific IgE antibody does not alone establish the clinical relevance of specific allergens. Determination of the relevance of the skin test data depends on a detailed and enlightened evaluation of the history and appropriate follow-up.
- A positive immediate skin test reaction is a function of (1) the presence of IgE antibody for a specific allergen, (2) the releasability of mast cell mediators, (3) the reactivity of the patient's skin to histamine (the primary mediator of the immediate wheal-and-flare skin test), and (4) the amount of allergen injected.
- Allergen skin testing as part of an allergy evaluation is indicated to (1) aid in establishing an allergic basis for the patient's symptoms, (2) assist in establishing specific causes of the patient's symptoms, and/or (3) help evaluate the degree of sensitivity to a specific allergen.
- The number of skin tests appropriate at any one time may vary depending on the nature of the clinical problem, the age of the patient, potential allergen exposures, and the area of the country in which the patient resides. To properly interpret the results of allergen skin testing, it is essential to know which aeroallergens are present locally and clinically important. Furthermore, it is important to know which allergens in the area cross-react extensively with botanically related species.
- Skin testing is not without risk; although rare, fatal reactions from skin testing have occurred, more commonly with intracutaneous than with percutaneous testing. Skin testing should be deferred in patients experiencing an asthma exacerbation.
- Most antihistamines will suppress allergen skin tests for several days, although astemizole may produce skin test suppression for many weeks. Other medications commonly used to treat allergic conditions and asthma do not significantly suppress immediate skin test reactions to histamine or allergens.

2. Laboratory evaluation of the asthmatic patient

- No single laboratory test or group of tests can conclusively establish the diagnosis of asthma.
- Determination of total serum IgE is an imperfect determinant of the presence or absence of allergy. If high, it supports the presence of allergy and/or a condition such as allergic bronchopulmonary aspergillosis.
- Determination of allergen-specific IgE by in vitro assays may be preferable to skin testing in a small number of asthmatic patients, such

as those with severe skin disorders or those taking certain medications.

- The eosinophil is considered an important effector cell in asthma because of its ability to produce respiratory epithelial damage and bronchocentric inflammation. Total serum eosinophil counts may be elevated in untreated patients with asthma.
- If recurrent pneumonia or sinus infection occurs in asthmatic patients, immune deficiencies could be evaluated by determination of quantitative immunoglobulin levels, IgG subclass levels, and specific antibody responses after natural infection and immunization.
- Allergic bronchopulmonary aspergillosis can be diagnosed by several criteria including elevated total serum IgE levels and the presence of allergen-specific IgE and IgG antibodies.

3. Allergen inhalation challenge

- Allergen inhalation challenge is used most often as an experimental procedure to clarify mechanisms of bronchial hyperresponsiveness.
- Allergen challenge can be used to clarify the role of specific allergens in patients with asthma or to establish causal relationship of asthma with an occupational agent.
- Allergen challenges may also be useful to evaluate therapeutic effectiveness of medications and immunotherapy.
- Allergen inhalation challenge can document specific allergenic sensitivity in certain patients when skin tests cannot be performed or as a comparison with in vitro diagnostic tests when evaluating specific IgE-mediated sensitivity.
- Allergen inhalation challenge can trigger severe late-phase bronchial obstruction in certain patients, and precautions should be taken to prevent or treat this type of reaction.

4. Other diagnostic techniques

- The presence of eosinophils and other formed elements (Curschmann's spirals, Charcot-Leyden crystals, and creola bodies) in the sputum may have diagnostic significance.
- A chest radiograph should be considered in some patients to aid in (1) differentiating asthma from other conditions that may cause wheezing and (2) demonstrating possible complications of asthma.
- Sinus radiographs and/or computed tomographic (CT) scans should be considered if chronic sinusitis is suspected.
- Direct visualization of the upper and/or lower airway may be required to determine if wheezing is caused by mechanical obstruction.
- Special diagnostic procedures may be required to exclude the diagnosis of pulmonary embolism.
- Special tests are available to distinguish other diseases, such as carcinoid, mastocytosis, cystic fibrosis, and α_1-antitrypsin deficiency, which may masquerade as or coexist with asthma.

ASTHMA MANAGEMENT

A. Classification of asthma severity

- Attempts have been made to categorize severity of asthma on the basis of symptoms, impairment of activity, pulmonary function, degree of bronchial hyperreactivity, number of emergency visits, number of hospitalizations, and medication use. Although there is no universal acceptance of formal severity designations, a combination of subjective and objective criteria can be used as a guide to severity in individual patients.
- Severity of asthmatic symptoms can be ranked on the basis of duration throughout the day or night, as well as persistence throughout the week.
- Restriction of activity in asthmatic patients can be based on inability to work or attend school, as well as how many days per week or month the restriction is present.
- Pulmonary function testing can be used to assess severity of asthma, based on the predicted normal value or the patient's best attainable value.
- Severity of asthma can be based on the number of office or emergency room visits, as well as the number of hospitalizations required because of exacerbations of asthma.
- Treatment philosophies vary considerably; however, most physicians only prescribe daily oral corticosteroids for patients with severe asthma and avoid their use in patients with mild asthma. Therefore long-term administration of oral corticosteroids can be used to classify asthma as severe.

B. Severe acute intractable asthma

- Severe acute intractable asthma (status asthmaticus) requires prompt recognition, and intervention.

- The treatment of intractable asthma requires an understanding of physiologic abnormalities occurring as a consequence of increased air flow resistance resulting from bronchospasm, inflammation, and mucus plugging.
- The history must establish the features of the current attack and the presence of medical conditions that could complicate treatment of intractable asthma.
- Early in an asthma exacerbation, ventilation/perfusion mismatches are the predominant physiologic abnormality, and partial pressure of oxygen in arterial blood (Pao_2) decreases. Therefore oxygen administration is indicated in patients with severe acute intractable asthma.
- With increasing obstruction, ventilation is compromised and partial pressure of carbon dioxide in arterial blood ($Paco_2$) rises from initially low levels to "normal" levels. Therefore a $Paco_2$ of 40 torr may be a sign of severe asthma.
- Early in the treatment of intractable asthma, parenteral and inhaled sympathomimetic agents are equally effective in most patients. However, parenteral sympathomimetic agents may be indicated for patients who are not ventilating well enough to deliver adequate amounts of nebulized drug to the lower respiratory tract.
- Patients with severe, acute, intractable asthma will require corticosteroid administration. Early use is recommended because a lag time of several hours may occur before any clinical effect is noted.
- If aminophylline/theophylline is used, it is especially important to monitor blood levels and cardiopulmonary function.
- Overhydration may increase vascular hydrostatic pressure and decrease plasma colloid pressure, increasing the possibility of pulmonary edema, which is also favored by large negative peak inspiratory intrapleural pressures associated with acute asthma.
- The need for mechanical ventilation should be anticipated. Intubation may be difficult and if possible should be done by an individual experienced with such procedures.
- Hospital management of an acute asthma exacerbation includes repetitive administration of nebulized β_2–selective agents and systemic corticosteroids.

C. Identification of the fatality-prone asthmatic patient: Crisis plans

- Risk factors for life-threatening exacerbations of asthma include severe asthma, poor control of symptoms, atopy, psychological factors and failure by patient and/or physician to recognize the severity of the patient's asthma.
- Poor asthma control is undesireable; poor control of asthma symptoms is a special risk factor in the period after hospitalization.
- Allergic response to airborne mold *(Alternaria)* has been associated with life-threatening or fatal exacerbations in asthmatic patients.
- Psychological factors that may place the patient at risk of severe life-threatening asthmatic exacerbations include poor ongoing care by the patient and/or family, disregarding asthma symptoms, manipulative use of asthma, and significant emotional problems.
- Fatality-prone asthmatic patients require special planning, including regular follow-up visits for assessment of asthma control, measurement of pulmonary function in the office and at home, monitoring of the patient's course with regard to the need for specialist referral, specific treatment of factors that result in fatality-prone status, identification of a reliable advocate, involvement of community resources, development of a crisis plan, and notification of patient/parents of fatality-prone status.

D. Environmental avoidance

1. Airborne triggers

- Important steps in environmental control are as follows:
  - Minimize house dust mite exposure in mite-allergic patients with asthma.
  - Reduce exposure to domestic animals in appropriate patients.
  - Do not allow smoking in the home.
  - Avoid strong odors and chemical fumes.
  - Install kitchen and bathroom exhaust fans.
  - Use humidifiers with caution in mite- and mold-sensitive patients.
  - Use air conditioners in bedrooms and family rooms when appropriate.
  - Use high-efficiency particulate air filters (HEPA) or electrostatic air purifiers.
  - Install a dehumidifier and reduce water entry in damp basements.

- Initiate other measures for specific allergies as appropriate.

- Health care providers should identify allergic and nonallergic environmental triggers of asthma and implement environmental measures to eliminate or to minimize exposure to these factors.
- House dust mite sensitivity is a significant risk factor for many patients with allergic asthma. Extensive cleaning procedures minimize mite exposure, decrease bronchial hyperresponsiveness, and reduce asthma morbidity. Proposed environmental controls should be commensurate with the severity of the patient's disease, economic status of the family, and other practical considerations.
- Cockroach allergen has been recognized as a major cause of allergic rhinitis and asthma, especially in inner-city urban asthmatic patients. Exposure to rodent allergen may also be a significant factor in some asthmatic patients living in this setting.
- Tree, grass, and weed pollen can produce significant exacerbations of asthma at specific times of year. Every effort should be made to minimize indoor pollen contamination at home and at work by keeping windows closed and using filtration devices and air conditioning.
- Molds and fungi are aeroallergens that are recognized as triggers for asthma and rhinitis. Their ability to produce severe life-threatening exacerbations of asthma is well documented. For indoor molds, environmental control procedures include use of dehumidifiers and air conditioning. Avoidance of outdoor molds requires an understanding of areas where extensive mold growth can be anticipated.
- Nonallergic environmental triggers, such as cigarette smoke, chemical irritants, or strong odors, can also produce significant exacerbations of asthma. Avoidance of these triggers may be just as important as avoidance of allergic triggers.
- Domestic animals, especially cats and dogs, are a common cause of allergic reactions in individuals with allergic rhinitis and asthma.

2. Food hypersensitivity and asthma

- Allergies to foods can induce wheezing in a small number of patients with asthma.
- Evaluation of food hypersensitivity should be considered in patients with chronic symptoms, especially those in the pediatric age group with a history of atopic dermatitis.
- A positive prick test to suspected foods may suggest specific food allergens that require further study.
- A definitive diagnosis of food allergy is based on a double-blind, placebo-controlled oral challenge. Under certain circumstances, a presumptive diagnosis may suffice based on less stringent criteria.

3. Other nutritional considerations in the asthmatic patient

- Adequate nutrition is an essential part of the general treatment plan for asthmatic patients and should be emphasized especially when there are dietary restrictions related to food sensitivities or blunted appetite caused by medications.

E. Pharmacotherapy

β-adrenergic agonist bronchodilators

- Treatment of the asthmatic patient must be individualized.
- β-agonist bronchodilators vary in their degree of selectivity and range from nonselective (e.g., isoproterenol) to relatively β-selective agonists (β_2-agonists) (e.g., albuterol).
- It is preferable to use a β_2-agonist rather than a nonselective β-agonist because β_2-agonists have a longer duration of action and are less likely to produce cardiovascular side effects.
- The use of sustained release oral β_2-agonists may be appropriate and indicated for some asthmatic patients, especially in situations in which a long duration of effect is desired or the patient does not tolerate inhaled β_2-agonists. Otherwise, *inhaled* β_2-agonists are preferable to *oral* drugs of this type in the treatment of chronic asthma because they have a rapid onset of action, are generally more effective than other routes of administration, and infrequently produce adverse reactions.
- *Inhaled* β_2-agonists may be more effective when administered on an as-needed basis rather than on a regular basis in the treatment of many patients with chronic asthma. If greater than eight inhalations per day (or approximately one canister per month) are needed, the addition of cromolyn, nedocromil, or inhaled cortosteroids should be considered.
- *Inhaled* β_2-agonists are generally the safest and most effective treatment for acute asthma. In general, *oral* β_2-agonists should

not be administered for the treatment of acute severe asthma.

- The administration of β_2-agonists in the treatment of acute or chronic asthma is not a substitute for the early use of anti-inflammatory drugs.
- Patients must be carefully instructed, often more than once, in the use of inhaled β_2-agonists because a large percentage of patients fail to use inhaler devices correctly. Spacers attached to inhaled β_2-agonists improve drug delivery in patients who do not correctly use inhalers.
- Inhaled β_2-agonists, when administered 15 to 30 minutes before exercise, prevent exercise-induced bronchospasm in many patients. Inhaled β_2-agonists are generally considered the agent of choice for this purpose.
- Tolerance to β_2-agonists, which is usually reversible after the administration of corticosteroids, may develop after continued use of these drugs and may be associated with an unrecognized decrease in efficacy and delay in seeking medical attention.
- Bronchial hyperresponsiveness may increase in patients who receive inhaled β_2-agonists on a regular basis. This possibility should be considered in patients whose asthma is worsening on a regimen that includes the regular use of these drugs.
- Tremor and central nervous system effects are minimized by inhalation of β_2-agonists, although hypokalemia and significant cardiovascular effects can occur when these drugs are administered by this route.
- Serious adverse effects from the administration of β_2-agonists, when administered in recommended doses, are uncommon when given orally and extremely uncommon when administered by inhalation.
- Both β_2-agonists and nonselective β-agonists, when administered by inhalation, can produce a sudden paradoxical increase in bronchospasm, which may be life-threatening in some asthmatic patients.
- Salmeterol is a long-acting, highly β_2-selective β-agonist bronchodilator.
- Well-controlled studies have shown that the duration of action of salmeterol is 12 hours or longer in most patients.
- Pretreatment with single doses of salmeterol also prevents bronchospasm from histamine, methacholine, and cold air challenge.
- Salmeterol can protect patients against exercise-induced bronchospasm for up to 12 hours after administration.
- Because salmeterol is inherently different than short-acting inhaled β agonists, special recommendations must be considered when prescribing salmeterol for patients. In this regard salmeterol metered dose inhaler: (1) should not be initiated in patients with significantly worsening or acutely deteriorating asthma; (2) should not be used to treat acute symptoms; and (3) should not be considered a substitute for inhaled or oral corticosteroids.

Theophylline

- For the treatment of acute severe asthma, theophylline is less effective than inhaled or injected β_2-selective agonists.
- Maintenance therapy with theophylline is effective in reducing the frequency and severity of the symptoms of chronic asthma. It may be similar in effectiveness to cromolyn or β_2-agonists, and long-acting preparations allow for effective control of nocturnal symptoms.
- Patients with mild chronic asthma may be controlled at steady-state theophylline serum concentrations less than 10 μg/ml; patients with more severe disease may require concentrations greater than 10 μg/ml for effective control of symptoms. Although patients may experience significant adverse reactions at less than 10 μg/ml, as the serum concentration increases, the frequency and severity of toxicity increase. With levels less than 15 μg/ml severe adverse reactions are unlikely to occur.
- The rate of theophylline metabolism varies greatly among patients in the same age group and is influenced by numerous medical conditions and pharmaceutical interventions.
- The rate of theophylline metabolism is reduced, thereby leading to increased serum levels and increased potential for toxicity, in the presence of such conditions as cardiac decompensation, respiratory failure, hepatic cirrhosis, sustained high fever, viral infections, hypothyroidism, and after administration of cimetidine, oral contraceptives, troleandomycin, erythromycin, ciprofloxacin, and disulfiram. In contrast, factors such as cigarette or marijuana smoking, hyperthyroidism, rifampin, phenytoin, carbamazipine, and phenobarbital increase the rate of metabolism.
- Oral slow-release formulations generally provide stable serum concentrations and favor

patient compliance. However, the rate and extent of absorption vary between formulations, between individuals, and possibly in the same individual from time to time. Food ingestion may also affect the rate of absorption in different ways depending on the specific formulation.

- Dosage for long-term therapy is based on the principle of slowly titrating the dose over several days to circumvent transient caffeine-like side effects. Final dosage is usually based on the peak serum concentration measurement obtained at steady state.
- Elevated blood levels may produce neurologic, gastrointestinal (including gastroesophageal reflux [GER]), and/or cardiovascular side effects.
- Orally administered activated charcoal or charcoal hemoperfusion dialysis should be considered at toxic theophylline concentrations. Intravenous phenobarbital should also be considered to prevent seizures; diazepam, but not phenytoin, should be used to terminate seizures.

4. Anticholinergic agents

- The regular use of anticholinergic bronchodilators appears to be most effective in patients with chronic obstructive pulmonary disease who have partially reversible airflow obstruction.
- Inhaled anticholinergic medication is not sufficiently effective to be used as a single agent in the treatment of acute severe asthma but may provide benefit when combined with a β-agonist or other primary therapeutic agent.
- Inhaled anticholinergic agents, such as ipratropium, appear to be more effective when used to treat patients with chronic mild to moderate degrees of airflow obstruction.
- Inhaled anticholinergic medications, such as ipratropium, may be indicated in patients in whom alternative agents have not been sufficiently effective, are inappropriate because of other medical conditions, or have produced unacceptable side effects.

5. Antihistamines

- Antihistamines can be safely used in most patients with asthma.
- Antihistamines may be effective in the treatment of asthma because histamine, acting through H_1 receptors, produces smooth muscle contraction, an increase in vascular permeability, and stimulation of parasympathetic nerves, all of which are pathophysiologic features of asthma.
- Based on their ability to block late-phase responses to allergen exposure, newer antihistamines may play a greater role in the future treatment of asthma.
- Antihistamines may alleviate asthma somewhat through their direct effect on the bronchial passageways.
- There is a strong clinical impression that improvement of upper respiratory tract symptoms by antihistamines in patients who have concomitant allergic rhinitis and asthma may facilitate the treatment of lower respiratory tract symptoms.
- Although antihistamines are not the treatment of choice for exercise-induced bronchospasm, pretreatment may attenuate exercise-induced bronchospasm in some patients.
- Histamine is not the only mediator responsible for asthma symptoms, and therefore antihistamines, if used, should be considered adjunctive therapy in the treatment of asthma.

Cromolyn and nedocromil

- Cromolyn can be effective in many patients, alone or in conjunction with bronchodilators, in preventing the symptoms of mild-to-moderate asthma.
- Cromolyn has been demonstrated to be extremely safe, although serious adverse effects, such as bronchospasm, have been reported.
- Cromolyn can be effective in preventing or diminishing exercise-induced asthma when given 15 to 30 minutes before exercise.
- Overall, there is similar effectiveness with use of the metered-dose inhaler, Spinhaler, and solution for nebulization, although individual response must be considered in the choice of the product.
- Cromolyn has the ability to attenuate both early and late-phase IgE-mediated reactions.
- Nedocromil sodium is a topically active anti-inflammatory, pyranoquinoline which has mast cell–stabilizing properties.
- Nedocromil sodium has a number of putative mechanisms of action, as suggested by both animal in vivo experiments and in vitro effects on a variety of animal and human cell preparations.
- Nedocromil sodium is primarily indicated as a preventive drug in the management of asthma-associated chronic inflammation. If used

appropriately in this manner, it is effective in improving symptom scores, reducing bronchodilator use, and in some cases, other concomitant medications such as inhaled corticosteroids or cromolyn sodium.
- Clinical dosing is based on its long-term preventive effects. Because it is not a bronchodilator, it is not indicated in the treatment of acute asthma.
- Long-term use of nedocromil sodium is generally safe.
- Nedocromil sodium is clinically useful in the preventive treatment of mild and moderate asthma.

Corticosteroids

- With renewed awareness of the importance of airway inflammation in the pathogenesis and chronicity of asthma, it is generally felt that inhaled corticosteroids should be used as primary therapy in patients with moderate and severe chronic asthma.
- Systemic corticosteroids should be considered in the management of acute asthma when the patient does not respond readily to bronchodilators. Early use of corticosteroids shortens the course of asthma, prevents relapses, and reduces the need for hospitalization. The early use of corticosteroids is of particular importance in patients who have a history consistent with fatality-prone asthma.
- Intravenous corticosteroids may be lifesaving in the treatment of severe intractable asthma. After episodes of severe intractable asthma, complete restoration of pulmonary function may require weeks of treatment. Therefore after such events, corticosteroids should be continued at least until symptoms are controlled and pulmonary function is restored.
- Because of the potential for significant side effects from the prolonged use of systemic corticosteroids (and possibly high-dose inhaled corticosteroids), the need for oral corticosteroids should be monitored by pulmonary function tests, and inadequate control with maximal use of other treatment approaches should be a prerequisite for the long-term administration of systemic corticosteroids.
- Patients receiving systemic corticosteroids on a chronic basis may need to be carefully monitored for changes in the hypothalamo-pituitary-adrenocortical axis, bone changes, glucose metabolism, hypertension, and other potential side effects of such therapy under certain circumstances.

Hydration and pharmacomucolytic agents

- Adequate hydration is recommended for patients with asthma, but overhydration should be prevented by careful monitoring of fluid and electrolyte balance, especially in infants, in severely ill patients, and in the elderly. Dehydration may occur with severe asthma and should be corrected. However, fluid overload may have adverse pulmonary and circulatory effects and must be prevented by careful monitoring of fluid and electrolyte balance.
- Guaifenesin and potassium iodide may be worth a trial in some asthmatic patients, although the mechanisms of action are unclear.

Other considerations

a. Alternative therapy

- Whatever the reasons for failure to respond to corticosteroids, several treatment regimens for asthmatic patients who have not responded to systemic corticosteroids now exist.
- Steroid-sparing regimens or alternatives to systemic corticosteroid therapy include troleandomycin, methotrexate, gold and intravenous γ globulin therapy, which may be effective in some patients with asthma.
- It should be recognized that certain of these regimens are contraindicated in some patients and/or may be associated with significant adverse effects.

b. Role of antibiotics/antivirals

- Infections associated with asthma exacerbations are almost always viral in origin and do not require antibiotic therapy. Under these circumstances, however, reevaluation of the patient's treatment program, including bronchodilators and corticosteroids, may be important.
- Bacterial infections, such as acute and chronic sinusitis, should be treated appropriately, including the prompt and adequate use of antibiotics.
- Influenza can be associated with increased asthma. Therefore appropriate immunization is essential in patients with moderately severe or severe asthma.

Immunizations

- Routine vaccinations are not contraindicated in patients with asthma or other allergic conditions.
- Patients who have a history of egg sensitivity should be skin tested with the vaccination material. If results of the skin test are positive, the patient may be immunized with small increasing doses with use of an established protocol.
- Short-term, low-to-moderate dose systemic corticosteroids, alternate-day corticosteroids, or topical corticosteroids are not immunosuppressive and are *not* a contraindication for immunization.
- Influenza vaccine and pneumococcal vaccine are recommended for patients with chronic pulmonary disease including asthma.

Comparability of therapeutic products

- Comparability of inhaled products cannot be assumed because of potential differences in patient response to excipients or other "inactive" components in these products.
- Substitution of a theophylline product different from the one the patient was previously receiving can produce decreased efficacy or toxicity in some patients.
- Any adverse reaction that is temporally related to use of a drug product may be caused by the drug product even if the patient has tolerated the same drug in another product.

Polypharmacy

- Polypharmacy may be necessary and indeed desirable in the management of patients with asthma.
- The physician must guard against the unnecessary addition of medications that could increase morbidity and mortality in asthmatic patients.

F. Immunotherapy in the asthmatic patient

- Allergen immunotherapy can be effective in patients with asthma and may reduce the effect of chronic allergen stimulation on hyperresponsive airways. In most cases allergen immunotherapy should be considered as a part of a well-planned program that includes pharmacotherapy and avoidance measures.
- Allergen immunotherapy should be considered a long-term therapeutic modality in patients with allergic asthma.
- Patient compliance is essential for the effective and safe application of allergen immunotherapy.
- Although precise mechanisms for efficacy of allergen immunotherapy are unknown, several specific immunomodulatory pathways have been implicated.
- Immediate and delayed local and systemic reactions may occur in the course of allergen immunotherapy.
- Patients should be informed about the relative risks of immediate and delayed reactions associated with allergen immunotherapy.
- Both patients and medical personnel should be instructed in detail about prevention and treatment of reactions to allergen immunotherapy.
- Although life-threatening reactions during allergen immunotherapy are rare, fatalities can occur. Therefore supervising health care providers should be prepared to treat such reactions as promptly and effectively as possible.

G. Patient education

Cooperative management through education

- Educating asthmatic patients, parents, and family about their disease and methods of treatment is essential in the effective control of asthma.
- Educational programs for asthmatic patients have generally been successful in producing increased patient understanding of asthma and decreased morbidity.
- Patients should be educated to effectively monitor their asthmatic status and know how to respond to changes in their status.
- Patients should be educated in the proper technique required for the effective use of inhaled medications.
- Physicians should recognize patient concerns and resolve these concerns through increased patient confidence in the management approach and their ability to implement this approach in the treatment of their asthma.
- Asthma education requires an understanding by the patient and physician of certain basic concepts related to pathophysiology and treatment but must also be individualized for each asthmatic patient.

Compliance in asthma

- Patient noncompliance can be manifested as underuse, overuse, or erratic use of prescribed medication.

- Improvement in patient compliance may be influenced by knowledge about therapy, the patient-physician relationship, perceived seriousness of the condition, perceived benefit of intervention, complexity of the program, frequency of taking the medication, and cost.
- The most successful programs to improve patient compliance combine techniques of education, reinforcement, and family interactions.
- Lack of patient compliance is one of the most important underrecognized problems in medicine today and can be the result of psychological, economic, or educational factors.

Rehabilitation of the patient with asthma

- Specific goals of rehabilitation include maximizing school/work attendance, encouraging participation and productivity, encouraging participation in age-appropriate physical activities with peers, promoting self-esteem and self-confidence, and decreasing anxiety about the illness.
- Information needed to evaluate the need for and the effectiveness of a rehabilitation program should be obtained on a regular basis in the continuing care of a patient.
- Problems in any area of rehabilitation should prompt the initiation of specific measures to correct this deficiency.
- Community resources including structured fitness programs are available and should be used when appropriate.
- Rehabilitation goals should be coordinated and monitored by the physician so that therapy can be adjusted appropriately.

Asthma camps

- The major goal of a camp for children with asthma is to provide a positive learning experience in an enjoyable setting. The camp provides an environment that encourages social interests, reduces anxiety, and allows for a sense of independence.
- Operational guidelines for the camp should include administrative structure, medical structure, appropriate structure of activities, and camp format.

SPECIAL CONDITIONS

A. Concomitant conditions

- Weight control should be advised in patients with asthma because exogenous obesity may complicate the treatment of asthma.
- Although the coexistence of obstructive sleep apnea and asthma is rare, nocturnal asthma may be exacerbated in patients with both conditions.
- A decision regarding antituberculous chemotherapy in an asthmatic patient who requires corticosteroids should be carefully individualized if there is a documented past history of tuberculosis.
- Hyperthyroidism may aggravate asthma and complicate the management of asthmatic patients.
- Asthma in patients with Addison's disease is usually severe but improves with glucocorticoids.
- The best method of avoiding the diabetogenic properties of corticosteroids in asthmatic patients with diabetes is use of inhaled corticosteroids if the patient's asthma can be controlled with this form of therapy.
- The treatment of asthma in patients with coexisting hypertension and/or heart disease should be based on an understanding of the potential for asthma medications to exacerbate cardiovascular status and the potential for antihypersensitive medication and cardiac drugs to exacerbate asthma.
- Asthma medications are often useful in managing so-called "fixed" obstructive lung diseases in adults and children.
- Cessation of smoking by patient and family members should be a major goal in the overall management of asthma.

B. Asthma and anaphylaxis

- Anaphylaxis may be accompanied by sudden severe bronchospasm.
- Patients taking β-blockers who develop life-threatening anaphylaxis may respond poorly to usual treatment for anaphylaxis.
- Inhaled β_2-selective agonist bronchodilators and intravenous aminophylline may be required to reverse bronchospasm in patients not immediately responsive to subcutaneous epinephrine.
- Oxygen, 5 to 10 L/min, should be used when bronchospasm is accompanied by significant dyspnea or cyanosis.
- Prolonged therapy, including corticosteroids, may be necessary to reverse protracted anaphylaxis or anaphylaxis that occurs later after exposure to the triggering agent.

C. Management of asthma during pregnancy

- There is more risk to the mother and fetus during pregnancy from poorly controlled asthma than from the usual medications used to treat asthma.
- Asthmatic patients should not smoke, especially during pregnancy.
- Identification and avoidance of potential triggers of asthma are essential during pregnancy.
- Assessment of asthma should include regular measurements of pulmonary function during pregnancy.
- Pregnancy is not a contraindication to continued allergen immunotherapy in patients who are at maintenance.
- Additional considerations apply to the management of asthma during labor and delivery.
- In general, the same medications used during pregnancy are appropriate during labor and delivery.
- Oxytocin is the preferred medication for labor induction, and intracervical prostaglandin E_2 gel can be used for cervical ripening before labor induction.
- For regional anesthesia during labor and delivery, the concomitant use of epidural analgesia should be considered; for general anesthesia, ketamine may be the agent of choice, possibly with preanesthetic use of a β_2-agonist.
- Currently, oxytocin is considered the medication of choice for postpartum hemorrhage. Ergonovine and methylergonovine have been associated with bronchospasm.

D. Nocturnal asthma

- A high percentage of deaths occur during nocturnal and early morning periods.
- Nocturnal asthma has been associated with factors such as decreased pulmonary function, hypoxemia, decreased mucociliary clearance, and circadian variations of histamine, epinephrine, and cortisol concentrations.
- A general goal of asthma therapy should be the complete control of nocturnal symptoms.
- Longer acting, sustained-release theophylline preparations, long-acting preparations of oral β_2-agonists, or long-acting inhaled β_2-agonists may be an effective way to control nocturnal asthma in many patients.
- Better overall control of the patient's asthma may be necessary before nocturnal symptoms will be adequately controlled (i.e., avoidance, immunotherapy, and daytime medications, especially anti-inflammatory drugs such as corticosteroids and cromolyn).

E. Exercise-induced asthma

- Exercise-induced asthma (EIA) occurs in up to 90% of patients with asthma.
- EIA is probably triggered by heat and water loss from the respiratory tract, which causes mediator release resulting from bronchial hyperosmolality.
- Inhalation of a β_2-agonist 15 to 30 minutes before exercise is the treatment of choice for EIA.
- Inhaled cromolyn sodium, taken alone or in conjunction with an inhaled β_2-agonist 15 to 30 minutes before exercise, can also effectively prevent or modify EIA.
- Pretreatment with theophylline, anticholinergic agents, antihistaminic agents, and other medications (see text) may benefit some patients with EIA.
- General stabilization of the patient's asthma may be required before effective control of EIA can be achieved.
- Nonpharmacologic methods can be effectively used in some patients to prevent EIA (e.g., exercise under conditions in which warm humid air is inhaled).

F. Nasal and sinus disease and asthma

- Frequently there is an association between asthma and sinusitis, and improvement in asthma may occur when sinusitis is properly treated.
- Sinusitis should be considered in patients with refractory asthma.
- Evaluation of sinus disease may require sinus radiographs, CT scans, and/or endoscopic procedures.
- Many local and/or systemic factors may increase the risk of sinusitis developing. Certain diseases, such as cystic fibrosis, and local factors, such as nasal polyps, may increase the risk of developing sinusitis.
- Nasal polyps may occur in association with sinus disease and both conditions may affect asthma.

G. Gastroesophageal reflux (GER) and asthma

- GER occurs commonly in patients with asthma.

- GER should be suspected in patients with nocturnal asthma or in patients who are not responding adequately to optimal medical management.
- A number of objective diagnostic modalities are available for establishing a relationship between GER and asthma.
- Medical or surgical treatment of GER in asthmatic patients may improve their respiratory symptoms.
- Surgical correction of GER should only be considered when medical therapy is unsuccessful and a causal relationship between GER and asthma has been objectively established.

H. Aspirin-sensitive asthma/nonsteroidal anti-inflammatory drug/preservative sensitivity

- Aspirin-sensitive asthma (ASA) and nonsteroidal anti-inflammatory drug (NSAID) idiosyncrasy occurs in up to 10% to 15% of all asthmatic patients and in 30% to 40% of asthmatic patients with nasal polyps and pansinusitis. These reactions are non IgE mediated and designated as idiosyncracies.
- Ultimately, many of these patients become steroid dependent.
- ASA desensitization may be a useful therapeutic adjunct in some of these patients, especially those who have concurrent diseases that require ASA or NSAIDs.
- Sulfite additives in drugs and foods may induce severe adverse reactions in susceptible asthmatic patients.
- Tartrazine in foods or drugs may induce asthma in a small number of patients with ASA idiosyncrasy.
- Similar to ASA reactions, almost all of the reactions to tartrazine are not IgE mediated.
- Asthma may occur in a few monosodium glutamate–susceptible patients after challenge with this food-flavoring agent.
- Several other dye and preservative additives in foods and drugs have also been implicated as inducers of asthma.

I. The effects of air pollution in asthmatic patients

- Although asthmatic patients living in urban environments are generally exposed to a large number of pollutants, only a few have been implicated in causing adverse effects.
- Inhalation of sulfur dioxide, nitrogen dioxide, or ozone is capable of inducing bronchospasm in patients with asthma.
- One of the common sources of air pollution in residential areas, especially in western states, is household woodburning devices.
- Albuterol is the most selective and potent blocker of sulfur dioxide (SO)–induced airflow obstruction in asthmatic patients, and cromolyn sodium has also been shown to block SO_2-induced bronchoconstriction.

J. Psychological factors

- Asthma affects psychological and social aspects of life for virtually all patients with this disease.
- The patient may or may not be aware of the presence of psychological problems, which may constitute significant impediments to the optimal management of asthma.
- The management of psychological or social problems that accompany asthma depends on the extent to which they interfere with medical management or produce severe dysfunction in the patient's life.
- Age and maturity are important considerations in both the medical and psychological treatment of asthma.
- Family members of patients with severe asthma or asthma that is out of control require support from the clinician because of the demands of caring for an individual with asthma. Referral to support groups and/or counseling can be helpful in these situations.

K. Occupational asthma

- Occupational asthma may be induced or aggravated by variable periods of exposure to fumes, gases, dusts, or vapors.
- Symptom patterns of occupational asthma are variable and range from acute symptoms at work to late-onset responses after work.
- Specific causes of occupational asthma include immunologic, irritant, and direct pharmacologic stimuli. Many patients with immunologically induced occupational asthma have IgE-mediated sensitization to a variety of animal- and plant-derived proteins that provoke their symptoms.
- Preexisting atopy may constitute an increased risk factor for asthma caused by many occupational proteins but not by most low molecular weight chemicals.

- Other obstructive airway diseases such as chronic bronchitis, bronchiolitis obliterans, and emphysema may mimic occupational asthma.
- Some low molecular weight chemicals may also induce IgE-mediated clinical sensitization.
- After careful review of past medical records and a detailed history and physical examination, the diagnosis of occupational asthma can be accomplished by a combination of pulmonary function tests, skin tests, and blood tests. Inhalation challenge should be done when warranted.
- Removal of either the patient or the precipitant from the workplace environment is the most effective long-term treatment strategy.
- Some workers have persistent asthma for years after they are removed from the offending occupational agent.

L. Asthma in the school setting

- Asthma must be identified early to optimize treatment that can decrease school absenteeism and increase opportunities for participation in physical activity.
- Asthma can be effectively treated in most children by the use of readily available inhaled medications.
- Every effort should be made to normalize physical activity in children with asthma.
- Education programs for patients, parents, and teachers should be encouraged to provide better management of asthma in the school setting.

M. Special problems in asthma management due to socioeconomic, geographic, and cultural factors

- Asthma may present special problems in management related to living conditions, geographic location, availability of and access to health care professionals and health care facilities, socioeconomic status of the patient, and cultural differences in orientations to disease.
- Exposure to outdoor and indoor respiratory pollutants and allergens may be intensified in relation to socioeconomic and geographic factors.
- Inaccessibility to specialists who care for asthma may lead to episodic care, lack of follow-up, inadequate patient education, and possibly increased asthma mortality in urban African-Americans.
- Inaccessibility to specialists who care for asthma can be the result of difficult geographic or economic conditions, lack of health care coverage, and structured health care plans ("gatekeeper" concept).
- The selection of medications for the treatment of specific patients with asthma should take into consideration the education of the patient, the patient's mental status, the economic status of the patient, cultural approaches to the use of medications, and accessibility to medical care while providing the best approach to treatment possible for that individual patient.

N. Asthma in children

- Asthma is the most common chronic condition of childhood. The prevalence and severity of childhood asthma have increased substantially in recent years. Age-related differences in diagnostic and therapeutic considerations in childhood require special attention.
- Asthma can begin in infancy, although rarely in the first few months of life. Wheezing is a common symptom encountered in infancy through the first 2 to 3 years of life and may be a transient phenomenon in this age group. Many children develop persistent or recurrent wheezing, i.e., asthma. Persistent asthma that begins early is likely to be more severe.
- Atopy in the child, parental atopy or asthmatic history and maternal smoking are risk factors for persistent and recurrent asthma. Low lung function and maternal smoking are risk factors for transient wheezing.
- The history and physical examination, the mainstay of diagnosis in all age groups, present special problems in infants and young children. The diagnosis and estimation of asthma severity must depend more on the history and response to therapy as assessed by inconstant third-party observations than more continuous as well as more objective assessments possible in the older child and adult. Information from observers in and out of the home is important. Education of parents and other caretakers regarding how to assess possible signs and symptoms, their severity, and possible incitants can aid in diagnosis and therapy.
- Recurrent symptoms of prolonged cough, often with shortness of breath, with or without wheeze, suggest asthma. Demonstration of a

favorable clinical response to bronchodilator therapy and, when measurable, bronchodilation as demonstrated by pulmonary function testing helps confirm the diagnosis. A positive family history for allergic diseases or asthma, although not essential, tends to support a suspected diagnosis of asthma.

- It is important to realize that asthma may coexist with other conditions. Alternative or additional diagnosis should be entertained when the history is atypical or the response to good medical management is poor.
- Any aspect of the history that is atypical for asthma, such as a history of sudden onset of symptoms, coughing or wheezing with feedings, neonatal requirement for ventilatory support, or symptoms of stridor, may suggest the need to consider alternative diagnoses.
- A large number of conditions can result in symptoms suggestive of asthma. The most common nonasthmatic conditions in childhood that involve obstruction of the large airways include foreign body in the trachea, bronchus or esophagus, and laryngotracheomalacia. Obstruction involving both the large and small airways are most commonly due to viral bronchiolitis and cystic fibrosis.
- The differential diagnosis of the child with wheezing can be approached on an age-related basis. Infants are at a higher risk for congenital abnormalities and some infectious conditions. Aspiration of a foreign body and cystic fibrosis may occur in any age group, but most commonly present early in life. GER with pulmonary involvement may occur at any age. Vocal cord dysfunction and the hyperventilation syndrome merit consideration mainly in the adolescent age group.
- General observations that may be helpful in the evaluation of the infant or young child include assessment of clubbing of fingers or toes (suggesting cystic fibrosis, other chronic lung disease such as bronchiectasis, congenital heart disease, hepatobiliary disease rather than asthma), activity level, and status of growth and nutrition.
- In addition to physical findings pertinent to all age groups, the evaluation of respiratory effort and speech—hoarseness, stridor, and the ability to speak or cry normally—is particularly helpful in the infant and young child, especially during symptomatic episodes.
- Objective measurement of pulmonary function is important whenever possible not only to confirm the clinical diagnosis but to monitor asthma as well. Expiratory spirometry should be used as soon as the child is old enough to cooperate. Peak flow monitoring and pulmonary function measurements can generally be done by age 6 or 7 years and in some children peak flow measured as young as 3 to 4 years old.
- A chest x-ray film should be obtained at least once in any child with asthmatic symptoms sufficient to require hospitalization.
- The child who has had several exacerbations of asthma requiring in-hospital treatment or who has had a history of recurrent pneumonia should be considered a candidate for a sweat chloride test to rule out cystic fibrosis.
- Children with recurrent wheezing who have repeated bronchopneumonia confirmed by x-ray film should have an immunologic evaluation, including quantitative immunoglobulins and possibly specific antibody titers.
- The determination of specific IgE antibody by skin or in vitro tests is useful to evaluate potential allergic trigger factors in children with asthma or when a history suspicious of atopic etiology is obtained. Allergy testing can be used even in infancy, but it is most commonly useful in children over two years of age.
- Treatment of the child with asthma includes *all* of the following: (1) environmental control; (2) use of appropriate medications; (3) immunotherapy when indicated; (4) education of patient, family, and caregivers; and (5) close monitoring and follow-up. Aspects of responsibility for treatment may apply to all environments in which the child spends a significant amount of time, such as preschool, school, or day care.
- Environmental control for the child includes limiting exposure to cigarette smoke and other irritants, as well as to house dust mite, cockroach, mold, animal, and pollen allergens. The greatest effort is spent in relation to the bedroom, where children spend a major part of their time.
- Pharmacologic management of the child with asthma includes the use of short-acting β_2-adrenergic bronchodilators as needed to relieve acute symptoms and anti-inflammatory agents routinely to control chronic symptoms. Anti-inflammatory agents for the child include cromolyn sodium and inhaled steroids.

Nedocromil sodium is approved for use beginning in adolescence. Theophylline and oral long-acting β_2-adrenergic agents are used as adjunctive therapy. Systemic corticosteroids are used in short bursts (usually days) for acute severe asthma; long-term use is reserved for severe chronic asthma not adequately controlled with inhaled steroids at approved higher doses, and bronchodilators.

- Aerosolized preparations are preferred for the child because these generally induce fewer side effects; however, not all agents are available for use or have Food and Drug Administration approval for use in this age group. β-agonists, ipratropium bromide, and cromolyn sodium can be delivered by nebulizer; nebulized corticosteroids are not available in the United States. Spacers with a face mask can be helpful for delivery of medications through metered dose inhalers in very young children.
- Present data are inadequate to establish if inhaled steroids pose a risk for a more complicated course with varicella or other viral infections in children. The use of acyclovir and/or varicella immune globulin should be considered in children who have a negative varicella history and/or antibody titer and who receive or recently have received systemic steroids and have been exposed to varicella.
- Immunotherapy can be safe and effective for children with well-defined allergies whose clinical symptoms correlate with the sensitivities identified on allergy testing.
- Exercise-induced bronchospasm is common in children. Pretreatment with β_2-agonists and/or cromolyn sodium can prevent symptoms; β_2-agonists are useful in reversing symptoms. Optimal control of chronic asthma by anti-inflammatory therapy also can decrease the frequency and intensity of exercise-induced asthma.
- Children with asthma need to have their medications conveniently available at school. Designated school personnel and children themselves need to understand the use of each medication. The physician and parent have a joint responsibility to provide simple instructions for medication use.

IV. Consultation with an asthma specialist

SUMMARY STATEMENTS

- The cooperative interaction between the patient and/or the patient's representative(s), the primary care physician/provider, and the asthma specialist is necessary to maximize the possibility of meeting the goals of asthma therapy, as stated in this document.
- It is important that the primary care physician/provider recognize the contribution that can be made by the asthma specialist in the management of asthma.
- The asthma specialist should recognize the importance of the primary care physician/provider in the continuing care of patients with asthma, which enhances the possibility of a successful outcome for the patient.
- Active participation of an asthma specialist in the continuing care of patients with asthma is associated with lower asthma morbidity, including fewer emergency room visits, decreased hospitalizations, reduced length of stay in the hospital, reduced number of days lost from school and work, and a reduction in the global cost of asthma care.
- There are a number of compelling reasons for recommending that a patient consult an asthma specialist, such as instability of the patient's asthma, the need for identification of possible allergenic or nonallergenic triggers, patient education and when the diagnosis of asthma is in doubt. For patients who meet these criteria, consultation with an asthma specialist should be obtained early in the treatment program.

Cooperative management between the patient and/or the patient's representative(s), the primary care physician/provider, and the asthma specialist is of paramount importance in implementing the strategies necessary for the total care of the asthmatic patient. In this regard it is essential that the primary care provider recognize the important contribution that can be made by the asthma specialist in the management of asthma. Primary care providers should expect the board-certified asthma specialist to be trained and experienced in the care of asthma, including the ability to identify etiologic agents/trigger factors, educate patients about environmental controls, and formulate an asthma management program. In addition, the primary care provider should expect a prompt report from the asthma specialist as well as availability for follow-up consultation and comanagement if requested.

It is no less important that the asthma specialist recognize the role of the primary care physician/provider in ensuring continuity of care for patients with asthma and enhancing the possibility of a successful outcome for the patient. The ultimate goal of asthma care must be to improve the outcome and thereby produce a better quality of life for the patient with minimal complications while reducing, if possible, the cost of the disease for the patient and society.

Evaluation of a chronic inflammatory disease, such as asthma,[1-6] where successful management depends heavily on active patient and/or family participation and where there is a major need for intensive patient education and monitoring, is particularly difficult. In this setting it is appropriate to note that management of asthma by an asthma specialist has been associated with lower asthma morbidity, including fewer emergency room visits, decreased hospitalizations, reduced length of stay in the hospital, reduced number of days lost from school and work, and a reduction in the global cost of asthma care.[7-12b]

With this in mind, there are strong reasons for recommending that a patient consult an asthma specialist early in the treatment program. Although some of these situations are obviously more compelling than others, it must be recognized that they are all important in the successful management of asthma. These include:

1. instability of the patient's asthma; uncontrolled asthma may be associated with widely variable pulmonary functions and possibly high morbidity and mortality. Early comprehensive intervention may prevent these untoward events.[13-23] Such intervention should include development of a long-term treatment plan.
2. when the patient's response to treatment is limited, incomplete, or very slow and poor control interferes with the patient's quality of life
3. When in spite of taking anti-inflammatory medications regularly, the patient must use an

inhaled β-agonist frequently, exclusive of its use in exercise-induced asthma.
4. if there is a need for frequent adjustments of therapy because of unstable asthma.
5. for identification of allergens or other environmental factors that may be causing the patient's disease; patients with asthma must have access to a thorough etiologic evaluation.*
6. when allergen immunotherapy is a consideration.†
7. when the patient and the primary caregiver need intensive education in the role of allergens and other environmental factors.
8. when family dynamics interfere with patient care and/or there is a need for further family education about asthma.
9. when a patient has a chronic cough, refractory to usual therapy.
10. when coexisting illnesses and/or their treatment complicate the management of asthma.
11. when the patient has recurrent absences from school or work due to asthma.
12. when the patient experiences continuing nocturnal episodes of asthma.
13. when the patient is unable to participate in normal daily activities and sports because of limited exercise ability despite use of inhaled β_2-agonists before exercise.
14. when the patient requires multiple medications on a long-term basis.
15. when frequent bursts of oral corticosteroids or daily oral corticosteroids are required.
16. when the patient exhibits excessive lability of pulmonary function, such as, highly variable peak flow rates.
17. when the diagnosis of asthma is in doubt.
18. when there is concern about side effects that have occurred or may occur, for example, with use of oral or orally inhaled corticosteroids in children.
19. when preventive measures need to be considered for the high-risk, predisposed infant with a family history of asthma or atopy.
20. sudden severe attacks of asthma.
21. hospitalization of the patient for asthma.
22. severe episodes of asthma resulting in loss of consciousness.
23. seizures, near-death episodes, or respiratory failure requiring artificial respiration.
24. when emergency visits are required to control the patient's asthma.
25. when the patient asks for a consultation.

Only through cooperative interaction between the patient and/or the patient's representative(s), the primary care provider, and the asthma specialist is it possible to maximize the possibility of meeting the stated goals of asthma therapy. The goals of asthma therapy should include:

1. individualization of assessment and treatment
2. general improvement in patients' quality of life
3. asthma co-management after a treatment plan developed with active participation of patient and caregivers
4. optimal control of asthma with the use of the least amount of medication possible, administered in a manner that permits the most normal lifestyle, and is associated with minimal side effects
5. reduction in emergency care visits
6. reduction in hospitalizations
7. prevention of nocturnal symptoms
8. minimization of time lost from work, school, and daily activities
9. tolerance to physical activity appropriate for the patient's age
10. prevention of asthma in high-risk (or predisposed) persons
11. prevention of complications, including fixed airway obstruction/chronic obstructive pulmonary disease
12. optimization of pulmonary function
13. improvement of the self-image of the patient

* Because the etiology of asthma may be elusive and often multifactorial, historical review by a person especially trained in uncovering environmental factors, as well as the appropriate use of diagnostic studies, such as skin testing, can enhance the search for causative and contributory factors of asthma. In this regard it should be noted that allergy plays a causal or contributory role in asthma.[24-26] Establishing the specific allergens to which a patient is allergic is a requisite to the development of an effective preventive program of avoidance of allergens. For example, exposure to high levels of dust mites and cockroach is associated with a markedly increased risk of developing asthma.[13-15, 27]

† When allergen immunotherapy is appropriate for the long-term management of asthma, only those physicians with acceptable training in the intricacies of this procedure should initiate such a program. This training should include an understanding of the principles involved in initiation of immunotherapy, selection of dosage, and safety surveillance of patients receiving immunotherapy. Immunotherapy should not be initiated casually or by persons who are not fully trained in its use.

based on a full understanding of the disease and confidence in outlining treatment approaches

Based on these comments, the importance of consultation and interaction between the primary care provider and the asthma specialist in achieving these goals is apparent.

REFERENCES

1. Woolcock AJ. Review, use of corticosteroids in treatment of patients with asthma. J ALLERGY CLIN IMMUNOL 1989; 84:975-8.
2. Kamm RD, Drazan JM, et al. Airway hyperresponsiveness and airway wall thickening in asthma: a quantitative approach. Am Rev Respir Dis 1992;145:1249-50.
3. Ollerenshaw SL, Woolcock AJ. Characteristics of the inflammation in biopsies from large airways of subjects with asthma and subjects with chronic airflow limitation. Am Rev Respir Dis 1992;145:922-7.
4. Barnes PJ. Allergic inflammatory mediators and bronchial hyperresponsiveness. Immunol Allergy Clin North Am 1990;10:241.
5. Hargreaves FE, Gibson PG, Ramsdale EH. Airway hyper responsiveness, airway inflammation, and asthma. Immunol Allergy Clin North Am 1990:10:439.
6. Schlosberg M, Liv MC, Bocher BS. Pathophysiology of asthma. Immunol Allergy Clin North Am 1993:13:721.
7. Bucnall CE, Robertson C, Moran F, Stevenson RD. Differences in hospital management. Lancet 1988:2:748-50.
8. Zeiger RS, Heller S, Mellon MH, Wald J, Falkoff R, Schatz M. Facilitated referral to asthma specialists reduces relapses in asthma emergency room visits. J ALLERGY CLIN IMMUNOL 1991;87:1160-8.
9. Doan T, Grammer LC, Yarnold P, Patterson R. An intervention program to reduce costs of asthma care in patients who have required intubation. J ALLERGY CLIN IMMUNOL 1993;91:319.
10. Mayo PH, Richman J, Harris HW. Results of a program to reduce admissions for adult asthma. Ann Intern Med 1990;112:864-72.
11. Fowles J, Schoenwetter W, Pheley A, McCoy C, Engel W, Lurie N. Measuring the severity and outcomes of asthma care by generalists and allergists. J ALLERGY CLIN IMMUNOL 1990;85:195.
12. Ross RN, Morris M, Berman BA. Cost effectiveness of including cromolyn sodium in the treatment programme for asthma: a retrospective record-based study. Clin Ther 1988;10:188-203.
12a. Kotses H, Bernstein IL, Bernstein DI, et al. A self-management program for adult asthma. Part I: development and evaluation. J ALLERGY CLIN IMMUNOL 1995;95:529-40.
12b. Taitel MS, Kotses H, Bernstein IL, Bernstein DI, Creer TL. A self-management program for adult asthma. Part II: cost-benefit analysis. J ALLERGY CLIN IMMUNOL 1995;95:672-6.
13. Gelber LE, Seltzer LH, Bouzoukis JK, Pollart SM, Chapman MD, Platts-Mills TA. Sensitization and exposure to indoor allergens as risk factors for asthma among patients presenting to hospital. Am Rev Respir Dis 1993;147:573-8.
14. Call RS, Smith TF, Morris E, Chapman MD, Platts-Mills TA. Risk factors for asthma in inner-city children. J Pediatr 1992;121:862-6.
15. Xang BC, Wu CW, Johnson J. Characteristics and diagnosis of cockroach-sensitive bronchial asthma. Ann Allergy 1992;68:237-44.
16. Sears MR, Hervison GP, et al. The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. Clin Exp Allergy 1989;19:419-24.
17. Squillace SP, Platts-Mills TAE, Hooker J, et al. The prevalence of asthma and its relationship to atopic status in children [Abstract]. J ALLERGY CLIN IMMUNOL 1993;91:308.
18. Sporik R, Rose B, Muller M, et al. Relationship between wheezing, bronchial hyperreactivity (BHR) and skin tests among school children in Los Alamos, NM [Abstract]. J ALLERGY CLIN IMMUNOL 1993;91:307.
19. Arruda K, Rizzo MC, Chapman MD, et al. Exposure and sensitization to dust mite allergens among asthmatic children in São Paulo, Brazil. Clin Exp Allergy 1991;21: 433-9.
20. Platts-Mills TAE, Thomas WR, Aalberse RC, et al. Dust mite allergens and asthma: report of a second international workshop. J ALLERGY CLIN IMMUNOL 1992;89:1046-60.
21. Sporik R, Holgate ST, Platts-Mills TAE, et al. Exposure to house dust mite allergen *(Der p1)* and the development of asthma in childhood: a prospective study. N Engl J Med 1990;323:502-7.
22. Lau S, Falkenhorst G, Weber A, et al. HLgh mite-allergen exposure increases the risk of sensitization in atopic children and young adults. J ALLERGY CLIN IMMUNOL 1989;84: 718-25.
23. Ehnert B, Lau-Schadendorf S, Weber A, et al. Reducing domestic exposure to dust mite allergen induced bronchial hyperreactivity in sensitive children with asthma. J ALLERGY CLIN IMMUNOL 1992;90:135-8.
24. Burrows B, Martinez FD, Halonen M, et al. Association of asthma with serum IgF levels and skin test reactivity to allergens. N Engl J Med 1989;320:271.
25. Kallid JN, Goldstein BM, Braman SS, Seltipane GA. High frequency of atopic asthma in a pulmonary clinic population. Chest 1989;96:1336-40.
26. Randolph C, Faser B. Inhalant allergy as a trigger for asthma. Am J Asthma Allergy Pediatricians 1993;6:129-37.
27. Kang BC, Johnson J, Veres-Thorner C. Atopic profile of inner-city asthma with a comparative analysis on the cockroach-sensitive and ragweed-sensitive subgroups. J ALLERGY CLIN IMMUNOL 1993;92:802-11.

V. Diagnosis and evaluation

A. CLINICAL EVALUATION OF ASTHMA

Summary Statements

- Evaluation of asthma should include a detailed medical and environmental history and focus on potential allergic and nonallergic triggers.
- Other illnesses and medications may impact on the safety and effectiveness of treatment.
- Asthma may present only with chronic cough or dyspnea.
- Illnesses, other than asthma, may also present with cough, wheezing, dyspnea, and tightness in the chest.
- Asthma severity should be accurately determined on the basis of history, physical examination, and some measure of pulmonary function.
- Known or suspected "triggers" of asthma can often be identified in the home, work, school, and recreational environments.
- An appropriate physical examination is essential.
- Clinical symptoms should be categorized according to intensity, duration, frequency, environmental or geographic changes, diurnal or circadian variation, and seasonal or nonseasonal occurrence.
- A careful assessment of the effectiveness and adverse effects of past medications is necessary.
- Treatment of patients with asthma must be individualized.

Evaluation of the asthmatic patient begins with a detailed history of the patient's symptoms and factors that precipitate these symptoms. Patient assessment should include not only a detailed history of the present illness but also an accurate determination of known or suspected triggers.

Asthma triggers

I. Allergic
   1. Pollen
   2. House dust mite
   3. Cockroach allergens
   4. Animal allergens
   5. Feathers
   6. Mold spores
   7. Food allergens
   8. Medications
   9. Occupational chemicals
   10. Allergenic extracts

II. Nonallergenic
   1. Outdoor and indoor air pollutants
   2. Cigarette smoke
   3. Strong odors
   4. Aerosolized sprays
   5. Medications (acetylsalicylic acid, nonsteroidal anti-inflammatory drugs [NSAIDs], β-blockers)
   6. Preservatives (sulfites)
   7. Viral upper respiratory tract infections
   8. Temperature changes
   9. Climatic conditions
   10. Occupational chemicals
   11. Exercise
   12. Emotional and psychological factors
   13. Sinusitis
   14. Gastroesophageal reflux
   15. Nasal reflexes
   16. Hormonal changes
   17. Localized obstruction

Asthma frequently has an allergic basis, particularly in children and young adults. Data suggest that allergic factors may be involved in all age groups.[1,2] Therefore in all asthmatic patients, the allergic status must be carefully considered, including the presence of other allergic conditions and/or an allergic family history. The presence of concomitant allergic conditions (e.g., atopic dermatitis, allergic rhinitis, and food hypersensitivity) may increase the physician's awareness about: (1) an underlying allergic basis of the patient's asthma; (2) whether the presenting symptoms actually represent asthma; and (3) whether treatment of the concomitant condition could impact on the management of asthma.

Evaluation of the asthmatic patient should include consideration of other medical conditions that could influence the diagnosis and treatment of asthma (e.g., hypertension or cardiac conditions for which β-blockers have been prescribed or musculoskeletal disease for which NSAIDs are indicated).

The history of the present illness should be used to determine as accurately as possible: (1) whether the patient has asthma or another medical condition (see below) that could present in the same way (i.e., patients with asthma may have cough or

dyspnea alone,[3] whereas patients with cardiac disease may have wheezing, cough, dyspnea, chest pain, and/or chest tightness); (2) the severity of the patient's asthma based on life-threatening episodes, hospitalizations, emergency or acute physician care visits, quality of life, chronic corticosteroid use, school or work days missed, limitation of activity, and impact on the patient's family; (3) the pattern of the patient's symptoms over time, including relationship to home and work environments, seasonal exacerbations or perennial nature of symptoms, effect of geographic location, frequency, and fluctuations of the patient's symptoms including lability and diurnal variation; (4) the circumstances surrounding the onset of the disease; and (5) the type of previous treatment and response.

Selected clinical conditions requiring consideration in the differential diagnosis of asthma*

I. Infants and children
   A. Airway obstruction resulting from foreign body or congenital abnormalities
   B. Viral bronchiolitis
   C. Cystic fibrosis
   D. Bronchopulmonary dysplasia
   E. Recurrent aspiration
   F. Immunodeficiency
   G. Cardiac disease
   H. Upper airway disease (infants and very young child)

II. Adults
   A. Laryngeal dysfunction
   B. Mechanical obstruction
   C. Chronic bronchitis and emphysema
   D. Left ventricular failure
   E. Pulmonary embolus
   F. Pulmonary infiltrates with eosinophilia

The evaluation of the asthmatic patient must be individualized. This includes: (1) establishing the profile of a typical asthmatic episode and the temporal development of the attack with management and outcome; (2) obtaining information about other medications that could influence response to asthma medications (i.e., drugs that affect theophylline clearance); (3) obtaining information about the patient's home environment (i.e., type of pillows, covering for mattresses, presence of pets, exposure to cigarette smoke, presence of cockroaches, frequency of cleaning, type of heating, presence of air conditioning); (4) evaluation of the patient's workplace may provide important clues regarding the cause of the patient's symptoms; and (5) development of the disease (e.g., age of onset, progression, etc.).

Physical examination of the patient with asthma should be directed primarily, but not exclusively, at the upper and lower respiratory tracts. Findings consistent with rhinitis and sinusitis may need further evaluation and treatment not only with regard to those conditions but also because of the recognized association between these conditions and exacerbation of asthma symptoms. Nasal polyps may contribute to upper respiratory symptoms with or without associated sinus disease and also alert the physician to increased risk from the administration of NSAIDs. Examination of the lungs may demonstrate findings consistent with asthma or may raise concern about other clinical conditions, such as left ventricular failure in the patient who has basilar rales associated with a gallop rhythm noted on examination of the heart.

The history and physical examination are not only important starting points in the evaluation of the patient with asthma, but they are also essential ingredients in establishing the diagnosis and subsequent management of the patient.

*For an expanded list see references 4 and 5.

REFERENCES

1. Burrows B, Martinez FD, Halonen M, et al. Association of asthma with serum IgE levels and skin test reactivity to allergens. N Engl J Med 1989;320:271.
2. Kalliel JN, Goldstein BM, Braman SS, Seltipane GA. High frequency of atopic asthma in a pulmonary clinic population. Chest 1989;96:1336-40.
3. Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: spectrum of frequency of causes and successful outcome of specific therapy. Am Rev Respir Dis 1981;123:413.
4. Ellis EF. Asthma in infancy and childhood. In: Middleton E Jr, ed. Allergy principles and practice. St. Louis: The CV Mosby Co, 1988:1037-62.
5. Mathison DA. Asthma in adults. In: Middleton E Jr, ed. Allergy principles and practice. St. Louis: The CV Mosby Co, 1988:1063-92.

B. PHYSIOLOGIC EVALUATION

1. Pulmonary function testing

Summary statements

- The patient's perception and the physician's assessment of asthma severity may correlate poorly with the degree of airway obstruction.
- The degree of physiologic impairment of asthma can be significantly underestimated in

some patients unless appropriate pulmonary function studies are obtained.

- A new patient evaluation for asthma generally should include spirometric determinations.
- Asthmatic patients may require some measurement of pulmonary function at each follow-up visit.
- Spirometry and peak expiratory flow rates are useful measures of airway function; spirometry provides more detailed information than does a peak flow rate.
- Spirometry helps differentiate obstructive from restrictive airway disease. However, other tests, such as lung volume and diffusing capacity, may be required.
- During treatment, lung function may remain significantly abnormal long after symptoms have abated and physical findings have returned to normal. Some patients may have complete resolution of symptoms despite little or no improvement in pulmonary function.
- There is a direct correlation between the amount of improvement in pulmonary function measurements after 4 to 6 hours of treatment for acute asthma, the rate of overall recovery, and the likelihood of relapse.
- High-dose, systemic corticosteroid therapy should be continued for acute asthma until the patient has sufficiently improved as measured by the clinical response and/or pulmonary function tests.

Patient and physician assessment of asthma often correlates poorly with degree of airway obstruction.[1-3] Despite intensive patient education, some patients continue to have difficulty perceiving the severity of their airway obstruction on the basis of symptoms alone. Even attempts to develop a multifactorial assessment index to predict asthma severity have been unsuccessful.[4-6] Because the degree of physiologic impairment, asthma severity, and clinical outcome cannot be reliably determined unless objective measures of airway function are used, it is recommended that pulmonary function testing be a consistent part of asthma evaluation and treatment. Because there may be patients in whom the correlation between ventilatory tests and arterial blood gas determinations is weak, arterial blood gases may also be required in the assessment of acute, severe asthma, especially if the possibility of respiratory failure is suspected.[7-12]

Diagnosis

Although both spirometry and peak expiratory flow rate (PEFR) are effort dependent tests, they are generally reliable and reproducible measures of airway function. This type of pulmonary function test is invaluable for diagnosing, assessing the severity of, and managing asthma.[13, 14] Every new patient evaluation should include spirometric measurements. Patients with stable asthma should have pulmonary function measured at periodic intervals. Either PEFR, measured with a reproducible flow measuring device such as a peak flow meter, or spirometric measurements are acceptable. However, spirometric measurements provide additional information about the respiratory pattern and degree of small airway obstruction, which is not obtained by measuring PEFR. If pulmonary function tests are used in clinical practice, their performance and interpretation should conform to guidelines set by the American Thoracic Society.[15] Because poor patient effort can only be ascertained by direct examination of a spirographic record, the PEFR may not be as reliable a test of airway obstruction as spirometry in certain cases. Those interpreting pulmonary function tests should take into consideration the fact that they are effort dependent, particularly PEFR.

Abnormal values consistent with airway obstruction are often considered to be less than 80% of predicted normal values for forced vital capacity (FVC), FEV_1, FEV_1/FVC, and PEFR and less than 65% predicted normal for forced expiratory flow (FEF_{25-75}).[16-19] Regression equations for predicted normal values of these ventilatory tests are readily available and are directly related to demographic variables of age, race, height, and weight. A 15% or greater increase in FEV_1 after administration of a bronchodilator indicates that a significant reversible component is present.[13] However, failure of FEV_1 to improve by at least 15% after administration of a bronchodilator does not necessarily mean that the patient will not benefit from long-term administration of corticosteroids or bronchodilators.[13, 9-21] Significant improvement in FEV_1 (15%) after the long-term administration (2 to 6 weeks) of asthma medications is still consistent with a diagnosis of asthma. Thus, patients with severe chronic asthma may require a 2-week course of high-dose corticosteroid treatment (e.g., 40 mg daily) before improvement of ventilatory function is apparent. Patients who fail to respond to this trial regimen may either have corticosteroid-resistant asthma or nonreversible pulmonary obstruction, which occurs in chronic bronchitis

and/or emphysema. In addition, patients who have paroxysms of wheezing and dyspnea and who are refractory to standard asthma therapy should be evaluated during symptomatic periods to rule out the presence of upper airway obstruction by inspiratory and expiratory flow-volume loops.[22, 23] Each patient's best FEV_1 should be used for comparison because asthmatic patients may have an FEV_1 greater or lower than the predicted normal value when in remission.

Severe asthma

In severe asthma dyspnea and wheezing are generally associated with functional derangement, but the extent of disease may not always be delineated by the clinical examination.[24, 25] The only signs that correlate well with severe airway obstruction are accessory muscle contraction and pulsus paradoxicus.[7, 24] However, after initiation of asthma therapy, these signs resolve rapidly and even after the patient becomes asymptomatic, lung function may remain markedly abnormal.[7, 24] In addition, as many as 8% of patients may have complete resolution of symptoms without improvement in FEV_1.[4-8] The FEV_1 may not return to baseline for weeks after a severe attack.

Adult patients with an initial PEFR less than 25% predicted or an FEV_1 less than 30% predicted frequently require hospitalization despite appropriate therapy in the emergency room setting.[2] Nevertheless, although neither the initial response to therapy nor the likelihood of relapse after emergency treatment can be consistently and accurately predicted by the initial severity of airway obstruction,[8, 26-29] a PEFR or an FEV_1 that improves to greater than 50% of the normal predicted value after emergency therapy frequently makes hospitalization unnecessary.[12] In addition, the degree of improvement in the FEV_1 or PEFR after 4 to 6 hours of treatment may predict the speed of recovery, as well as the likelihood of relapse if the patient is discharged.[8, 9, 26] For example, it has been shown in adult asthmatic patients that improvement of less than 400 ml in FEV_1 is associated with a relapse rate of 67%, whereas only 4% of patients whose FEV_1 improves 1300 ml relapse.[8] It is important to note that these values are only rough guidelines. Although it is unlikely that a single variable will predict the outcome of acute asthma well enough to be solely relied on for early planning of patient disposition, pulmonary function testing should be considered a vital guide in predicting the outcome of emergency therapy.[27]

Hospitalized patients

Once patients are admitted to the hospital, signs and symptoms of asthma frequently resolve within 24 hours.[7, 9, 26] For this reason, high-dose corticosteroid therapy should be maintained until the patient's FEV_1 returns toward baseline after bronchodilator use. If patients are discharged before this time, relapse is more likely. In addition, nearly 80% of hospitalized patients continue to have a significant degree of diurnal variation in lung function despite initial improvement.[26] Persistent nocturnal asthma is known to be associated with an unfavorable prognosis for relapse.[30-33] It may be necessary to measure lung function as frequently as every 4 hours to determine whether a patient is experiencing nocturnal bronchoconstriction.[26] Once patients have responded to treatment and are not experiencing significant nocturnal variation in lung function, discharge can be considered. However, physiologic derangement may continue and the partial pressure of oxygen in arterial blood (Pao_2) may not normalize for an additional 1 to 2 weeks.[7, 9] Because recovery after hospitalization may not be immediate, pulmonary function tests at appropriate intervals may be helpful in guiding further treatment. Patients should be monitored frequently until airway function is stabilized, particularly while corticosteroid therapy is being tapered.

Chronic asthma

Evidence of airflow limitation is frequently present in chronic, asymptomatic asthma, and patients with episodic asthma show considerable variability in pulmonary function even when they are free of symptoms. Although FEV_1 and PEFR may be normal during these asymptomatic periods, abnormalities of dynamic compliance and forced flow rates at low lung volumes may be detected.[34] One of the low lung volume flow rate tests, the FEF_{25-75}, is a more variable measurement of airway obstruction than FEV_1, but decrease of this parameter may suggest the presence of residual small airways obstruction in some asthmatic patients. Such a finding is more likely to portend spontaneous asthma recurrence and increased levels of bronchial hyperresponsiveness.[35, 36] Irreversible airflow obstruction may be related to the persistence of small airway obstruction and duration and severity of the patient's asthma.[37, 38] Therefore one goal of long-term asthma therapy should be to maintain airway function as near normal as possible.[39] The only realistic way to achieve this goal is to measure pulmonary function

routinely in these patients. It is not usually difficult to educate adults about the use of a peak flow meter or how to perform spirometry. With appropriate training, 4- to 5-year-old children can frequently use a peak flow meter correctly, and most 6- to 7-year-old children can perform spirometry. Because asthma patients find it difficult to perceive the severity of their airway obstruction, the home use of a peak flow meter is highly recommended when following a patient with unstable disease. Twice-daily PEFR measurements before and after bronchodilator use on awakening and between 4 and 6 PM are particularly valuable for monitoring both the caliber and responsiveness of a patient's airways and for measuring the degree of nocturnal bronchoconstriction. One indication of nocturnal lability, which should guide treatment strategies, is a greater than 20% difference between morning and evening PEFR values. Serial PEFR tests during work and off-work periods should also be considered for detection of occupational asthma.

REFERENCES

1. Shim CS, Williams MS Jr. Evaluation of the severity of asthma: patients versus physicians. Am J Med 1980;68:11-3.
2. Sly PD, Landau LI, Weymouth R. Home recording of peak expiratory flow rates and perception of asthma. Am J Dis Child 1985;139:479-82.
3. König P, Rejent A. Subjective and objective means of assessing cystic fibrosis and asthma. Ann Allergy 1982;49: 86-92.
4. Fischl MA, Pitchenik A, Gardner LB. An index predicting relapse and need for hospitalization in patients with bronchial asthma. N Engl J Med 1982;305:783-9.
5. Rose CC, Murphy JG, Schwartz JS. Performance of an index predicting the response of patients with acute bronchial asthma to intensive emergency department treatment. N Engl J Med 1984;310:573-7.
6. Centor RM, Yarbrough B, Wood JP. Inability to predict relapse in acute asthma. N Engl J Med 1984;310:577-80.
7. Rebuck AS, Read J. Assessment and management of severe asthma. Am J Med 1971;51:788-98.
8. Kelsen SG, Kelsen DP, Fleegler BF, Jones RC, Rodman T. Emergency room assessment and treatment of patients with acute asthma. Am J Med 1978;64:622-8.
9. Jenkins PF, Benfield GFA, Smith AP. Predicting recovery from acute severe asthma. Thorax 1981;36:835-41.
10. McFadden ER Jr, Lyons HA. Arterial blood gas tensions in asthma. N Engl J Med 1968;278:1027-32.
11. Rebuck AS, Pengelly LD. Development of pulsus paradoxus in the presence of airway obstruction. N Engl J Med 1973;288:66-9.
12. Nowak RM, Tomlanovich MC, Saka DD, Kvale PA, Anderson JA. Arterial blood gasses and pulmonary function testing in acute bronchial asthma. JAMA 1983;249: 2043-6.
13. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987;136: 225-44.
14. Gold WM. Clinical and physiologic evaluation of asthma. Chest 1985;87 (suppl):30s-2s.
15. American Thoracic Society. Standardization of spirometry—1987 update. Am Rev Respir Dis 1987;136:1285-98.
16. Wall MA. Office pulmonary function testing. Pediatr Clin North Am 1984;31:773-83.
17. Weng TR, Polgar G. The functional development of the respiratory system from the period of gestation to adulthood. Am Rev Respir Dis 1979;120:625-95.
18. Hsu KHK, Jenkins DE, Hsi BP, et al. Ventilatory functions of normal children and young adults—Mexican-American, white and black: spirometry. J Pediatr 1979;95:14-23.
19. Ramsdell JW, Nachtway FJ, Moser KM. Bronchial hyperreactivity in chronic obstructive bronchitis. Am Rev Respir Dis 1982;126:829-32.
20. Eaton ML, Green BA, Church MS, McGowan T, Niewoehner DE. Efficacy of theophylline in "irreversible" airflow obstruction. Ann Intern Med 1980;92:758-61.
21. Hill NS. The use of theophylline in "irreversible" chronic obstructive pulmonary disease. Arch Intern Med 1989;148: 2579-84.
22. Kryger M, Bode F, Antic R, Anthonisen N. Diagnosis of obstruction of the upper and central airways. Am J Med 1976;61:85-93.
23. Christopher KL, Wood RP, Eckert RC, Blager FB, Raney RA, Souhrada JF. N Engl J Med 1983;308:1566-70.
24. McFadden ER Jr, Kiser R, DeGroot WJ. Acute bronchial asthma, relations between clinical and physiologic manifestations. N Engl J Med 1973;288:221-5.
25. Shim CS, Williams MH Jr. Relationship of wheezing to the severity of obstruction in asthma. Arch Intern Med 1983; 143:890-2.
26. Petheram IS, Jones DA, Collins JV. Patterns of recovery of airflow obstruction in severe acute asthma. Postgrad Med J 1979;55:877-80.
27. Ownby DR, Abarzna J, Anderson JA. Attempting to predict hospital admission in acute asthma. Am J Dis Child 1984;138:1062-6.
28. Lulla S, Newcomb RW. Emergency management of asthma in children. J Pediatr 1980;97:346-50.
29. Martin TG, Elenbass RM, Pingleton SH. Failure of peak expiratory flow rate to predict hospital admission in acute asthma. Ann Emerg Med 1982;11:466-70.
30. Bellia V, Bonsignore G. Validation of morning dip of peak expiratory flow as an indicator of the severity of nocturnal asthma. Chest 1988;94:108-10.
31. Hetzel MR, Clark TJH, Branthwaite MA. Asthma: analysis of sudden death and ventilatory arrest in hospital. Br Med J 1977;1:808-11.
32. Bellia V, Cibella F, Migliara G, Peraita G, Bonsignore G. Characteristics and prognostic value of morning dipping of peak expiratory flow rate in stable asthmatic subjects. Chest 1985;88:89-93.
33. Turner-Warwick M. On observing patterns of airflow obstruction in chronic asthma. Br J Dis Chest 1977;71:73-86.
34. Ferguson AC. Persisting airway obstruction in asymptomatic children with asthma with normal peak expiratory flow rates. J ALLERGY CLIN IMMUNOL 1988;82:19-22.
35. McFadden ER Jr. Asthma: airway dynamics, cardiac function and clinical correlates. In: Middleton E Jr, Reed CE, Ellis ER, eds. Allergy principles and practice, Vol 2. St. Louis: The CV Mosby Co, 1978:687-707.

36. Benson MK. Bronchial hyperreactivity. Br J Dis Chest 1975;69:227.
37. Brown PJ, Greville HW, Finucane KE. Asthma and irreversible airflow obstruction. Thorax 1984;39:131-6.
38. Kraemer R, Meister B, Schaad UB, Rossi E. Reversibility of lung function abnormalities in children with perennial asthma. J Pediatr 1983;102:347-50.
39. Woolcock AJ. Inhaled drugs in the prevention of asthma. Am Rev Respir Dis 1977;115:191-4.

2. Bronchoprovocation

Summary statements

- A positive inhalation challenge to "nonspecific" bronchoconstrictive substances, such as methacholine or histamine, demonstrates the presence of increased bronchial responsiveness and is highly associated with asthma, but may also be seen in patients with other pulmonary diseases and even some normal individuals.
- A positive "nonspecific" challenge can help identify patients with atypical asthma, patients with cough, chest tightness, or dyspnea alone, or patients with asthma who are in relative remission.
- A negative "nonspecific" bronchoconstrictive challenge can also alert the clinician to the possibility that the patient's "asthmatic" symptoms could be caused by other respiratory disorders such as endobronchial disease (e.g., tumor) or vocal cord adduction.
- Viral infections, viral vaccines, certain occupational exposures, and pollutants may produce increased bronchial hyperresponsiveness and hence a positive response to methacholine or other "nonspecific" challenge.
- A relationship may exist between the degree of bronchial hyperresponsiveness and the extent of treatment required to control symptoms in a certain subset of patients.
- Methacholine or other "nonspecific" forms of challenge need not be carried out in patients with well-established asthma and should not be carried out in patients with compromised pulmonary function.

By definition, asthmatic patients have bronchial hyperresponsiveness to one or more triggers, including allergens, irritants, temperature and osmolar changes, and exercise. Nonallergic stimuli have been referred to as "nonspecific" and have been used to help establish the presence of hyperresponsive airways. Methacholine for inhalation challenge is the only "nonspecific" substance approved by the Food and Drug Administration for this indication and is marketed for this purpose as Provocholine. Other techniques, such as exercise, sulfur dioxide (SO_2) inhalation, cold air challenge, nonisotonic aerosols, including ultrasonic nebulized distilled water, and hypertonic saline, have been used as an alternative to the procedures mentioned above.[1, 2]

Clinical indications for assessment of airway reactivity

The primary clinical indication for methacholine (or histamine) inhalation challenge is for the identification of atypical or occult asthma, which characteristically presents as cough, dyspnea, and/or chest tightness with or without other symptoms, but with normal or near-normal pulmonary function.[3, 4] In addition, assessment of induced bronchial hyperresponsiveness by methacholine challenge may be helpful diagnostically in patients with suspected occupational asthma where there is continued exposure to a suspected trigger. It is also a generally accepted procedure in the evaluation of chronic cough or respiratory distress of unknown cause, especially in patients with normal physical examination and normal or near-normal pulmonary function, who have failed a therapeutic trial with a bronchodilator. If methacholine challenge is positive in such patients, the physician is generally justified in attempting a more aggressive asthma treatment regimen. On the other hand, a negative methacholine challenge requires consideration of a more comprehensive workup for endobronchial disease, including tumor. Bronchial hyperresponsiveness, as demonstrated by histamine or methacholine challenge, also correlates generally with degree of illness in terms of symptom scores and medication requirements.[5, 6] It should be noted that a negative methacholine challenge does not rule out nor a positive methacholine challenge rule in the diagnosis of asthma.

Interpretation of inhalation challenge data

Patients are generally considered to have increased bronchial hyperresponsiveness if there is a 20% or greater fall in FEV_1 after inhalation of a concentration of up to 8 to 25 mg/ml.

Several factors can influence response to "nonspecific" inhalation challenge and must be considered when the test is conducted. Most important of these is the current medication being used by the patient. Most bronchodilators, cromolyn sodium, and possibly antihistamines may partially or completely inhibit "nonspecific" inhalational challenges. The recommended time

interval between the last dose of specific types of medication and inhalation challenge has been published.[7]

Acute viral infections, including influenza, vaccines for influenza, rubeola vaccination, and exposure to pollutants such as nitrous oxide and sulfur dioxide, can increase airway responsiveness to pharmacologic bronchoconstrictors such as methacholine.[8] Recent exposure to allergen has also been associated with increased "nonspecific" hyperresponsiveness.[9] On the other hand, seasonal exposure to naturally occurring allergens may not always increase cholinergic reactivity.[10]

Inhalation challenge with pharmacologic bronchoconstrictors, such as methacholine, is not necessary for diagnostic purposes in most patients with well-established asthma. However, these patients may be challenged within the confines of clinical and research protocols, which are generally reviewed by an institutional review board and require informed consent. Generally, patients with an FEV_1 less than 70% of predicted should not undergo inhalation challenge.

Methodology

Standard methodology for inhalation challenge has been published.[11] A dose schedule for challenge with methacholine (Provocholine) can be found in the package insert for this product.

The provocative dose that produces a 20% fall in FEV_1 (PD_{20} FEV_1) is a measure of the degree of patient sensitivity to an inhaled agent. PD_{20} FEV_1 for methacholine is quite reproducible; the end point usually varies by only threefold or 0.5 log. Other pulmonary function tests can also be used. These include FVC, FEV-1, MMEF ($FEF_{25-75\%}$), PEFR, specific airway conductance, and functional residual capacity.[8] Although not generally used, patient reactivity to inhalation challenge can be assessed by the slope of the dose-response curve. Another method of analysis computes the area under the dose-response curve, a type of analysis that is primarily used for research.[11]

Patients who do not respond to five standardized inhalations of methacholine at the 25 mg/ml concentration are generally considered to have a negative challenge, although some normal individuals will react at a concentration between 10 and 25 mg/ml or less.[12]

Summary

Methacholine challenge, as well as other types of "nonspecific" challenge, can provide valuable information on the degree of airway hyperresponsiveness. A positive methacholine challenge demonstrates the presence of *increased* bronchial hyperresponsiveness, which is one of the characteristic features of asthma. It must be remembered, however, that a positive methacholine challenge is not seen in all asthmatics and not all patients with a positive methacholine challenge have asthma.

REFERENCES

1. Anderson SD, Smith CM. Provocative challenge procedures: background and methodology. In: Spector SL, ed. The use of nonisotonic inhalants for evaluating bronchial hyperresponsiveness. Mt. Kisco, New York: Futura Publishing, 1989:227-52.
2. Eliasson A, Phillips Y, Rajagopal KR, Howard RS. Sensitivity and specificity of bronchial provocation testing—an evaluation of four techniques in exercise-induced bronchospasm. Chest 1992;102:2.
3. Pratter MR, Hingston DM, Irwin RS. Diagnosis of bronchial asthma by clinical evaluation: an unreliable method. Chest 1983;84:42.
4. Corrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. N Engl J Med 1979;300:633.
5. Cockcroft DW, Lillin DN, Mellon JJA, Hargreave FE. Bronchial reactivity to inhaled histamine: a clinical survey. Clin Allergy 1977;7:235.
6. Lam S, Wong R, Yeung M. Nonspecific bronchial reactivity in occupational asthma. Allergy Clin Immunol 1979;63:28.
7. Allergen inhalation challenge procedures. In: Spector SL, ed. Provocative challenge procedures: background and methodology. Mount Kisco, New York: Futura Publishing Co, 1989:316.
8. Cropp GJA, Bernstein IL, Boushey HA, et al. Guidelines for bronchial inhalation challenges with pharmacologic and antigenic agents. Am Thoracic Soc News 1980;67:11.
9. Cockcroft DW, Ruffin RE, Dolovich J, Hargreave FE. Allergen-induced increase in nonallergic bronchial reactivity. Clin Allergy 1977;7:503.
10. Rosenthal RR, Bleecker ER, Laube B, Norman PS, Permutt S. Effect of environmental antigen on cholinergic hyperreactivity. Chest 1979;75:228.
11. Chai H, Farr RS, Froehlich LA, et al. Standardization of bronchial inhalation challenge procedures. J ALLERGY CLIN IMMUNOL 1975;56:323.
12. LaBraico JM, Reed CE, Rosenthal RR, Shapiro G, Spector SL, Townley RG. Multicenter evaluation of airway hyperreactivity using a standardized methacholine challenge. J ALLERGY CLIN IMMUNOL 1984;73(suppl):124.

C. SPECIFIC DIAGNOSTIC TECHNIQUES
Skin testing in the asthmatic patient

Summary statements

- Allergen skin testing, as performed by percutaneous and intracutaneous techniques, is the

most sensitive method for detecting specific IgE antibody. The presence of specific IgE antibody does not, however, alone establish the clinical relevance of specific allergens. Determination of the relevance of the skin test data depends on a detailed and enlightened evaluation of the history and appropriate follow-up.

- A positive immediate skin test reaction is a function of (1) the presence of IgE antibody for a specific allergen, (2) the releasability of mast cell mediators, (3) the reactivity of the patient's skin to histamine (the primary mediator of the immediate wheal-and-flare skin test), and (4) the amount of allergen injected.
- Allergen skin testing as part of an allergy evaluation is indicated to (1) aid in establishing an allergic basis for the patient's symptoms, (2) assist in establishing specific causes of the patient's symptoms, and/or (3) help evaluate the degree of sensitivity to a specific allergen.
- The number of skin tests appropriate at any one time may vary depending on the nature of the clinical problem, the age of the patient, potential allergen exposures, and the area of the country in which the patient resides. To properly interpret the results of allergen skin testing, it is essential to know which aeroallergens are present locally and clinically important. Furthermore, it is important to know which allergens in the area cross-react extensively with botanically related species.
- Skin testing is not without risk; although rare, fatal reactions from skin testing have occurred, more commonly with intracutaneous than with percutaneous testing. Skin testing should be deferred in patients experiencing an asthma exacerbation.
- Most antihistamines will suppress allergen skin tests for several days, although astemizole may produce skin test suppression for many weeks. Other medications commonly used to treat allergic conditions and asthma do not significantly suppress immediate skin test reactions to histamine or allergens.

A positive immediate hypersensitivity skin test to an allergen demonstrates the presence of specific IgE antibody to that allergen on mast cells in the patient's skin. It has been reported that 73% to 84% of asthmatic patients undergoing diagnostic evaluation in several large clinics had positive immediate skin tests to common inhalant allergens.[1-3] However, not all of these positive skin test reactions were clinically relevant. Nevertheless, the high prevalence of positive immediate hypersensitivity skin test reactions in the asthmatic population is a strong argument for the inclusion of skin testing in the initial evaluation of patients with asthma.

Used in conjunction with a carefully obtained history, allergen skin testing can be helpful in determining an allergic basis for the patient's symptoms. In general, the patient's history is not a definitive means for ruling out sensitivity to indoor allergens to which they are continuously exposed, and only objective testing for immediate hypersensitivity will provide this information.

The presence of specific IgE antibodies, as demonstrated by positive immediate hypersensitivity skin tests, is a risk factor for chronic persistent asthma.

The immunologic and pathophysiologic basis for the immediate skin test reaction

As mentioned previously, the immediate wheal-and-flare skin test, produced by introduction of an allergenic extract into the skin, is a reflection of the presence of IgE specific for that allergen. IgE on mast cells in the skin is in turn in equilibrium with levels of IgE in the blood. When allergen bridges at least two molecules of receptor-bound IgE, a series of events within the mast cell is initiated that result in the release of a variety of mediators, most notably histamine. Histamine acts directly on the postcapillary venules to increase vascular permeability, which results in the wheal of the immediate skin test reaction. It also stimulates nerve endings, thereby initiating an axon reflex. This results in the release of neuropeptides, such as substance P, which give rise to the zone of erythema (flare) surrounding the wheal.

Skin testing versus in vitro testing

The presence of specific IgE antibodies can be determined by either allergen skin testing or in vitro tests. Both skin tests and in vitro tests can be performed with standardized and stable materials, and both can be made as quantitative as is required. The major differences between these two methods are that skin tests are faster, more

sensitive, and measure mast cell releasability, whereas in vitro tests are not influenced by medications. Even percutaneous tests (prick/puncture), which are less sensitive than intradermal skin tests, are generally more sensitive than in vitro tests.[4-7] On the other hand, in vitro tests might be considered if dermatographism or extensive dermatitis is present and could be considered in certain children and in other clinical situations.

Techniques of skin testing

Skin testing for the diagnosis of immediate hypersensitivity is performed by one of two methods, percutaneous or intracutaneous. Both methods yield similar information. The intracutaneous method is more sensitive and reproducible, whereas the percutaneous (prick/puncture) method is more rapidly performed, less painful, and probably associated with fewer systemic reactions.[8] Because of these advantages, percutaneous testing is usually performed initially followed by intracutaneous testing for those allergens that fail to react on percutaneous testing. Because intracutaneous tests are 100 to 1000 times more sensitive than prick/puncture tests for a given antigen, an alternative method is to use an appropriately lower concentration of antigen by the intracutaneous method.

Percutaneous testing can be performed by three methods. A scratch can be made in the skin onto which a drop of allergenic extract is placed. Alternatively, a drop of extract can be placed on the intact skin followed by insertion of a needle downward at a 90-degree angle to the skin (puncture) or at approximately a 45-degree angle with subsequent upward motion (prick). A number of devices are commercially available for performing these tests, varying from simple needles to multiple-headed devices for performing tests in batches.[9] Intracutaneous testing is performed by injecting 0.01 to 0.02 ml of diluted extract into the epidermis. Intracutaneous testing is most conveniently performed on the arm, whereas percutaneous testing is usually performed on the back or arm.

Quality control is vital in skin testing. The reagents should be properly prepared, standardized, and stored. A negative control (saline) and a positive control (e.g., histamine) should always be included to assess the general skin reactivity of the patient.

Interpretation of skin tests

The presence of specific IgE antibody does not alone establish the clinical relevance of specific allergens.[10, 11] Determination of the relevance of the skin test data depends on a detailed and enlightened evaluation of the history and appropriate follow-up (see section on clinical evaluation). In some instances, positive skin tests are predictive of future development of symptoms when the patient is exposed to these allergens.[12] However, in many cases, the degree of sensitivity, extent of exposure to that allergen, and end organ susceptibility are not sufficient to produce clinical symptoms. Interpretation of late-phase skin test reactions occurring 4 to 6 hours after skin testing requires further assessment in the future.

Selection of allergens for testing

To properly interpret the results of diagnostic allergen testing, it is essential to know which aeroallergens are present locally and clinically important. Furthermore, it is important to know which allergens in the area cross-react extensively with botanically related species.[13] Based on a knowledge of the local aerobiology and the extensiveness of the allergenic cross-reactivity, it may be possible to determine a patient's allergic status with fewer skin tests and avoid treating sensitivities that are not clinically relevant. However, the number of skin tests necessary to adequately assess sensitivity to local inhalant allergens will vary greatly with the botanical complexity of the region, mobility of the patient and in some instances cannot be numerically limited because of diversity of exposure and minimal cross-reactivity. For example, the number of tree and mold skin tests will generally be greater in areas of high precipitation.

Selection of patients for skin testing

Skin testing is not without risk; although rare, fatal reactions from skin testing have occurred[14] more commonly with intracutaneous than with percutaneous testing (perhaps because allergen is introduced deeper and systemic absorption is more rapid). Such reactions have also occurred more commonly after skin testing with very potent allergens such as cottonseed, flaxseed, nuts, and penicillin. Skin testing should be deferred in patients experiencing an asthma exacerbation.

Asthmatic patients who have experienced an anaphylactic reaction and pregnant women warrant special consideration with regard to skin testing.

Skin testing can generally be safely performed

during pregnancy,[15] although the rare occurrence of a systemic reaction could initiate uterine contractions and possibly abortion. Despite this slight risk, information about specific sensitivities may enhance the management of an asthmatic patient during pregnancy.

Skin testing in infants and elderly

The positive immediate skin test reaction is a function of (1) the presence of IgE antibody for a specific allergen, (2) the releasability of mast cell mediators, (3) the reactivity of the patient's skin to histamine (the primary mediator of the immediate wheal-and-flare skin test), and (4) the amount of allergen injected. The latter in turn is dependent on the potency of the allergenic extract and whether the route of administration is percutaneous (prick/puncture) or intracutaneous. Specific IgE antibody levels (on which a positive skin test depends) are low or nondetectable at birth, rise to a peak in the second and third decade, and then gradually decline throughout the remainder of the patient's life. Reactivity to histamine is also low at birth, rises rapidly during infancy,[16] peaks in the third decade, and declines again after age 50.[17] As a result, interpretation of an allergen skin test reaction in infants and the elderly must be based on degree of reaction to the histamine control. If this is done, allergen skin testing can provide reliable results in patients of any age.

Suppression of skin tests by medication

H_1 histamine receptor antagonists, (e.g., chlorpheniramine, diphenhydramine, hydroxyzine, terfenadine, and astemizole) have a marked and often prolonged suppressive effect on immediate skin tests. Most antihistamine will suppress allergen skin tests for several days,[18] although astemizole may produce skin test suppression for a number of weeks.[19, 20] Therefore H_1 histamine receptor antagonists should be stopped 48 to 72 hours before skin testing except for astemizole, which should be discontinued at least 6 weeks before skin testing. The degree of skin test suppression can be gauged by a histamine control skin test. H_2 receptor antagonists (e.g., cimetidine and ranitidine) also have a small suppressive effect on allergen skin tests (up to 10% to 15% of the diameter of the skin test response),[21] which can add to the suppression by H_1 antagonists.[22] Discontinuation of H_2 antagonists on the day of testing is probably sufficient to prevent significant suppression of skin tests. In addition to classic antihistamines, tricyclic antidepressants, most notably doxepin, can significantly suppress immediate skin test reactivity.[23]

Other medications commonly used to treat allergic conditions and asthma do not significantly suppress immediate skin test reactions to histamine or allergens. This includes theophylline, β-adrenergic agonist bronchodilators,[24] anticholinergic medications, cromolyn, and corticosteroids (at least in doses equivalent to 24 mg/day of methylprednisolone or less, administered for a period of 1 week or less).[25]

REFERENCES

1. Cooke RA. Infective asthma: indications of its allergic nature. Am J Med Sci 1930;183:309.
2. Chafee FH, Settipane GA. Aspirin intolerance: I. Frequency in an allergic population. J ALLERGY CLIN IMMUNOL 1974;53:193.
3. Hendrick DJ, Davies RJ, D'Souza MF, et al. An analysis of skin prick test reactions in 656 asthmatic patients. Thorax 1975;30:2.
4. Malling H-J, Dreborg S, Weeke B. Diagnosis and immunotherapy of mold allergy. III: diagnosis of cladosporium allergy by means of symptom scores, bronchial provocation test, skin prick test, RAST, CRIE, and histamine release. Allergy 1986;41:57.
5. Vanto T. Efficiency of different skin prick testing methods in diagnosis of allergy to dog. Ann Allergy 1982;49:340.
6. Brown WE, Halonen MJ, Kaltenborn WT, et al. The relationship of respiratory allergy, skin test reactivity, and serum IgE in a community population sample. J ALLERGY CLIN IMMUNOL 1979;63:328.
7. Nelson HS. Clinical relevance of IgE. Ann Allergy 1982;49:73.
8. Nelson HS. Diagnostic procedures in allergy: I. Allergy skin testing. Ann Allergy 1983;51:411.
9. Adinoff AD, Rosloniec DM, McCall LL, et al. A comparison of six epicutaneous devices in the performance of immediate hypersensitivity skin tests. J ALLERGY CLIN IMMUNOL 1989;84:168-74.
10. Curran WS, Goldman G. The incidence of immediate reacting allergy skin tests in a "normal" adult population. Ann Intern Med 1961;55:777.
11. Lindblad JH, Farr RS. The incidence of positive intradermal reactions and demonstration of skin sensitizing antibody to extracts of ragweed and dust in humans without history of rhinitis or asthma. J Allergy 1961;32:392.
12. Hagy GW, Settipane GA. Prognosis of positive allergy skin tests in an asymptomatic population: a three-year follow-up of college students. J Allergy 1971;48:200.
13. Martin BG, Nelson HS, Mansfield LE. Cross-allergenicity among the grasses. Ann Allergy 1985;54:91.
14. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy and skin testing. J ALLERGY CLIN IMMUNOL 1987;79:660.
15. Metzger WJ, Turner E, Patterson R. The safety of immunotherapy during pregnancy. J ALLERGY CLIN IMMUNOL 1978;61:268.
16. Menardo JL, Bousquet J, Rodiere M, et al. Skin reactivity in infancy. J ALLERGY CLIN IMMUNOL 1985;75:646.
17. Barbee RA, Brown WG, Kaltenborn W, Halonen M,

Allergen skin-test reactivity in a community population sample: correlation with age, histamine skin reactions, and total serum immunoglobulin E. J ALLERGY CLIN IMMUNOL 1981;68:15.
18. Cook TJ, MacQueen PM, Wittig HJ, et al. Degree and duration of skin test suppression and side effects with antihistamines. J ALLERGY CLIN IMMUNOL 1973;51:71.
19. Davies R, Brooke M, Griffith J. Skin test recovery after astemizole therapy. Rev Esp Allergol Immunol Clin 1987; 2:79.
20. Malo JL, Fu L, L'Archeveque J, Ghezzo H, Cartier A. Duration and the effect of astemizole on histamine inhalation tests. J ALLERGY CLIN IMMUNOL 1990;56:323.
21. Miller J, Nelson HS. Suppression of immediate skin tests by ranitidine [Abstract]. Ann Allergy 1988;60:154.
22. Harvey RP, Schocket AL. The effect of H_1 and H_2 blockade on cutaneous histamine response in man. J ALLERGY CLIN IMMUNOL 1980;65:136.
23. Sullivan TJ. Pharmacologic modulation of the whealing response to histamine in human skin: identification of doxepin as a potent in vivo inhibitor. J ALLERGY CLIN IMMUNOL 1982;69:260.
24. Abramowitz PW, Perez MM, Johnson CE, et al. Effect of theophylline, terbutaline, and their combination on the immediate hypersensitivity skin test reaction. J ALLERGY CLIN IMMUNOL 1980;66:123.
25. Slott RI, Zweiman B. A controlled study of the effect of corticosteroids on immediate skin test reactivity. J ALLERGY CLIN IMMUNOL 1974;54:229.

Laboratory evaluation of the asthmatic patient

Summary statements

- No single laboratory test or group of tests can conclusively establish the diagnosis of asthma.
- Determination of total serum IgE is an imperfect determinant of the presence or absence of allergy. If high, it supports the presence of allergy and/or a condition such as allergic bronchopulmonary aspergillosis.
- Determination of allergen-specific IgE by in vitro assays may be preferable to skin testing in a small number of asthmatic patients, such as those with severe skin disorders or those on certain medications.
- The eosinophil is considered an important effector cell in asthma because of its ability to produce respiratory epithelial damage and bronchocentric inflammation. Total serum eosinophil counts may be elevated in untreated patients with asthma.
- If recurrent pneumonia or sinus infection occurs in asthmatic patients, immune deficiencies could be evaluated by determination of quantitative immunoglobulin levels, IgG subclass levels, and specific antibody responses after natural infection and immunization.
- Allergic bronchopulmonary aspergillosis can be diagnosed by several criteria including elevated total serum IgE levels and the presence of allergen-specific IgE and IgG antibodies.

No single in vitro or in vivo test can conclusively establish a diagnosis of asthma.[1] Demonstration of bronchial hyperresponsiveness by methacholine challenge is useful diagnostically and therapeutically (see Section V B 2), but a positive methacholine challenge alone is insufficiently specific to establish a diagnosis of asthma because not all patients with asthma have a positive methacholine challenge, and not all patients with a positive methacholine challenge have asthma.[2] Skin testing (see Section V C 1) is a sensitive technique for the determination of specific IgE antibodies. Under certain conditions, such as certain skin disorders or patients taking certain medications, determination of specific IgE antibodies by in vitro testing is an acceptable or even preferred substitute for skin testing.[3] Nevertheless, neither in vitro nor in vivo demonstration of specific IgE antibodies can differentiate asthma from other diseases that can simulate this clinical condition.

Total and specific IgE

Elevated total serum IgE, particularly in infants and young children with chronic or recurrent respiratory symptoms, may be indicative of an allergic basis for the patient's asthma. However, increased IgE levels also occur in nonallergic diseases such as the hyper-IgE syndrome, bullous pemphigoid, chronic osteomyelitis, and allergic bronchomycotic conditions.[4] The most commonly used and widely validated methods for determination of serum IgE are a solid-phase immunoassay system known as the paper radioimmunosorbent test and an enzyme-linked analogous procedure.[3] Results are reported in International Units (IU) per milliliter of serum, where 1 IU = 2.4 ng. Serum IgE levels must be interpreted with proper attention to age-related normal ranges and do not absolutely discriminate atopic from nonatopic individuals because considerable overlap exists. Moreover, a normal or low total IgE level does not exclude an allergic basis for the patient's symptoms. Total IgE values tend to be higher in black patients in the United States in the absence of allergic disease.[5]

A number of in vitro assays for the determination of specific IgE antibodies to common allergens are commercially available.[3] The most com-

monly used and widely validated procedure is the RAST or an enzyme-linked analog. In this test, an allergen is chemically coupled with an insoluble matrix such as nitrocellulose paper disks. Incubation of allergen-coated disks with serum results in binding of serum antibodies to the solid-phase allergosorbent. The bound IgE antibodies are then detected with radioactively or enzymatically labeled monospecific or monoclonal antibodies specific for human IgE. Levels of specific IgE antibodies are reported in arbitrary semiquantitative units with reference to a standard allergen-IgE antibody curve. The results of this test can be subject to error because of high levels of total IgE causing irrelevant IgE binding, high levels of IgG binding antibody, and cross-reactions between apparently unrelated allergens.

Eosinophilia

Asthma is characterized by airway inflammation.[6] Eosinophils in particular play a crucial role in this process. When activated, the eosinophil releases a variety of toxic granule-associated products, such as major basic protein, which is capable of causing respiratory epithelial damage and further bronchial inflammation. The differential blood count often but not invariably reveals modest eosinophilia in patients with asthma. Total eosinophil counts, corrected for age, sex, and diurnal variation, are usually elevated in untreated symptomatic patients with asthma. Total eosinophil counts are not useful in differentiating allergic from nonallergic asthma but may be useful in distinguishing patients with asthma versus bronchitis/emphysema and those more likely to respond to corticosteroid therapy.[7] Eosinophils usually are not detected in corticosteroid-responsive patients while they are receiving corticosteroids but are present (either in the normal or increased range) in corticosteroid-resistant patients, indicating lack of response to systemic corticosteroids.

Immunodeficiency

Patients with recurrent pneumonitis and sinus infections may have underlying immune deficiency states.[8, 9] Preliminary evaluation of humoral immunodeficiencies should include determination of quantitative serum immunoglobulin levels (IgA, IgG, and IgM). This assessment may reveal partial or complete IgA deficiency or common variable hypogammaglobulinemia (low IgG, low IgA, and low IgM). The interpretation of immunoglobulin levels must be referenced to age-related normal ranges. Determination of IgG1, IgG2, IgG3, and IgG4 subclass levels, as well as the functional status of these subclasses (especially IgG2 to polysaccharide antigens), may be useful in evaluating patients with recurrent respiratory infections and normal total IgG levels. Functional tests may be required for a more complete evaluation of humoral immunity, including measurement of naturally derived and/or postimmunization-specific antibody responses to common protein (tetanus and diphtheria toxoids) and polysaccharide antigens (pneumococcal polysaccharide and *Hemophilus influenzae* type b capsular polyribophosphate). Because some patients may have a specific deficiency of functioning antibodies despite normal levels of immunoglobulins and IgG subclasses, evaluation of such antibody responses may be invaluable in determining a basis for recurrent respiratory symptoms.[10]

Recurrent respiratory infections that may lead to exacerbations of asthma may also be caused by complement deficiency, neutrophil phagocytic insufficiency, and chemotactic dysfunction. Acquired immune deficiency states may pose unusual risks for corticosteroid-dependent asthmatic patients. When immunodeficiency is suspected, an anergy skin test battery and determination of T and B cell counts, as well as functional antibody tests, are appropriate. When impaired cell-mediated immunity is suspected, skin tests for anergy, CD4+/CD8+ ratios, and mitogen-induced lymphocyte proliferation may be pursued.

Evaluation of allergic bronchopulmonary aspergillosis

Patients with suspected or proven asthma who have pulmonary infiltrates should be evaluated for allergic bronchopulmonary aspergillosis (ABPA), a condition resulting from hypersensitivity to endobronchial colonization with *Aspergillus fumigatus* and other fungal species. The diagnosis of ABPA is based on several criteria, including a positive *A. fumigatus* skin test (prick and/or intracutaneous), positive precipitins (IgG antibodies to *A. fumigatus*), a high total IgE, the presence of infiltrates on chest radiograph, brownish or black colored mucus plugs containing hyphae, central bronchiectasis, and asthma.[11]

The presence of specific IgE antibodies for *A. fumigatus* can be determined either by immediate skin tests or RAST. Precipitating antibodies to this organism are determined by double-gel immunodiffusion tests.[12] More precise quantitation of IgE antibodies may be obtained by radioimmunoassays or enzyme-linked immunoassays.[13] In all these in vitro tests, it is essential that a reliable antigen be

used. *A. fumigatus* antigen obtained from some commercial sources may not be satisfactory. When doubt exists about the quality of the test antigen, consultation with a central reference laboratory is recommended. Measurement of total IgE and tests for *A. fumigatus*–specific IgE and IgG antibodies are also useful in studying a patient's response to corticosteroid treatment.

In addition to ABPA, asthmatic patients may develop other forms of allergic bronchopulmonary mycotic syndromes. A number of organisms, including *Candida albicans, Alternaria alternata, Cladosporium herbarium, Curvularia, Helminthosporium,* and *Mucor* have been recognized as causes of a disease complex similar to that caused by *A. fumigatus* and other *Aspergillus* species. If allergic bronchopulmonary mycosis is suspected, appropriate in vitro assays relative to the above organisms should be performed.

Other considerations

A tuberculin skin test should be considered in any patient with suggestive symptoms, a personal or family history of tuberculosis, history of exposure to an actively infected individual, need for chronic daily systemic corticosteroid therapy, and patients with immune deficiency.

Research methods

In vitro assays of allergen-induced histamine release from whole blood or partially purified blood basophil preparations are primarily research methods at present.[3]

Increased eosinophil levels have been found in bronchoalveolar lavage fluid obtained from allergic asthmatic patients several hours after allergen inhalation.[14] Although total and differential cell counts based on bronchoalveolar lavage fluid are useful in studying the pathophysiologic findings of a number of pulmonary diseases, including asthma, these tests are not definitive at present for the diagnosis of asthma, evaluation of asthma severity, or response of asthmatic patients to treatment.

In the future, measurement of local or circulating granule-specific, eosinophil-derived mediators such as major basic protein or other eosinophil cationic proteins may become valuable diagnostic tests, but their usefulness remains to be determined by further research. Similar cautious optimism applies to tests for various mast cell–derived mediators (e.g., histamine, sulfidopeptides, tryptase, tumor necrosis factor, IL-1, IL-6, and chemotactic factors) or mononuclear cell–derived cytokines.

REFERENCES

1. Mathison DA. Asthma in adults: diagnosis and treatment. In: Middleton E, Reed CE, Ellis EF, eds. Allergy: Principle and Practice, 2nd ed. St. Louis: The CV Mosby Co, 1988:1063.
2. Cropp GJA, Bernstein IL, Boushy HA, et al. Guidelines for bronchial inhalation challenges with pharmacologic and antigenic agents. Am Thoracic Soc News 1980;67:11.
3. Proceedings of the Task Force on Guidelines for Standardizing Old and New Technologies Used for the Diagnosis and Treatment of Allergic Disease. Bernstein IL, ed. J ALLERGY CLIN IMMUNOL 1988;82:487-526.
4. Heiner DC, Rose B. Elevated levels of IgE in conditions other than clinical allergy. J Allergy 1970;45:30.
5. Grundbacher FJ. Causes of variation in serum IgE levels in normal populations. J ALLERGY CLIN IMMUNOL 1975;56: 104-11.
6. Beasley R, Roche WR, Roberts JA, Holgate ST. Cellular events in the bronchi in mild asthma and after bronchial provocation. Am Rev Respir Dis 1989;139:806-17.
7. Horn BR, Robin ED, Theodore J, Van Kessel A. Total eosinophil counts in the management of bronchial asthma. N Engl J Med 1975;292:1152-5.
8. Berger M. Immunoglobulin G subclass determination in diagnosis and management of antibody deficiency syndromes. J Pediatr 1987;110:325-8.
9. Smith TF, Morris EC, Bain RP. IgG subclasses in nonallergic children with chronic chest symptoms. J Pediatr 1984;105:896-900.
10. Ambrosino DM, Umetsu DT, Siber GR, et al. Selective defect in the antibody response to *Hemophilus influenzae* type b in children with recurrent infections and normal serum IgG subclass levels. J ALLERGY CLIN IMMUNOL 1988;81:1175-9.
11. Patterson R, Greenberger PA, Radin RC, Roberts M. Allergic bronchopulmonary aspergillosis: staging as an aid to management. Ann Intern Med 1982;96:286.
12. Greenberger PA, Patterson R. Application of enzyme linked immunosorbent assay (ELISA) in diagnosis of allergic bronchopulmonary aspergillosis. J Lab Clin Med 1982; 99:288.
13. Patterson R, Greenberger PA. A radioimmunoassay index for allergic bronchopulmonary aspergillosis. Ann Intern Med 1983;99:18.
14. Diaz P, Gonzalez MC, Galleguillos FR, et al. Leukocytes and mediators in bronchoalveolar lavage during allergen-induced late-phase asthmatic reactions. Am Rev Respir Dis 1989;139:1383-9.

Allergen inhalation challenge

Summary statements

- Allergen inhalation challenge is used most often as an experimental procedure to clarify mechanisms of bronchial hyperresponsiveness.
- Allergen challenge can be used to clarify the role of specific allergens in patients with asthma or to establish causal relationship of asthma to an occupational agent.
- Allergen challenges may also be useful in evaluating therapeutic effectiveness of medications and immunotherapy.

- Allergen inhalation challenge can document specific allergenic sensitivity in certain patients when skin tests cannot be performed or as a comparison with in vitro diagnostic tests, when evaluating specific IgE-mediated sensitivity.
- Allergen inhalation challenge can trigger severe late-phase bronchial obstruction in certain patients, and precautions should be taken to prevent or treat this type of reaction.

At present, allergen inhalation challenge is used most often as an experimental procedure to better understand mechanisms of asthma, especially as they relate to early- and late-phase reactions and mediator release. Clinically, allergen inhalation challenge can be used to determine whether a specific allergen is an important cause of asthma or to evaluate the ability of a new pharmacologic agent to block early, late phase, or both types of reaction. Occasionally, this procedure is used to establish an etiologic role for a specific allergen in an individual patient or to confirm the efficacy of allergen immunotherapy with the allergen. In an occupational setting, allergen challenge can help establish a causal relationship between the patient's symptoms and the agent to which the patient is exposed (see Section VII K). To establish the most appropriate dose for allergen inhalation challenge, the patient should generally be skin tested before challenge. Skin test–negative patients will usually not respond to allergen inhalation challenge with the allergen that produced the negative skin response, although exceptions to this may be encountered, such as with certain occupational agents. (see Section VII K.)

Types of response to allergen inhalation challenge

Exposure to allergen by inhalation can produce an isolated immediate reaction, an isolated late-phase reaction, or a dual (biphasic) reaction. Late-phase reactions characteristically occur 3 to 8 hours after allergen inhalation and may persist for days, during which time a continuous or fluctuating decrease in pulmonary function is seen.[1]

Late-phase asthmatic reactions

Keen interest has been shown in late-phase reactions after allergen inhalation challenge in allergic individuals. Although the late phase has been defined in various ways, a strong relationship exists to an inflammatory bronchial response.[1] Although the prevalence of these types of reactions varies depending on the allergen used and is controversial, late-phase reactions generally occur in 50% of individuals who are not taking medications that block these reactions.[2-5]

A strong relationship exists between the late-phase reaction after allergen inhalation challenge, subsequent development of bronchial hyperresponsiveness and inflammation, and persistence of asthmatic symptoms. Experimentally, allergen inhalation increases the maximal response to methacholine in those individuals who have a late asthmatic response.[6] In addition, natural exposure to allergen has been associated with development of bronchial hyperresponsiveness. In support of this relationship, a reduction in both the magnitude of late-phase reactions and bronchial hyperresponsiveness occurs after prolonged allergen avoidance[7] or appropriate allergen immunotherapy[2] and anti-inflammatory medications useful in the treatment of asthma generally block late-phase reactions as well.

On the other hand, findings that do not support such a relationship are that: (1) nonallergic asthmatic patients without a positive response to allergen challenge can also have bronchial hyperresponsiveness; (2) challenge with 48/80, exercise, and possibly distilled water have been associated with increased late asthmatic reactions without increased nonspecific responsiveness[8, 9]; (3) indomethacin, which inhibits late asthmatic responses in some patients, is not useful in the treatment of asthma[10, 11]; (4) increased airway responsiveness can follow an isolated early response after protein or chemical exposure[12, 13]; and (5) after rhinovirus infection many individuals can develop an increased late-phase reaction associated with increased histamine reactivity and yet not develop clinical asthma.[14]

Technical considerations

Inhalation challenge is usually started with that concentration of allergen that produces a wheal greater than 5 mm in diameter above the wheal produced by the diluent control, as determined by intracutaneous skin test titration showing an appropriate dose response. Challenges should be performed so as to minimize suggestibility because this can influence the study results.[15] Recommendations have been made in regard to an adequate length of time that specific medications should be withheld before challenge.[16] Although astemizole may suppress skin testing response and response to histamine challenge for 6 weeks or longer,[17] it is not clear what effect this drug has on allergen inhalation challenge.

Reproducibility

Immediate reactions to allergen challenge are generally reproducible from one day to the next but are more variable than methacholine responses. In this regard, a 10-fold day-to-day variation in PD_{35} specific airway conductance (SGaw) can be expected.[18] Although more data are needed to determine the reproducibility of the late-phase asthmatic response, one investigator studied five patients and found that it was reproducible in only one.[19]

Expression of data

Cumulative doses required to produce a positive response, generally considered to be a 20% fall in FEV_1, is an acceptable method of expressing data resulting from allergen challenge. There are five breaths per dilution in the standard challenge procedure, and the results are usually extrapolated from a dose-response curve and are expressed as PD_{20} or PD_{35} (i.e., a provocative dose that produces a 20% or a 35% fall in FEV_1).

Safety considerations

It is not recommended that allergen inhalation challenge become a routine office procedure. This type of challenge requires the presence of resuscitation equipment, oxygen, and appropriate medication to treat significant bronchoconstriction, including inhaled bronchodilators and epinephrine. A physician or other health care provider, who is familiar with the challenge procedure and how to treat patient responses to the challenge, should be immediately available during the challenge and for sufficient time after the challenge. Provisions must always be made for possible late-phase reactions.

REFERENCES

1. Lemanske RF Jr, Kaliner M. Late-phase IgE-mediated reactions. J Clin Immunol 1988;8:1-13.
2. Warner JO, Price JF, Soothill JF, et al. Controlled trial of hyposensitization to *Dermatophaagoides pteronyssinus* in children with asthma. Lancet 1978;2:912-5.
3. Price JF, Warner JO, Hey EN, et al. A controlled trial hyposensitization with absorbed tyrosine: *Dermatophagoides peteronyssinus* antigen in childhood asthma: in vivo aspects. Clin Allergy 1984;14:209-19.
4. Robertson D, Kerigan AT, Hargreave FE, et al. Late asthmatic responses induced by ragweed pollen allergen. J ALLERGY CLIN IMMUNOL 1974;54:244.
5. Paggiaro PL, Chan Yeung M. Pattern of specific airway response in asthma due to Western red cedar *(Thuja plicata)*: relationship with length of exposure and lung function measurements. Clin Allergy 1987;17:333-9.
6. Boonsawat W, Salome CM, Woolcock AJ. Effect of allergen inhalation on the maximal response plateau of the dose-response curve to methacholine. Am Rev Respir Dis 1992;146:565-9.
7. Platts-Mills TA, Mitchell EB, Nock P, et al. Reduction of bronchial hyperreactivity during prolonged allergen avoidance. Lancet 1982;2:675-8.
8. Spector SL. Allergen inhalation challenge procedures. In: Spector SL, ed. Provocative challenge procedures: background and methodology. Mount Kisco, New York: Futura Publishing, 1989:293-339.
9. Foreal A, Mattoli S, Corbo GM, et al. Late bronchial responses and increase in methacholine hyperresponsiveness after exercise and distilled water challenge in atopic subjects with asthma with dual asthmatic response to allergen inhalents. J ALLERGY CLIN IMMUNOL 1986;78:1130-9.
10. Fairfax AJ. Inhibition of the late asthmatic response to house dust mite by non-steroidal anti-inflammatory drugs. Prostaglandins Leukot Med 1982;8:239-48.
11. Joubert JR, Shephard E, Mouton W, et al. Non-steroidal anti-inflammatory drugs in asthma: dangerous or useful therapy? Allergy 1985;40:202-7.
12. Machado L. Increased bronchial hypersensitivity after early and late bronchial reactions provoked by allergen inhalation. Allergy 1985;40:580-5.
13. Thorpe JE, Steinberg D, Bernstein IL, Murlas CG. Bronchial reactivity increases soon after the immediate response in dual-responding asthmatic subjects. Chest 1987;91:21 5.
14. Lemanske RF Jr, Dick EC, Swanson CA, et al. Rhinovirus upper respiratory infection increases airway hyperreactivity and late asthmatic reactions. J Clin Disease 1989;83:1-10.
15. Spector SL, Luparello TJ, Kopetsky MT, et al. Response of asthmatics to methacholine challenge and suggestion. Am Rev Respir Dis 1976;113:43-50.
16. Spector SL. Bronchial provocation tests. In: Weiss EB, Segal MS, Stein M, eds. Bronchial asthma: mechanisms and therapeutics. 2nd Edition. Boston: Little Brown & Co, 1985:360-79.
17. Malo J, LiYi Fu C, L'Archevéque J, Ghezzo H, Cartier A. Duration of the effect of astemizole on histamine-inhalation tests. J ALLERGY CLIN IMMUNOL 1990;85:729-36.
18. Kopferschmitt-Kubler MC, Bigot H, Pauli G. Allergen bronchial challenge tests: variability and reproducibility of the early response. J ALLERGY CLIN IMMUNOL 1987;80:730-40.
19. Bundgaard A, Boudet L. Reproducibility of the late asthmatic response. Eur J Respir Dis 1986;68:41-3.

Other diagnostic techniques

Summary statements

- The presence of eosinophils and other formed elements (Curschmann's spirals, Charcot-Leyden crystals, and creola bodies) in the sputum may have diagnostic significance.
- A chest radiograph should be considered in some patients to aid in (1) differentiating asthma from other conditions that may cause wheezing and (2) demonstrating possible complications of asthma.

- Sinus radiographs and/or computed tomographic (CT) scans should be considered if chronic sinusitis is suspected.
- Direct visualization of the upper and/or lower airway may be required to determine if wheezing is caused by mechanical obstruction.
- Special diagnostic procedures may be required to exclude the diagnosis of pulmonary embolism.
- Special tests are available to distinguish other diseases, such as carcinoid, mastocytosis, cystic fibrosis, and α_1-antitrypsin deficiency, which may masquerade as or coexist with asthma.

Special adjunctive diagnostic methods can be used to confirm the diagnosis of asthma, to differentiate other diseases where wheezing is a presenting symptom, and to evaluate the major complications of asthma.

Examination of respiratory secretions

Microscopic examination of the sputum (expectorated or induced) may be useful. The presence of eosinophils, Curschmann's spirals, and Charcot-Leyden crystals is strongly suggestive of asthma.[1] However, eosinophils may be seen in other diseases such as chronic eosinophilic pneumonia. Identification of creola bodies may indicate that a significant inflammatory component is present because they are produced by sloughing of denuded epithelium. Allergic bronchopulmonary mycosis[2-5] should be considered if hyphal or mycelial fragments are found. On the other hand, sputum cultures are rarely helpful in asthma except when nosocomial superinfection in severely ill hospitalized patients or bacterial pneumonia is suspected. Viral cultures may be valuable in young children to determine whether respiratory syncytial virus is a causative factor in wheezing associated with bronchiolitis.

Medical imaging

A chest radiograph should be considered in some asthmatic patients to aid in differentiating asthma from other conditions that may cause wheezing and demonstrating possible complications of asthma (e.g., pneumothorax or pneumonia). CT has now replaced bronchography as the diagnostic technique of choice for the detection of bronchiectasis and mucoid impaction. It also may be useful in confirming the diagnosis of emphysema.

Visualization of the paranasal sinuses should be considered whenever chronic nasal blockage and infection of the paranasal sinuses are suspected. The osteomeatal complex should be evaluated carefully, even if findings on routine sinus radiographs are normal. CT scans of the sinuses, particularly the coronal views, may be necessary to exclude involvement of this pivotal anatomic area. Inasmuch as certain sinuses develop very early in life, the possibility of sinusitis cannot be ignored in children, although the signs and symptoms may be more subtle than in adults.[6-9]

Special diagnostic procedures may be required to exclude the diagnosis of pulmonary embolism.[10, 11] Extensive pulmonary infarcts can be seen on radiographs after pulmonary embolism, and in such cases electrocardiographic signs of acute cor pulmonale may also be present. In most cases, however, routine laboratory tests, including electrocardiograms and chest radiographs, are not helpful. If prior existence of asthma and/or other chronic obstructive pulmonary disease can be excluded, the proper clinical approach is to perform ventilation/perfusion imaging (high-probability V/Q scan). Absent perfusion with normal ventilation is pathognomonic of pulmonary embolism. However, mismatching of ventilation with abnormal perfusion does not differentiate between embolism and preexistent asthma because asthma is almost always associated with regional abnormalities in perfusion. In this case, pulmonary angiography is the preferred diagnostic procedure.

Occasionally both invasive and noninvasive diagnostic techniques may be required to determine whether asthma is complicated by concomitant valvular heart disease, cardiomyopathy, and/or congestive heart failure.

X-ray densitometric techniques are reliable indicators of osteopenia developing in steroid-dependent asthmatic patients. Occasionally, magnetic resonance imaging may be necessary to detect sites of avascular necrosis, an infrequent complication in steroid-dependent asthmatic patients.

Direct visual methods

Bronchoscopy. Bronchoscopy is required for diagnosis and delineation of suspected endobronchial lesions (including those caused by inflammatory processes), centrally located tumors, large mucus plugs, and foreign bodies.[12]

Nasal endoscopy. Direct visualization of the nose, nasophraynx, and larynx by intranasal endoscopy (either fixed or flexible fiberoptic instruments) is recommended for direct examination of the osteomeatal complex and vocal cords. This procedure is particularly useful during acute epi-

sodes of vocal cord dysfunction. Adequate visualization of the nasal passages can also be used to determine whether foreign objects or nasopharyngeal malignancy is present. Diagnosis of immotile cilia or primary ciliary dyskinesia syndrome is made by biopsy of nasal or bronchial cilia, which shows a lack of dynein arms, loss of radial spokes, or loss of function.[13-15]

Gastroesophageal endoscopy. Gastroesophageal reflux in asthmatic patients is a possible precipitant of nocturnal asthma. In most cases an esophogram and upper gastrointestinal series are sufficient to establish but not refute this diagnosis. Information obtained from pH probe studies along with gastroesophageal endoscopy provide the most useful approach to the diagnosis (see Section VII G).

Chemistry studies

Appropriate tests for the diagnosis of systemic mastocytosis,[16, 17] which may occasionally be associated with bronchospasm, may need to be considered. The presence of 5-hydroxyindoleacetic acid in the urine is strong presumptive evidence of a carcinoid tumor.[18]

Occasionally, the differential diagnosis of asthma suggests the possibilities of α_1-antitrypsin deficiency,[19-21] cystic fibrosis,[22, 23] or the immotile cilia syndrome (primary ciliary dyskinesia syndrome). If α_1-antitrypsin deficiency is discovered, proteinase inhibitor typing is helpful to determine specific subclasses of patients. Quantitative sweat chloride levels are elevated in children and young adults with cystic fibrosis.

Sleep apnea evaluation

Special sleep laboratory studies may be required in asthmatic patients with sleep apnea. This complication is most likely to be encountered in patients with unsuspected nasal polyps or concomitant morbid obesity, or in children with upper airway obstruction.[24, 25]

REFERENCES

1. Mathison DA. Asthma in adults: diagnosis and treatment. In: Middleton E Jr, Ellis E, et al, eds. Allergy: principles and practice, 3rd ed. St. Louis: The CV Mosby Co, 1988: 1063-92.
2. Wang JLF, Patterson R, Mintzen R, et al. Allergic bronchopulmonary aspergillosis in pediatric practice. J Pediatr 1979;94:376-81.
3. Greenberger PA. Allergic bronchopulmonary aspergillosis. J ALLERGY CLIN IMMUNOL 1984;74:645-53.
4. Greenberger PA, Patterson R. Diagnosis and management of allergic bronchopulmonary aspergillosis. Ann Allergy 1984;55:444-8.
5. Greenberger PA, Patterson R. Allergic bronchopulmonary aspergillosis and the evaluation of the patient with asthma [Editorial]. J ALLERGY CLIN IMMUNOL 1988;81:646-50.
6. Shapiro G, Rachelefsky G, eds. Mechanisms, diagnosis and treatment of sinusitis in children and adults. J ALLERGY CLIN IMMUNOL 1992;90(part 2):417-536.
7. Shapiro G, Rachelefsky G. Introduction and definition of sinusitis. J ALLERGY CLIN IMMUNOL 1992;90:417-30.
8. Slavin RG. Asthma and sinusitis. J ALLERGY CLIN IMMUNOL 1992;90:534-7.
9. Druce HM, Slavin RG. Sinusitis: a critical need for further study. J ALLERGY CLIN IMMUNOL 1991;88:675-7.
10. Webster JR, Saadel GB, Eggum PR, Suker JR. Wheezing due to pulmonary embolism. N Engl J Med 1966;274: 931.
11. Biello DR, Mattar AG, McKnight RC, Siegel BA. Ventilation-perfusion studies in suspected pulmonary embolism. Am J Rad 1979;133:1033.
12. Wood RE, Postma D. Endoscopy of the airway in infants and children. J Pediatr 1988;112:1-5.
13. Rutland J, Delongi RU. Random ciliary orientation. N Engl J Med 1990;323:1681-4.
14. Boat TF, Carson JL. Ciliary dysmorphology and dysfunction primary or acquired [Editorial]. N Engl J Med 1990; 323:1689-702.
15. Mauveil L. Primary ciliary dyskinesia. West J Med 1991; 155:280-3.
16. Metcalfe DD. Classification and diagnosis of mastocytosis: current status. J Invest Dermatol 1991;96:2S-5S.
17. Horan RF, Auster KF. Systemic mastocytosis: retrospective review of a decade's clinical experience at the Brigham and Women's Hospital. J Invest Dermatol 1991;96:5S-14S.
18. Todd TR, Cooper JD, Weissberg D, et al. Bronchial carcinoid tumors. J Thorac Cardiovas Surg 1980;79:532.
19. Eriksson S. Alpha 1 antitrypsin deficiency and lessons learned from the bedside to the gene and back again. Chest 1989;95:181-9.
20. Scientific update: Intervention, screening play crucial roles in the management of AAT deficiency emphysema. Immunol Allergy Pract 1990;12:279-81.
21. Wall M, Moe E, Eisenberg J, et al. Long term follow up a cohort of children with alpha 1 antitrypsin deficiency. J Pediatr 1990;116:248-51.
22. Gaddes DM. Cystic fibrosis. In: Mitchell DM, ed. Recent advances in respiratory medicine. London: Churchill Livingstone, 1992:203-27.
23. Farrell PM, Muschler EH. Newborn screening for cystic fibrosis. Advances in pediatrics. Vol 39. St. Louis: Mosby–Year Book, 1992:35-69.
24. Loughlin GM. Obstructive sleep apnea in children. Advances in pediatrics. Vol 39. St. Louis: Mosby–Year Book, 1992:307-35.
25. Hudgel DW. Mechanisms of obstructive sleep apnea. Chest 1992;101:541-9.

VI. Asthma management

A. CLASSIFICATION OF ASTHMA SEVERITY

Summary statements

- Attempts have been made to categorize severity of asthma based on symptoms, impairment of activity, pulmonary function, degree of bronchial hyperreactivity, number of emergency visits, number of hospitalizations, and medication use. Although there is no universal acceptance of formal severity designations, a combination of subjective and objective criteria can be used as a guide to severity in individual patients.
- Severity of asthmatic symptoms can be ranked on the basis of duration throughout the day or night, as well as persistence throughout the week.
- Restriction of activity in asthmatic patients can be based on inability to work or attend school, as well as how many days per week or month the restriction is present.
- Pulmonary function testing can be used to assess severity of asthma based on the predicted normal or the patient's best attainable value.
- Severity of asthma can be based on the number of office or emergency room visits, as well as hospitalizations required because of exacerbations of asthma.
- Treatment philosophies vary considerably; however, most physicians prescribe only daily oral corticosteroids for patients with severe asthma and avoid their use in patients with mild asthma. Therefore chronic administration of oral corticosteroids can be used to classify asthma as severe.

No categorization for severity of asthma is universally accepted. Nevertheless, attempts have been made to rank asthma severity by symptoms, degree of activity, pulmonary function tests, degree of bronchial hyperresponsiveness, number of emergency room visits, number of hospitalizations, and medication use. Reasons for the lack of universal acceptance of a classification of asthma based on severity are multifactorial.

Severity of asthma will fluctuate in patients from one time to another, requiring reassessment of clinical status. Different philosophies of asthma management exist in different clinical settings (e.g., which medication should be used first, which medication should be used either on an as-needed or a constant basis, and whether the goal or treatment should be the patient's best attainable lung function or symptomatic control). Many asthmatics who have chronic airway obstruction and require daily medication rarely, if ever, come to emergency departments or are hospitalized, whereas others who have near-normal lung function most of the time may have sudden severe episodes that may be life-threatening. This makes assessment of asthma severity based on the type and extent of medication usage difficult. Both the severity and the pattern of an individual's asthma may change over a period of time because of alterations in identifiable and nonidentifiable factors. Moreover, variability of lung function, as assessed by use of peak flow measurements throughout the day, correlate imperfectly with bronchial hyperresponsiveness and asthma symptoms.

The relationship between a patient's perception of the degree of airflow limitation and the need for bronchodilator medication is highly variable, and many patients do not perceive airflow limitation until obstruction is less than 50% of normal airflow. Moreover, the degree of bronchial hyperresponsiveness in individual patients may not correlate with the severity of asthma.

For these and other reasons, universal acceptance of a classification of asthma severity is virtually impossible. Therefore we have chosen to stress characteristics of asthma that deserve consideration in assessment of asthma severity, rather than to classify asthma by strict criteria. Although the terms *mild*, *moderate*, and *severe* are used in this document for functional consideration of management, it is emphasized that asthma severity is a continuum across the population and often within a given individual, and that some characteristics of asthma may be more applicable in defining the severity in one patient, whereas different characteristics may be more applicable in another. Treatment of the asthmatic patient must be individualized, and classifications of asthma severity do not readily lend themselves to this approach.

Symptoms

There is a great deal of variability of asthmatic symptoms in different patients and in the same patient at different times. No data exist to support a consistent relative ranking of the major symptoms of asthma, namely, wheezing, cough, chest tightness, and breathlessness. The frequency or duration of asthma symptoms tends to parallel asthma severity. However, patients with relatively mild asthma may have frequent symptoms, whereas some patients with life–threatening exacerbations can have infrequent symptoms. Despite the aforementioned reservations, two approaches to classifying the severity of asthmatic symptoms are provided: (1) ranking of symptoms based on their duration throughout a 24-hour period (i.e., mild = ≤4 hours; moderate = ≤12 hours; severe = continuous symptoms) or (2) frequency of symptoms throughout a 7-day period (i.e., mild = 0 to 3 days per week; moderate = 4 to 6 days per week; severe = daily symptoms). Assessment of symptom severity should take into account whether symptoms are evaluated while the patient is receiving or not receiving medications. To illustrate the difficulties inherent in such a classification, some patients with sudden life–threatening asthma might not be considered to have severe asthma based on either of these categories.

Restriction of activity

Interference with the ability to function normally for daily activities at work, school, or play; with sleep; or with exercise is an important indicator of asthma severity, as are the frequency and duration of such restriction. However, the degree to which symptoms interfere with daily activity is a product of not only the severity of obstruction but individual patient tolerance and drive, which should be taken into account when severity is assessed based on restriction of activity. Thus many highly motivated patients will work through considerable bronchial obstruction at work or play, whereas others have difficulty tolerating relatively little bronchial obstruction. Consideration can be given to the number of days per week or month when restriction of activity is present. One arbitrary classification might be as follows: mild = general restriction of activity for 0 to 1 day per month; moderate = up to 2 days per week; and severe = 3 to 7 days per week. If loss of time at work or school were measured in days per month, an arbitrary ranking might be as follows: mild = less than 1 day per month; moderate = 1 to 3 days per month; and severe = more than 4 days per month. For an activity such as walking or running, based on age and other considerations, mild might be 95% to 100% of desired or expected capacity; moderate, 75% to 95% of desired or expected capacity; and severe, less than 75% of desired or expected capacity.

Pulmonary function tests

Because asthma is an obstructive airway disorder, measurement of limitation of airflow, when possible, is the touchstone of assessment of this disorder. In this regard, should a patient be classified on the basis of predicted normal values or their own "personal best" value? Furthermore there is a lack of agreement on which pulmonary function parameter should be used to make such an assessment. Airflow limitation relates to asthma severity, and somewhat arbitrary classifications of severity based on degree of obstruction have been published. For example, 70% to 100% predicted FEV_1, recorded most times during the day, is considered to represent mild asthma; 50% to 70% predicted FEV_1, moderately severe asthma; and less than 50% FEV_1, severe asthma. Either published predicted values for normal populations or the patient's established normal can be used for calculation. Whereas these values reflect asthma severity at the time, the lability of airflow limitation, which varies between asthmatics within a given general range of FEV_1, needs to be considered in assessment of asthma severity (e.g., marked increase in obstruction overnight ["morning dippers"] but with relatively milder obstruction during most of the waking hours). Also, according to the aforementioned classification, long–standing mild–to–moderate obstruction may present less difficulty for some asthmatics than others who have mild or near–normal pulmonary function most of the time but who have periodic, profound, acute obstruction, which may be life–threatening.

Nonspecific bronchial hyperresponsiveness

Although increased airway reactivity cannot be directly equated with asthma, investigators have suggested a classification of asthma severity based on methacholine, histamine, or other provocative challenge. Methacholine challenge is better standardized than other procedures and has been available for a relatively long time, making it the logical choice to be used in any classification of asthma severity. Some studies suggest that the patients with the most severe asthma will have the greatest degree of bronchial hyperresponsiveness based on methacholine challenge, but notable individual exceptions exist. Therefore, although it has been argued that patients with greater bron-

chial reactivity should be treated more vigorously than others, there are insufficient data to justify this generalization at present.

Nevertheless, a suggested classification of asthma severity based on methacholine reactivity could be as follows: mild = a 20% or greater fall in FEV_1 after inhalation of a 5 to 8 mg/ml concentration of methacholine; moderate = a 20% or greater fall in FEV_1 after inhalation of a 0.125 to 5 mg/ml concentration of methacholine; severe = a 20% or greater fall in FEV_1 after inhalation of less than a 0.125 mg/ml concentration of methacholine.

Hospitalization and emergency care visits

The frequency of urgent care requirements in the form of emergent office or emergency department visits as well as hospitalization for asthma bears a strong proportional relationship to asthma severity. At the same time, patterns of health care utilization impact heavily on such visits—indigent populations using emergency health care facilities more routinely in place of continual care in physicians' offices. Consequently, assessment of urgent care requirements in evaluation of asthma severity ideally should take into account socioeconomic and cultural orientation toward use of emergency care facilities for asthma care. Despite these reservations, a classification of asthma severity can arbitrarily be based on exacerbation indices, such as visits at an office or urgent care facility for treatment of asthma, as follows: mild = none; moderate = none to five visits per year; and severe = more than five visits per year. Number of hospitalizations also can be used as follows: mild = none; moderate = none to one hospitalization per year; and severe = more than one hospitalization per year.

Medication use

Medication use is another means of classifying the severity of asthma, although philosophic differences about prescribing medication make this a controversial issue. The editors have concluded that a detailed classification of asthma severity based on the type of medication used or the frequency of medication use is not feasible, with one exception: Long-term dependency on oral corticosteroids implies moderate to severe asthma. Because of appropriate emphasis on long-term treatment goals to decrease underlying bronchial hyperresponsiveness and inflammation, cromolyn nedocromil and inhaled corticosteroids are being recommended with increasing frequency as first-line therapy for asthma. For example, some propose that high doses of inhaled corticosteroids should be used even in patients with mild asthma. It is clear, therefore, that a stepwise approach to medication therapy has changed and is still evolving. Furthermore, the decision whether to attempt to normalize lung functions even in the absence of ongoing symptoms or rather to base treatment requirements mainly on complete symptomatic relief is a subject of legitimate debate until results of long-term studies or the beneficial or detrimental effects of more or less aggressive pharmacologic therapy have been determined. With these reservations in mind, a patient with mild asthma might arbitrarily be classified as one who relies on a single medication (i.e., theophylline, inhaled cromolyn, inhaled corticosteroid, or β-agonist). A patient with moderate asthma could be classified as one in whom at least two medications are required on a regular basis, with moderate doses of inhaled corticosteroids and possibly with low-dose, alternate-day corticosteroids; a patient with severe asthma would be receiving high-dose inhaled corticosteroids; high-dose, alternate-day corticosteroids; and/or daily corticosteroids, along with other regular medications.

Although all of the aforementioned parameters are reasonable indicators of asthma severity in individual patients, no classification that is universally acceptable exists. A cogent argument could be made against any attempt to pigeonhole patients into a mild, moderate, or severe category because of all the variables that need to be considered in such a determination and limitations of such classifications. Nevertheless, the authors have reluctantly included them because they often are demanded by governmental organizations or others who must make decisions regarding such things as compensation or limitation of activity.

B. SEVERE ACUTE INTRACTABLE ASTHMA

Summary statements

- Severe acute intractable asthma (status asthmaticus) requires prompt recognition and intervention.
- The treatment of intractable asthma requires an understanding of physiologic abnormalities occurring as a consequence of increased airflow resistance resulting from bronchospasm, inflammation, and mucous plugging.
- The history must establish the features of the current attack and the presence of medical conditions that could complicate treatment of intractable asthma.
- Early in an asthma exacerbation, ventilation/perfusion mismatches are the predominant physiologic abnormality, and Pao_2 decreases. Therefore oxygen administration is indicated

in patients with severe acute intractable asthma.

- With increasing obstruction, ventilation is compromised and $Paco_2$ rises from initially low levels to "normal" levels. Therefore a $Paco_2$ of 40 torr may be a sign of severe asthma.
- Early in the treatment of intractable asthma, parenteral and inhaled sympathomimetic agents are equally effective in most patients. However, parenteral sympathomimetic agents may be indicated for patients who are not ventilating well enough to deliver adequate amounts of nebulized drug to the lower respiratory tract.
- Patients with severe acute intractable asthma will require corticosteroid administration. Early use is recommended because a lag time of several hours may occur before any clinical effect is noted.
- If aminophylline theophylline is used, it is especially important to monitor blood levels and cardiopulmonary function.
- Overhydration may increase vascular hydrostatic pressure and decrease plasma colloid pressure, increasing the possibility of pulmonary edema, which also is favored by large negative peak inspiratory intrapleural pressures associated with acute asthma.
- The need for mechanical ventilation should be anticipated.
- Intubation may be difficult and, if possible, should be done by an individual experienced in such procedures.

A useful working definition of severe acute intractable asthma is persistent asthma that fails to improve or continues to worsen while the patient is receiving optimal initial doses of inhaled or injected sympathomimetics (and possibly intravenous aminophylline). Although it is possible to characterize the physiologic conditions of mild, moderate, or severe asthma by use of objective criteria,[1-5] it is not possible to predict with certainty which patients will respond to therapy.[6-12]

Severe asthma may develop quite rapidly and occasionally will move from a mild attack to a fatal outcome in a matter of minutes.[13-15] More commonly, poorly controlled symptoms are present for much longer periods and increase in severity more slowly. This provides the opportunity for aggressive clinical intervention to prevent life-threatening respiratory failure and death.[14-20]

Refractory asthma requires prompt recognition and an understanding of the physiologic abnormalities occurring as a consequence of increasing airflow resistance that results from bronchospasm, inflammation, and mucous plugging. Worsening of the ventilation/perfusion ratio leads to increasing hypoxia and ultimately hypercapnia.[4] As airway resistance increases, patients also must work harder to breathe because air trapping requires breathing at a high lung volume where elastic lung tension is greater[21, 22] and ultimately leads to interference with venous return to the heart.

Various guidelines for hospitalization and intensive care unit admission of the patient with severe intractable asthma have been suggested,[1, 8, 11, 12, 23-25] and for the most part, are a reflection of the severity of airflow obstruction. Perhaps the most prudent criterion for hospitalization would be based on the physician's clinical assessment, including objective parameters, that outpatient therapy is failing. Poor response to bronchodilators may be due to mucosal edema of the lower airways, inspissated tracheobronchial secretions, and resistance to relaxation of contracted bronchial smooth muscle. Such resistance to relaxation may be due to acidosis, β-adrenergic blockade, and tolerance or subsensitivity caused by downregulation of β-adrenergic receptors, which may follow continued treatment with β-adrenergic agonists in some patients.

Evaluation of the patient with severe intractable asthma

Evaluation of the patient with severe intractable asthma includes a history focused on respiratory status, a physical examination to evaluate adequacy of ventilation, and a limited number of laboratory studies. The history must establish the features of the current attack: when it started, precipitating factors, rate of progression, and treatment that has been used, including details of doses and timing of medications. It is important to determine how the current increase in symptoms resembles previous exacerbations and the course of previous attacks. The presence of medical conditions and medications that could complicate treatment of severe intractable asthma (e.g., coronary disease or β-adrenergic blocking agents) must be established. Information about recent oral intake, vomiting, and frequency of urination may suggest dehydration.

A systematic physical examination is helpful in evaluation of the adequacy of ventilation. Expiratory wheezing usually is prominent but may diminish if increasing airway obstruction causes extreme limitation of airflow. As increasing airway obstruc-

tion develops, patients may demonstrate restlessness, agitation, orthopnea, tachypnea (frequently greater than 30 breaths/min in adults), use of accessory muscles of respiration, diaphoresis, coughing, and wheezing (grunting, retracting, and flaring in infants). The patient frequently will be found to have a widened pulse pressure, and a pulsus paradoxus greater than 10 mm Hg is commonly noted. Dryness of the mucous membranes and skin, poor skin turgor, and, in infants, depression of the fontanel may indicate dehydration. Fever and purulent nasopharyngeal or tracheobronchial secretions suggest infection.

Appropriate laboratory procedures include a complete blood count (and possibly a total eosinophil count); determination of serum electrolytes; urinalysis; and, if applicable, measurement of serum theophylline level. Leukocytosis may suggest infection, but it also may be due to dehydration, subcutaneous administration of adrenergic agonists, or administration of corticosteroids. The specific gravity of the urine is helpful in evaluation of the state of hydration. Serum electrolyte determinations provide a baseline for intravenous administration of fluids and electrolytes and may be especially important in a patient receiving large doses of β–adrenergic agonists, theophylline, and/or corticosteroids, which may produce or augment already existing hypokalemia. Hypomagnesemia also has been described in patients with asthma[26] and needs to be considered in the evaluation of patients with severe, intractable asthma. The serum theophylline concentration is necessary to guide further theophylline administration.

In addition to these laboratory studies, arterial blood gas determination, or pulse oximetry, may be required to provide objective evidence of pending respiratory insufficiency. Early in an asthma exacerbation, ventilation/perfusion mismatches are the predominant physiologic abnormality, and Pao_2 decreases. Ventilation is increased to compensate for the decrease in Pao_2, and $Paco_2$ also falls. With increasing obstruction, ventilation is eventually compromised, and $Paco_2$ begins to increase, first to levels within the normal range and finally to more abnormal levels. Repeated measurement of arterial blood gases is necessary to follow up a patient with severe asthma who is not responding to management. Even experienced clinicians cannot always "guess" what the $Paco_2$ will be just by examining a patient. Measurement of oxygen saturation noninvasively by pulse oximetry is useful in determining adequacy of oxygenation. Although decreasing saturation at a time when the patient is receiving a constant flow of oxygen can be a sign of increasing airway obstruction, monitoring oxygen saturation does not substitute for $Paco_2$ measurement.

Measurement of peak expiratory flow rate (PEFR) or FEV_1 provides objective evidence of the extent of airway obstruction, and periodic determinations indicate response to treatment. In patients with severe airway obstruction, such measurements may have to be deferred until some improvement has occurred in response to treatment because the inspiratory and expiratory efforts required for measurement may provoke further constriction of hyperirritable airways. Chest radiographs may be useful when the patient has clinical findings suggesting a complication such as atelectasis, pneumonitis, pneumomediastinum, or pneumothorax.

Treatment

Patients in respiratory failure as a result of severe acute intractable asthma probably are best treated in an intensive care unit setting. Those with less severe airflow obstruction usually can be managed in an adequately monitored hospital setting, provided it is recognized that sudden deterioration may occur. Access to aggressive interventional therapy should be readily available. The main objective of therapy is to improve ventilation/perfusion mismatch, thereby improving gas exchange and reducing the work of breathing. Specific management will depend on the severity of the respiratory impairment, but careful and frequent monitoring of the patient is essential.

Oxygen

Initial therapy of severe intractable asthma should always include the administration of oxygen. Humidified oxygen can be delivered either by nasal "prongs" or mask, depending on the age and comfort of the patient. A reasonable goal of oxygen therapy is to increase the Pao_2 to at least 60 mm Hg, equivalent to an arterial oxygen saturation of 90%, which can be monitored continuously by a pulse oximeter.

Sympathomimetics

Parenteral and inhaled sympathomimetic agents are equally effective in the treatment of severe intractable asthma in most patients and should be used promptly. Some patients may improve more with the use of an injected sympathomimetic because they are not breathing well enough to deliver adequate amounts of the nebulized drug. Inhaled β–agonists usually are administered two to three times in the first hour of treatment but also may be administered with

continuous nebulization while the patient is evaluated for responsiveness clinically and during measurement of expiratory flow rates (either PEFR or FEV_1). Treatment is limited only by development of tachyarrhythmias, tremor, or tachycardia (especially in patients with underlying heart disease). Both injected and inhaled forms of these drugs should be given with oxygen because sympathomimetic agents produce transient increases in ventilation/perfusion mismatches and worsening hypoxemia. Aqueous epinephrine and terbutaline sulfate administered by the subcutaneous route are equally effective[27-29] and unlikely to be associated with adverse cardiovascular effects up to the age of 45 years.[30] However, the potential hazard in patients with underlying coronary artery disease or cardiac arrhythmias must be considered in younger patients as well.

Dosing of nebulized β–agonists after the initial hour depends on the patient's course and response to treatment. Generally, nebulizations are repeated every 20 to 60 minutes, with the interval between inhalation treatments gradually lengthened until they are being given every 4 to 6 hours. However, in some patients, nebulizations repeated every 20 minutes may not be adequate, indicating the severity of the attack and impending respiratory failure. Recently, several investigators have used continuously nebulized terbutaline or albuterol in this setting.[31, 32] Another option is the use of intravenous β–adrenergic agonist bronchodilators, although they should not be used unless absolutely necessary so as to avoid intubation and mechanical ventilation. In the United States, only isoproterenol is available for intravenous use, and such use is not without substantial risk.[33, 34] Intravenous isoproterenol, and to a lesser extent β_2–selective agonists, have been used effectively, especially in children. Because of the substantial risk, cardiac rhythm[34] must be monitored continuously and 12-lead electrocardiograms must be obtained frequently (to determine whether ischemia is developing) because serious cardiac events can occur when this approach is used. In addition, adequate provisions for emergency ventilation and intubation should be available.

Corticosteroids

Patients with acute severe intractable asthma should receive systemic corticosteroids. Early use is recommended because a lag time of several hours occurs before any clinical effect is appreciated.[35, 36] Maximal response to corticosteroids usually occurs only after 6 hours, although they start to reverse tolerance to β–agonists within 1 hour.[37] Although the optimal dose of systemic corticosteroids is not known, in adults, 40 to 80 mg of methylprednisolone (or a loading dose of 0.8 mg/kg) or its equivalent, administered every 4 to 6 hours, followed by 2 to 4 mg/kg per day given in four to six divided doses, probably is adequate.[38] For children, methylprednisolone given in doses of 1 to 2 mg/kg every 4 to 6 hours is suggested for initial treatment.

As improvement in airflow obstruction is noted, patients may be switched to oral corticosteroid therapy and the dose gradually tapered as appropriate. If a patient appears to be resistant to high–dose corticosteroid therapy, a thorough search for complicating medical conditions should be initiated. In general, if eosinopenia occurs (eosinophil count $<50/mm^3$), corticosteroid resistance is usually not a consideration.

Theophylline

The additive effect of aminophylline administered concomitantly with optimal amounts of β–agonists is controversial. Those few patients who do not respond to inhaled β–agonists, however, may respond to intravenous aminophylline. An initial loading dose followed by a continuous–drip infusion is the customary method of delivery. The loading dose is reduced or eliminated in a setting of prior oral theophylline use, known underlying heart disease, or liver disease. In patients with severe acute asthma, serum theophylline levels should be maintained between 10 and 15 μg/ml, with 20 μg/ml as the upper limit.[39, 40] Periodic monitoring of theophylline levels is essential (see Section V, Specific Diagnostic Techniques).

Fluids

Intravenous infusion of 5% dextrose in water or 0.25 normal saline solution at a rate of 1500 $ml/m^2/24$ hr usually is sufficient to maintain hydration, but as much as 3000 $ml/m^2/24$ hr may be necessary to correct dehydration. On the other hand, in patients who are not dehydrated, administration of excessive amounts of fluid should be avoided. No data exist to indicate that such an approach will decrease viscosity or increase clearance of secretions. After establishment of renal flow, potassium or other electrolyte replacement should be implemented as soon as possible to prevent hypokalemia. Increased secretion of antidiuretic hormone associated with severe intractable asthma may cause water intoxication with hyponatremia after administration of excessive

volumes of fluid. In addition, extreme care must be taken not to overhydrate patients because this may increase vascular hydrostatic pressure and decrease plasma colloid pressure, increasing the possibility of pulmonary edema, which also is favored by large negative peak inspiratory intrapleural pressures associated with acute asthma.

Intubation and mechanical ventilation

Absolute indications for mechanical ventilation have not been delineated. A $Paco_2$ greater than 50 to 60 torr, although serious, is not an absolute indication. Generally indications would include (1) severe agitation requiring sedation to permit administration of therapy; (2) mental obtundation and/or coma; (3) hypoventilation with reduction in tidal volume; (4) sudden or progressively rising $Paco_2$ and falling pH; (5) progressive clinical deterioration with obvious fatigue, usually accompanied by a rising $Paco_2$ and falling pH; and (6) cardiopulmonary arrest.[24] Intubation may be difficult and, if possible, should be done by an individual skilled in intubation. The size of the endotracheal tube depends on the age of the patient; when possible, nasal is preferable to oral intubation. Sedation and neuromuscular blockade (pancuronium) may be necessary to mechanically ventilate these patients. High peak airway pressures should be avoided if possible because barotrauma is increased in this setting.

Additional measures

Correction of acidosis with sodium bicarbonate can be helpful in restoration of responsiveness to β–adrenergic agonists[41] and lowering of peak airway pressures during mechanical ventilation,[42] although this therapy remains controversial. Intravenous infusion of sodium bicarbonate, 1.5 to 2 mEq/kg over 15 minutes and then repeated more slowly over the next 45 minutes, is safe and effective if the arterial pH is less than 7.2. The same dose may be repeated hourly if acidosis persists, with pH less than 7.2 and serum sodium less than 135 mEq/L.

Once intubation has been accomplished, diffuse inspissated mucous impaction should be suspected if excessively high pressures are required to overcome intrabronchial resistance. Under these unusual circumstances, patients may require lung lavage under general anesthesia using saline solution and *N*–acetyl–L–cysteine[43, 44] combined with a β_2–agonist. Some anesthetic agents also have bronchial relaxant properties. Antibiotics are indicated only when evidence of bacterial infection exists or is suspected. Sedatives, tranquilizers, and morphine or other opiates are contraindicated before intubation because of their depressant effect on the respiratory center. When mechanical ventilation is imminent, however, sedation is appropriate to facilitate intubation and maintain proper ventilatory parameters.

Hospital management of the asthmatic patient

In many cases the treatment of severe episodes of asthma in a closely monitored environment for a sufficient period of time may prevent hospitalization. However, if hospitalization is required, the following principles apply. **Long–acting inhaled β_2–agonists (salmeterol) should not be used for or during the treatment of acute or unstable asthma. When hospitalized, patients should not be allowed to continue to take their regular asthma medications without reassessment and supervision.** Hospital management of an acute asthma exacerbation includes repetitive administration of β_2–selective agents by means of nebulization and systemic corticosteroids. Generally, a β_2–selective agent such as albuterol is administered by nebulization, with the frequency dependent on the severity of the patient's asthma. This approach may include continuous nebulization.[45, 46] As the patient's status improves, the interval can be increased and/or the delivery system changed to a metered–dose inhaler. Although there is some evidence that β–adrenergic agonists can be delivered successfully to patients with asthma by means of metered–dose inhaler, nebulization should be considered the preferred treatment.

Systemic corticosteroids should be used for virtually all patients hospitalized for asthma.[47] Because oral corticosteroids are well absorbed, some asthma experts have advocated delivery of corticosteroids by the oral route, if possible, instead of intravenously for patients hospitalized with asthma. However, the intravenous route is preferred for most patients, and the route of administration can be changed to oral as the patient improves. Certain patients hospitalized for asthma may benefit from intravenous aminophylline therapy,[48] although use of aminophylline in the treatment of acute asthma is currently controversial. Other patients may benefit from the addition of an anticholinergic medication.[49, 50]

Supportive care for the hospitalized patient with asthma usually will include supplemental oxygen and intravenous fluid replacement.

Impending respiratory failure or frank respiratory arrest are indications for mechanically assisted ventilation. An important principle in managing the mechanically ventilated asthma patient is

avoidance of barotrauma through carefully controlled ventilation. Low tidal volumes, increased inspiratory flow rates, and peak airway pressure not exceeding 40 cm of water reduce the risk of barotrauma and hypotension.

REFERENCES

1. Spagnolo SV. Clinical assessment of the patient with pulmonary disease. In: Spagnolo SV, Medinger A, eds. Handbook of pulmonary emergencies. New York: Plenum, 1986.
2. Rebuck AS, Read J. Assessment and management of severe asthma. Am J Med 1971;51:788-98.
3. McFadden ER, Kiser R, DeGroot WJ. Acute bronchial asthma: relation between clinical and physiological manifestations. N Engl J Med 1973;288:221-4.
4. McFadden ER, Lyons HA. Arterial-blood gas tension in asthma. N Engl J Med 1968;278:1027-31.
5. Brenner BE, Abraham E, Simon RR. Position and diaphoresis in acute asthma. Am J Med 1983;74:1005-9.
6. Webb AK, Bilton AH, Hanson GC. Severe bronchial asthma requiring ventilation: a review of 20 cases and advice on management. Postgrad Med J 1979;55:161-70.
7. Kelsen SG, Kelsen DP, Fleegler BF, et al. Emergency room assessment and treatment of patients with acute asthma: adequacy of conventional approach. Am J Med 1978;64: 622-8.
8. Fischel MA, Pitchenik A, Gardner LB. An index predicting relapse and need for hospitalization in patients with acute bronchial asthma. N Engl J Med 1981;305:783-9.
9. Rose CC, Morphy JG, Schwartz JS. Performance of an index predicting the response of patients with acute bronchial asthma to intensive emergency department treatment. N Engl J Med 1984;301:573-7.
10. Centor RM, Yarbrough B, Wood JP. Inability to predict relapse in acute asthma. N Engl J Med 1984;301:577-80.
11. Silver RB, Ginsberg CM. Early prediction of need for hospitalization in children with acute asthma. Clin Pediatr 1984;23:81-4.
12. Ownby DR, Aborzua J, Anderson JA. Attempting to predict hospital admission in acute asthma. Am J Dis Child 1984;138:1062- 6.
13. McDonald JB, Seaton A, Williams DA. Asthma deaths in Cardiff 1963-1974: 90 deaths outside the hospital. BMJ 1976;1:1493-5.
14. Bondi E, Williams MH Jr. Severe asthma: course and treatment in hospital. N Y State J Med 1977;77:350-3.
15. Williams MH Jr. Life-threatening asthma. Arch Intern Med 1980;140:1604-5.
16. Sheely AF. Treatment of status asthmaticus. Arch Intern Med 1972;130:37-42.
17. Westerman DE, Benatar SR, Potgieter PD, et al. Identification of high-risk asthmatic patients: experience with 39 patients undergoing ventilation for status asthmaticus. Am J Med 1979;66:565-72.
18. Strunk RC, Mrazek DA, Fuhrmann GS, LaBrecque JF. Physiology and psychological characteristics associated with deaths due to asthma in childhood. JAMA 1985;254:1193-8.
19. Rubenstein S, Hendi RD, Moss RB, et al. Sudden death in adolescent asthma. Ann Allergy 1984;53:311-8.
20. Kravis LP, Kolski GB. Unexpected deaths in childhood asthma: a review of 13 deaths in ambulatory patients. Am J Dis Child 1985;139:558-63.
21. Martin J, Powell E, Shore S, et al. The role of respiratory muscles in the hyperinflation of bronchial asthma. Am Rev Respir Dis 1980;121:441-7.
22. Buda AJ, Pensky MR, Ingels NB Jr, et al. Effects of intrathoracic pressure on left ventricular performance. N Engl J Med 1979;301:453-9.
23. Spagnolo SV. Acute respiratory failure in the patient with chronic airflow obstruction. In: Spagnolo SV, Medinger A, eds. Handbook of pulmonary emergencies. New York: Plenum, 1986.
24. Delaney MD: Asthma. In: Spagnolo SV, Medinger A, eds. Handbook of pulmonary emergencies. New York: Plenum, 1986.
25. Banner AS, Shah RS, Addington WW. Rapid prediction of need for hospitalization in acute asthma. JAMA 1976;235: 1337-8.
26. Mansmann HC Jr. Point/counterpoint: Consider magnesium homeostasis. In: Mansmann HC Jr, ed. Pediatric asthma, allergy and immunology, vol 5. New York/Basel: Mary Ann Liebert, 1991:273-9.
27. Karetzky MS. Acute asthma: the use of subcutaneous epinephrine in therapy. Ann Allergy 1980;44:12-4.
28. Pang LM, Rodriguez-Martinez F, Davis WJ, et al. Terbutaline in the treatment of status asthmaticus. Chest 1977;72:469-73.
29. Smith PR, Heurich AE, Leffler CT, Henis MMJ, Lyons HA. A comparative study of subcutaneously administered terbutaline and epinephrine in the treatment of acute bronchial asthma. Chest 1977;71:129-33.
30. Rossing TH, Fanta CH, Goldstein DH, Snapper JR, McFadden L Jr. Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. Am Rev Respir Dis 1980;122:365-71.
31. Dean NC, Brown JK. Status asthmaticus: early institution of treatment. Postgrad Med 1988;84:103-10.
32. Moler FW, Hurwitz ME, Auster JR. Improvement in clinical asthma score and $PaCO_2$ in children with severe asthma treated with continuous nebulized terbutaline. J ALLERGY CLIN IMMUNOL 1988;81:1101-9.
33. Santo M, Sidi Y, Pinkhas Y. Acute myocardial infarction following intravenous salbutamol [letter]. S Afr Med J 1980;58:394.
34. Kurland G, Williams J, Lewiston NJ. Fatal myocardial toxicity during continuous infusion of intravenous isoproterenol therapy of asthma. J ALLERGY CLIN IMMUNOL 1979;63:407-11.
35. Collins JV, Clark TJH, Brown D, Townsend J. The use of corticosteroids in the treatment of acute asthma. J Med 1975;174:259-73.
36. Fanta CH, Rossing TH, McFadden ER Jr. Glucocorticoids in acute asthma: a critical controlled trial. Am J Med 1983;75:781- 3.
37. Elllul-Micallef R, Fenech FF. Effect of intravenous prednisolone in asthmatics with diminished adrenergic responsiveness. Lancet 1975;2:1269-71.
38. Tanaka RM, Santiago SM, Kuhn GJ, Williams RE, Klaustermeyer WB. Intravenous methylprednisolone in adults in status asthmaticus. Chest 1983;82:438-40.
39. Weinberger M, Hendeles L. Reassessing the therapeutic range for theophylline: another perspective. Pharmacotherapy 1993;13:598-601.
40. Jenne J. Reassessing the therapeutic range for theophylline on laboratory report forms: another viewpoint. Pharmacotherapy 1993;13:595-7.
41. Mithoefer JC, Runser RH, Karetsky MS. The use of sodium bicarbonate in the treatment of acute bronchial asthma. N Engl J Med 1965;272:1200-3.

42. Menitove SM, Goldring RM. Combined ventilator and bicarbonate strategy in the management of status asthmaticus. Am J Med 1983;74:898-901.
43. Rogers RM. Bronchopulmonary lavage in bronchial asthma. Chest 1973;63:62-4.
44. Shridharani M, Reed TM. Pulmonary lavage in a patient in status asthmaticus receiving mechanical ventilation: a case report. Ann Allergy 1982;49:156-8.
45. Guidelines for the diagnosis and management of asthma: National Heart, Lung, and Blood Institute National Asthma Education Program—expert panel report. J ALLERGY CLIN IMMUNOL 1991;88:506.
46. Moler FW, Horowitz MC, Cister JR. Improvement in clinical asthma score and $PaCO_2$ in children with severe asthma treated with continuously nebulized terbutaline. J ALLERGY CLIN IMMUNOL 1988;81:1101-9.
47. Haskell RJ, Wong BM, Hansen JE. A double-blind, randomized clinical trial of methylprednisolone in status asthmaticus. Arch Intern Med 1983;143:1324-7.
48. Huang D, O'Brien RG, Harmen E, et al. Does aminophylline benefit adults admitted to the hospital for an acute exacerbation of asthma. Ann Intern Med 1993;119:12:1155-67.
49. O'Driscoll BR, Taylor RJ, Horsley MG, Chambers DK, Bernstein H. Nebulized salbutamol with and without ipratropium bromide in acute airflow obstruction. Lancet 1989; 1:1418-20.
50. Reisman J, Galdes-Sebah M, Kazim F, Canny A, Levison H. Frequent administration by inhalation of salbutamol and ipratropium bromide in the initial management of severe acute asthma in children. J ALLERGY CLIN IMMUNOL 1988; 81:16-20.

C. IDENTIFICATION OF THE FATALITY-PRONE ASTHMATIC PATIENT

Summary statements

- Risk factors for life-threatening exacerbations of asthma include severe asthma, poor control of symptoms, atopy, psychologic factors, and failure by patient and/or physician to recognize the severity of the patient's asthma.
- Poor asthma control is undesirable; poor control of asthma symptoms is a special risk factor in the period after hospitalization.
- Allergic response to airborne mold *(Alternaria)* has been associated with life-threatening or fatal exacerbations in asthmatic patients.
- Psychologic factors that may place the patient at risk of severe life-threatening asthmatic exacerbations include poor ongoing care by the patient and/or family, disregard of asthma symptoms, manipulative use of asthma, and significant emotional problems.
- Fatality-prone asthmatic patients require special planning, including regular follow-up visits for assessment of asthma control, measurement of pulmonary function in the office and at home, monitoring of the patient's course with regard to the need for specialist referral, specific treatment of factors that result in fatality-prone status, identification of an advocate, involvement of community resources, development of a crisis plan, and notification of the patient or parents of fatality-prone status.

The possibility that asthma can be fatal has been recognized since antiquity. There has been increasing concern about asthma-related mortality since epidemics of asthma deaths in England and Wales in the early 1960s and in New Zealand in the late 1970s.[1, 2] In the 1980s an increase in mortality from asthma was recognized in the United States.[3, 4] Increases in asthma-related mortality have occurred despite improvement in the treatment of asthma over the past several decades.[5]

Analysis of epidemics of asthma deaths in the United Kingdom and New Zealand suggests that potentially preventable factors contributed to as many as two thirds of the deaths, and that had these factors been corrected, at least some of the deaths might have been prevented. In particular, there is a strong association between asthma-related deaths and failure by both patients and physicians to recognize the severity of their asthma.[6] This may reflect a failure to use objective measurement of pulmonary function, failure to provide adequate follow-up after a severe exacerbation of asthma, and/or failure to use corticosteroids appropriately. This determination has stimulated interest in identifying patients who are "fatality-prone" and giving them the special attention that could prevent a fatal outcome.

Identification of the fatality-prone asthmatic patient

Severity of asthma. Most patients who die of asthma have a history of severe disease (see box Special Planning for Patients With Fatality-Prone Asthma). Although fatalities are quite rare when the entire population of asthmatic patients is considered, approximately 1% to 2% of patients with severe asthma have a fatal outcome.[7, 8] These patients fall into two general groups: patients who have had a near-fatal episode in the past, which was of sudden onset and required resuscitation (these patients may or may not have ongoing severe symptoms[7, 9]), and patients who have chronic severe symptoms that require corticosteroid therapy for control. These patients also may have had a history of hypoxic seizures, respiratory failure requiring ventilation, severe nighttime

SPECIAL PLANNING FOR PATIENTS WITH FATALITY–PRONE ASTHMA

- Regular follow–up visits for assessment of asthma control
- Measurement of pulmonary function in the office and at home
- Monitoring of course with regard to need for specialist referral
- Specific treatment of factors that contribute to fatality–prone status
- Identification of an advocate
- Involvement of community resources
- Development of a crisis plan
- Notification of patients or parents of fatality–prone status
- Cooperative management through education

wheezing, or wide rapid fluctuations in pulmonary function from normal to abnormal.[8]

Poor asthma control. Patients with extremely poor control of their asthma are also at increased risk. This is especially true for the period immediately after hospitalization for severe refractory asthma. Even patients with moderate asthma that is poorly controlled are at greater risk.[10] This fact was highlighted by the cluster of five asthma deaths in African-American adolescents that occurred in St. Louis during the summer of 1987.[11] Only one of the five children who died had severe asthma, and none had ever had a life–threatening attack. However, all five had very poor control of their asthma in the months before the sudden fatal attacks.

Atopy. Atopy has been mentioned as another risk factor. In the United Kingdom a spring–fall predominance of deaths was noted in patients with atopic asthma.[12] Some patients were exposed to large amounts of allergen immediately before their deaths. A rapid onset of severe bronchospasm appeared to develop in these patients. Furthermore, a correlation has been noted between the sudden onset of respiratory arrests during summer and fall months and *Alternaria* sensitivity.[13, 14] Therefore an allergy evaluation in all patients with asthma is important, particularly in the patient with fatality–prone asthma, because *Alternaria* sensitivity may be a risk factor for respiratory arrest or even sudden death.

Psychologic factors. Psychologic factors frequently are mentioned in histories of patients who have died of asthma and probably play an important role in determining the outcome in some patients.[8, 15] Psychologic factors can interfere with the adequate delivery of chronic and acute care, and poor ongoing care of asthma by the patient or the patient's family is seen commonly in cases of fatal asthma. This includes lack of compliance in taking medications, especially excessive use of metered–dose inhalers and self–initiated reduction in use of corticosteroids. It also includes a disregard of or failure to recognize symptoms, as demonstrated, for example, by continuation of exercise despite wheezing. These patients characteristically use asthma symptoms for secondary gain (manipulative use of asthma) so as to avoid unpleasant tasks or to place pressure on others to respond to their wishes. These features are exacerbated by conflict between parent and physician, patient and physician, or patient and parent. Conflict is identified by ongoing disagreement, frustration, or dissatisfaction with the performance of any of the identified persons.

Reports of various psychiatric diagnoses, especially depression, are noted frequently in histories of patients who have died of asthma. Some patients have expressed hopelessness about their asthma or a wish to die; this may be related to ongoing depression or other emotional problems. Significant family dysfunction (e.g., alcoholism, physical abuse of children and wives, problems with employment, and frequent changes of physicians) also may be present.

Summary. In summary, patients with severe asthma, particularly those with a previous life–threatening attack, are at increased risk of fatal exacerbation of asthma. Asthma out of control, even with moderate illness, is probably an important factor as well. The risk of fatal asthma is increased by the presence of one or more of the associated factors listed earlier.

It has been suggested that lack of appropriate anti–inflammatory therapy may play a role in sudden, severe episodes of asthma.[16] In addition, comparison of lung specimens obtained at autopsy from patients with sudden–onset fatal asthma and slower–onset fatal asthma have indicated differences in inflammatory cell populations in the airway submucosa.[17] This would suggest possible pathological differences between sudden–onset and slower–onset attacks. In one study of near–fatal asthma,[16] patients with a rapid onset of symptoms had a shorter duration of mechanical ventilation once bronchodilator therapy was initiated. This may represent a subset of asthma patients in whom there is a primary role for bronchospasm in near–fatal attacks. Patients with fatal attacks may have an absence of airway secretions noted at autopsy.[18]

CRITERIA FOR IDENTIFICATION OF FATALITY–PRONE ASTHMATIC PATIENTS

- *Severe disease characterized by one of two patterns:* (1) patients with a single life–threatening episode of asthma that may or may not be accompanied by ongoing severe symptoms; and (2) patients with severe asthma of any type, especially if systemic corticosteroid therapy has been required to control symptoms or if there is a history of hypoxic seizures, respiratory failure requiring ventilation, severe nighttime wheezing, or wide rapid fluctuations in pulmonary function from normal to abnormal
- *Associated factors that may increase risk:* (1) poor control of asthma symptoms, especially immediately after emergency treatment or hospitalization for severe refractory asthma; (2) atopy patients may be at increased risk during their allergy season or with intense exposure to an allergen; (3) poor ongoing care by patient and family, such as not taking medication as prescribed, disregarding perceived asthma symptoms, and manipulative use of asthma; (4) significant emotional problems, such as depression, hopelessness, and family dysfunction

Special planning for the fatality–prone asthmatic patient

Fatality–prone asthmatic patients must be followed more frequently and intensely than patients with less severe illness (see box Criteria for Identification of Fatality–Prone Asthmatic Patients). These patients should have office visits at intervals of weeks or months, depending on the severity of their asthma, even if their asthma is stable. Some measurement of pulmonary function (minimally PEFR) should be performed at each visit. Furthermore, a peak flow meter should be provided for home use, accompanied by specific instructions on interpretation of results and what steps to take when specific levels are observed. The physician should consider the need for specialist referrals, such as a mental health professional, otolaryngologist, or gastroenterologist. Features that identify fatality–prone status should be treated specifically, including (1) more intensive education for poor self–care (this may be particularly important for patients who tend to overuse metered–dose inhalers) and (2) mental health referral to resolve family dysfunction or emotional problems in the patient that could interfere with compliance with the medical regimen.

In addition, the treatment plan for these patients should include (1) identification of an advocate, a stable individual close to the patient who can watch out for the patient's welfare; (2) involvement of community resources in the treatment program, including school personnel if the patient is a child; and (3) development of a crisis plan. Finally, physicians should notify their patients about their high–risk status. The content of this discussion will vary widely depending on the developmental stage and the capabilities of the patient and family to deal with the issue. At a minimum, patients should be told that they have severe disease and that serious problems can develop if they do not pay attention and communicate well with a physician early in the course of an attack. In addition, physicians should not support the myth that asthma can never be fatal.[19]

Use of a crisis plan for patients with fatality–prone asthma

Planning for periods of increasing asthma, especially emergencies associated with sudden onset of severe asthma, is particularly important for the patient who has been identified as having fatality–prone asthma. One approach that can facilitate and formalize planning is the development of a crisis plan. The plan is filled out with the patient and copied for the chart. This plan can be reviewed at the time of regular office visits to ensure continued understanding and appropriateness. The plan should emphasize avoiding delays in obtaining medical care during an acute attack. Such a plan should include (1) initiating a planned response to subjective feeling or objective findings (e.g., decrease in peak flow meter reading below a specific number or use of an inhaled β–agonist more frequently than every 4 hours on a continuing basis); (2) calling the physician at an early stage; (3) taking certain medications even if the physician cannot be reached (e.g., a predesignated dose of corticosteroids); (4) recognizing those signs and symptoms that should prompt the patient to go directly to an emergency room (or perhaps call a paramedic squad)—both the emergency room and the paramedic squad to be used should be predesignated; and (5) planning for vacations (e.g., the patient should determine what health care facilities and emergency rooms will be available in the new location). Additionally, it is recommended that the patient carry information from the physician that would be of help to emergency personnel who have never seen the patient before.

REFERENCES

1. Speizer FE, Doll R, Heaf P. Observations on recent increase in mortality from asthma. BMJ 1968;1:335-9.

2. Sears MR, Rea HH, Beaglehole R. Asthma mortality: a review of recent experience in New Zealand. J ALLERGY CLIN IMMUNOL 1987;80:319-25.
3. Evans R, Mullally DI, Wilson RW, et al. National trends in the morbidity and mortality of asthma in the US: prevalence, hospitalization and death from asthma over two decades: 1965-1984. Chest 1987;91:65S-74S.
4. Sly RM. Mortality from asthma, 1979-1984. Ann Allergy 1988;433-43.
5. Sly M. Asthma mortality, east and west [Editorial]. Ann Allergy 1992;69:81.
6. Nguyen B, German D, Wilson S. Patients' perception versus objective ratings of asthma severity [Abstract]. Presented at Annual Meeting of The American College of Allergy and Immunology. Chicago, November 14-18, 1992.
7. Rea HH, Scragg R, Jackson R, Beaglehole R, Fenwick, Sutherland DC. A case–control study of deaths from asthma. Thorax 1986;41:833-9.
8. Strunk RC, Mrazek DA, Fuhrmann GSW, LaBrecque JF. Physiologic and psychological characteristics associated with deaths due to asthma in childhood. JAMA 1985;254: 1193-8.
9. Wasserfallen JB, Schaller MD, Feihl F, Perret CH. Sudden asphyxic asthma: a distinct entity? Am Rev Respir Dis 1990;142:108-11.
10. Kunitoh H, Yahikozawa H, Kakuta T, et al. Fatal and near fatal asthma. Ann Allergy 1992;69:111.
11. Birkhead G, Attaway NJ, Strunk RC, Townsend MC, Teutsch S. Investigation of a cluster of deaths of adolescents from asthma: evidence implicating inadequate treatment and poor patient adherence with medications. J ALLERGY CLIN IMMUNOL 1989;84:484-91.
12. British Thoracic Society. Comparison of atopic and nonatopic patients dying of asthma. Br J Dis Chest 1987;81:30-4.
13. O'Hollaren MT, Sachs MI, Yunginger JW, O'Connell EJ, Wynn SR. *Alternaria* sensitivity as a possible risk factor for respiratory arrest in children with asthma. [Abstract]. J ALLERGY CLIN IMMUNOL 1986;77:199.
14. O'Hollaren MT, Sachs MI, O'Connell EJ, Yunginger J. Allergen exposure as a possible precipitating factor for respiratory arrest in young adults with asthma. J ALLERGY CLIN IMMUNOL 1988;80:256.
15. Miller BD, Strunk RC. Circumstance surrounding death due to asthma in children: a case–controlled study. Am J Dis Child 1989;143:1294-9.
16. Kallenbach JM, Frankel AH, Lapinsky SE, et al. Determinants of near fatality in acute severe asthma. Am J Med 1993;95:265-72.
17. Sur S, Hunt LW, Crotty TB, Gleich GJ. Sudden-onset fatal asthma [Editorial]. Mayo Clinic Proc 1994;69:495-6.
18. Reid LM. The presence or absence of bronchial mucus in fatal asthma. J ALLERGY CLIN IMMUNOL 1987;80(suppl): 415-6.
19. Strunk RC. Workshop on the Identification of the Fatality Prone Patient With Asthma: summary of workshop discussion. J ALLERGY CLIN IMMUNOL 1987;80:455-8.

D. ENVIRONMENTAL AVOIDANCE

Airborne triggers

Summary statements

- Important steps in environmental control are (1) to minimize house dust mite exposure in mite–allergic patients with asthma, (2) to lessen exposure to domestic animals in appropriate patients, (3) to not allow smoking in the home, (4) to avoid strong odors and chemical fumes, (5) to install kitchen and bathroom exhaust fans, (6) to use humidifiers with caution in mite– and mold–sensitive patients, (7) to use air conditioners in bedrooms and family rooms, when appropriate, (8) to use high–efficiency particulate air filters or electrostatic air purifiers, (9) to install a dehumidifier and reduce water entry in damp basements, and (10) to initiate other measures as indicated for specific allergies as appropriate.
- Health care providers should identify allergic and nonallergic environmental triggers of asthma and implement environmental measures to eliminate or to minimize exposure to these factors.
- House dust mite sensitivity is a significant risk factor for many patients with allergic asthma. Extensive cleaning procedures minimize mite exposure, decrease bronchial hyperresponsiveness, and reduce asthma morbidity. Proposed environmental controls should be commensurate with the severity of the patient's disease, economic status of the family, and other practical considerations.
- Cockroach allergen has been recognized as a major cause of allergic rhinitis and asthma, especially in inner–city asthmatic patients. Exposure to rodent allergen also may be a significant factor in some asthmatic patients living in this setting.
- Tree, grass, and weed pollen can produce significant exacerbations of asthma at specific times of the year. Every effort should be made to minimize indoor pollen contamination at home and at work by keeping windows closed and using filtration devices and air conditioning.
- Molds and fungi are aeroallergens that are recognized as triggers for asthma and rhinitis. Their ability to produce severe life–threatening exacerbations of asthma has been well documented. For indoor molds, environmental control procedures include use of dehumidifiers and air conditioning. Avoidance of outdoor molds requires an understanding of areas where extensive mold growth can be anticipated.
- Nonallergic environmental triggers, such as cigarette smoke, chemical irritants, or strong odors, also can produce significant exacerbations of asthma. Avoidance of these triggers may be just as important as avoidance of allergic triggers.

- Domestic animals, especially cats and dogs, are a common cause of allergic reactions in individuals with allergic rhinitis and asthma.

IgE–mediated sensitivity to specific allergens is quite common among asthmatic patients.[1-5] Furthermore, the presence of IgE antibody to dust mites, cockroach allergen, cat allergen, grass pollen, and ragweed pollen can be associated with increased risk of acute asthma that requires emergency care in children and adults.[4-6]

Health care providers should strive to identify both allergic and nonallergic environmental triggers of asthma and implement environmental controls to eliminate or minimize exposure to these factors. The five major IgE–mediated triggers of asthma are house dust mites, cockroach allergens, animal allergens, pollens, and molds. Initially, only outdoor allergens, specifically pollens and molds, could be microscopically identified and quantitatively assayed. Amounts of airborne allergen, as determined by pollen or mold counts, that triggered clinical symptoms could then be correlated with asthma–related morbidity. The development of sensitive monoclonal antibody and immunoassay techniques for specific indoor allergens, such as house dust mite, cockroach allergen, and cat allergen, has allowed researchers to identify and quantitatively measure important indoor allergens as well.[7] This has allowed investigators to examine and define the potential risk factors for people with asthma who are exposed to diverse levels of these potent allergens, and to evaluate the efficacy of environmental control measures.[8-11]

House dust mite. The major allergen in house dust remained obscure until 1967, when it was suggested that the most important source of house dust allergy was dust mites belonging to the genus *Dermatophagoides*.[12] Ensuing studies have shown that two species of the *Dermatophagoides*, *pteronyssinus* and *farinae*, are the most important house dust mite allergens in Europe and North America, although other species may prove to be important in specific localities.[13] House dust mites are microscopic (0.33 mm long), sightless, eight–legged acarids that flourish by feeding on the approximately 50 million skin scales shed daily by each individual. The most allergenic parts of the house dust mite are its body parts and fecal residue. One ounce of house dust can contain up to 42,000 dust mites. Thus a bed, a common site of mite habitation, can contain up to 2 million mites. It has been reported that acutely ill mite–sensitive asthmatic patients usually reside in homes with more than 500 mites per gram of dust (equivalent to 10 μg of Der P 1.)[13] Subsequent studies in Denmark,[14] Australia,[15-17] and the United States[18-20] verified these observations, and exposure to dust mites is widely recognized as a significant risk factor for asthma. One epidemic of asthma in the highland villages of New Guinea was found to be related to the use of blankets infested with dust mites.[21] Studies now indicate that the critical level of house dust mites that poses a risk factor for asthma ranges from 100 to 500 mites per gram of house dust.[21]

House dust mite levels will vary with climate, season, and type of home furnishings.[19, 22-24] The major factor influencing growth of house dust mites, however, is humidity.[25] Mite–sensitive asthmatic patients who live in homes with suitable sites for mite growth (i.e., bedding, carpeting [especially wall to wall], and upholstered furniture) are more at risk in more humid climates because mites propagate in bedding and carpeting in locales where the relative humidity in the home is higher than 50%.[14, 19, 26-28] A lower incidence of asthma has been found in areas at high altitudes,[29] where there are reduced levels of dust mites in furnishings and mattresses.[30, 31] Changes in home construction methods and household cleaning habits introduced over the past 50 years that promote the proliferation of house dust mites include[32] the following: (1) the introduction of vacuum cleaners, because carpets are no longer picked up and beaten outdoors but are permanently installed wall to wall; dust mite allergen is essentially aerosolized when vacuum cleaners are turned on,[33] and vacuuming does not effectively remove house dust mites from bedding, upholstered furniture, or carpeting[34]; (2) increased use of central heating sources in new home construction, which allows areas in the home, other than the bedroom, to be maintained at optimal temperature and humidity for dust mite growth; (3) the fashion of using cool–water detergents to wash bedding, which promotes dust mite growth because only hot water kills mites; and (4) modern air–humidification systems and reduced ventilation in energy–efficient dwellings, which promotes higher indoor humidity levels, which also encourage house dust mite infestation.

Environmental control studies using relatively simple hygienic measures have shown no effect on asthma symptoms or reduction in mite growth,[35-37] whereas use of extensive cleaning and dust– proofing (e.g., covering mattress and pillow) procedures to minimize mite exposure have been associated with a reduction in asthmatic symptoms, medication use, and morbidity.[38-40] Patients exposed to lower levels of house dust mites not only have

decreased asthma symptoms and medication use but also have improvement in nonspecific bronchial hyperresponsiveness.[41-43]

Patients with documented IgE–mediated asthma in whom house dust mite sensitivity has been demonstrated by either skin testing or in vitro testing are candidates for such preventive environmental measures. Proposed environmental controls should be commensurate with the severity of the patient's disease, patient capability for such modifications, and the economic status of the family.[44, 45] Although the bedroom is the most important room in environmental control, other areas of the home, such as the living or family room, that contain upholstered furniture or carpeting must be considered as potential sites of house dust mite infestation.[13, 46] Fundamental steps for reducing house dust mite exposure include (1) removing bedroom and family room carpeting (if the subflooring is plywood, consider installing a vinyl or wooden floor); small, washable area rugs are acceptable alternatives to wall–to–wall carpeting; (2) covering pillows, mattresses, and box springs with zippered encasing and removing all potential sources of dust mite infestation, such as older mattresses, mattress pads, comforters, and pillows; (3) washing all bedding in a hot cycle of 60° C (130° F) every 10 to 14 days; (4) reducing home humidity levels by use of air conditioners and dehumidifiers, by opening windows in drier climates unless pollen exposure is a cause of symptoms, and by avoiding overuse of home humidifiers; (5) vacuuming, preferably done by someone other than the patient (if done by the patient, the patient should wear a mask); (6) advising patients to move to a drier carpet–free home or apartment if the above measures cannot be implemented, although patients should not move to homes built on slabs or with basements if possible; (7) installing air–filtering devices, preferably high–energy particular air filters, in bedrooms or family rooms; and (8) using acaricides and dust mite assay kits.

The major excretion product of mites and other arachnids is guanine. Concordance between dust mite levels and guanine content has been reported.[47] Quantitative tests for guanine are now available. These tests may prove to be a convenient and reliable method to substitute for complicated monoclonal antibody and immunoassay techniques now used to quantitate mite content of dust, provided the home does not also contain birds, which also excrete guanine, and the test is done properly.

Several acaricides have been studied and developed in Europe and Australia, including benzoic acid ester (kills scabies mites), pirimiphos methyl (kills storage mites and mosquitoes), liquid nitrogen, and polyphenolbenzyl derivatives.[48,49] Benzyl benzoate has been evaluated in several controlled studies and has been shown to be effective on a short–term basis.[50-55] In one study, which used a semiquantitative guanine assay to measure mite content, 66% of dust samples had medium–to–large house dust mite concentrations before benzyl benzoate was applied. After application, only 7% of dust samples had medium dust mite concentrations and none had heavy content.[52]

Cockroach allergy. Cockroach allergen has been identified as a major cause of allergic rhinitis and asthma.[56-60] The ability of cockroach allergen to stimulate the formation of specific IgE antibodies has been demonstrated by endpoint skin test titration and RAST studies, and a causal relationship between bronchospasm and sensitivity to cockroach allergen has been proved in bronchial provocation studies.[61-63] Positive skin tests to cockroach allergen are present in 20% to 53% of allergic patients and 49% to 61% of asthmatic patients.[56, 64-66] Fifty–five species of cockroaches live in the United States, but so far only three, the American, German, and the Oriental species, have been shown to induce specific IgE antibodies. Cockroach allergen usually is found in kitchen cabinets and kitchen floor dust. Exposure is higher in substandard housing and older apartment complexes. A study in urban asthmatic patients has shown that cockroach sensitivity may be as important a risk factor for intercity asthmatic patients as house dust mite allergy.[65] Because elimination of cockroach infestation requires vigorous and repeated extermination maneuvers, often with irritant chemicals, it is best performed by professional exterminators. If this is done, physicians should be aware of possible complications in patients exposed to organophosphate insecticides.

Animal allergy. Domestic animals, especially dogs and cats, are a common cause of allergic reactions in individuals with allergic rhinitis and asthma.[66-69] All furry or feathered animals, including guinea pigs, hamsters, and rabbits, are capable of inducing an IgE–mediated reaction, and allergens on feathers can remain a source of symptoms when feathered animals are present as pets or when used in feather products. Animal allergens are widely distributed in our society: 30% to 40% of American homes have pets, and small amounts of cat or dog allergen can be found in virtually any home.[70, 71] Positive skin tests to cat or dog can be found in 18% to 52% of allergic patients,[67, 69, 72, 73]

and 19% to 30% of workers in animal laboratories have animal-related allergic symptoms.[74-76]

The allergenic composition of environmental dust can be increased greatly by the presence of animal allergen. Acute symptoms may develop in dog- or cat-sensitive asthmatic patients within minutes after a home where these animals reside is entered. In contrast, dust mite-sensitive asthmatic patients are rarely aware of symptoms immediately, even when the level of dust mite allergen in a home is quite high. Although not well studied, the potential for sensitization to rodent urine allergens may be significant, especially in inner-city asthmatic patients.

Cat allergens (cat saliva and cat dander), the most widely studied animal allergens to date, are indeed quite different from house dust mite allergen. The particle size and amount of cat allergen in the air at any given time are highly variable,[77-80] depending on differences in home heating and ventilation systems.[81] In most cases cat sensitivity is mediated by a single cat allergen, denoted Fel d 1.[82] It is produced in cat salivary glands and in the sebaceous glands of the cat's skin, and may be present in the urine of male cats as well. Common allergens are present in all breeds of cat. The particle size of cat allergen is quite small (3 μm) compared with that of mite allergen (10 μm). This unique characteristic may allow it to remain suspended in the air for longer periods and to be inhaled more deeply into the lungs, possibly accounting for its greater potential to produce asthma. The precise level of cat allergen that will induce asthma symptoms is not well defined.[78, 79, 83] Cat allergen has been found in areas where cats are not present, but available data suggest that these low levels are unlikely to induce clinical symptoms.[84-86]

Allergy to dogs has been implicated in 56% of asthmatic patients in a Finnish population,[87] but relatively little is known about the composition of dog allergen. In contrast to cat allergen, where the major antigenic component has been identified and isolated, dog allergen appears to be a more complex mixture containing many varied allergens.[88] Dogs have common allergens, but differences may exist in patient response to a particular breed of dog or possibly even specific dogs of a specific breed. Contrary to popular belief, there is no "nonallergenic" breed of dog.

The treatment of choice for animal allergy is avoidance, including removal of the animal that is triggering allergic symptoms from the home. However, the psychologic and perhaps physical effect of such a decision must be weighed carefully in each patient. The recent development of specific immunoassays for cat allergen now make it possible to study the environmental distribution of cat allergen before and after the animal is removed from the home. Cat allergen levels decline very slowly after removal of the cat, and it generally takes about 20 weeks for allergen levels to reach those found in homes without cats.[89] Furthermore, the level of cat allergen remains quite high in some homes for even longer periods. Preliminary studies indicate that the reduction of allergen levels may be accelerated by aggressive cleaning measures, such as removal of all upholstered furniture and carpeting; steam cleaning of carpets, however, appears to have no added benefit over vacuuming. Patients who are advised to remove an offending cat from the home should be informed that brief trials of cat avoidance are useless, and improvement in asthma symptoms may not be seen for as long as 4 to 6 months after the cat has been removed from the home. When removal of the animal is not possible, confinement of the animal in carpet-free areas of the home, outside the bedroom, combined with the use of high-efficiency particulate air or electrostatic air filters may reduce airborne allergen by 90%.[90] Kitty litter should be removed wherever possible or placed in an area where it will not enter the general circulation of the home. Frequent (weekly) washing of cats also may help to decrease aerosolized cat allergen.[91] In addition, allergens can be denatured and allergenicity removed by use of tannic acid on upholstered furniture and rugs (it should be noted that tannic acid stains fabrics and carpets).[92]

Pollen allergy. Pollen allergens that trigger asthma, namely, trees, grasses, and weeds, are predominantly derived from wind-borne (rather than insect-borne) pollen.[93, 94] Even though whole pollen grains are quite large and have limited access to the lower respiratory tract,[95] the relationship of pollen to clinical asthma is quite convincing.[96] Probably this is partly because plants can produce allergen-containing particles that are less than 10 μm and because protein allergens can be extruded from the pollen grain through pores in the outer covering. Inciting allergens vary with locale and climate. In general, tree pollen predominates in the spring, grasses in late spring and early summer, and weeds in late summer and early autumn.

Pollen-sensitive patients can have significant asthma relapses during specific pollen seasons. For example, the inland area of northern California encounters a period of intense grass pollination each year during the second or third week in May,

which is accompanied by a striking rise in the incidence of asthma–related emergency clinic visits and hospitalizations.[6] One study of patients with acute asthma who required emergency care during this California grass pollen season found that the presence of IgE antibody to grass pollen increased the patient's chances of acute asthma developing at that time.[4] These investigators found that grass pollen not only was airborne outdoors but also gained entry into homes and was found in high levels in carpeting, bedding, and furniture. The presence of grass pollen in the home is facilitated by the use of window and attic fans. Indoor pollen can contribute significantly to the patient's overall pollen exposure during periods of peak pollination.

Patients should be educated about specific pollen seasons because the best way for the patients to reduce exposure to airborne pollen to which they are sensitive is to remain indoors as much as possible during times of increased pollen levels. Recognizing that this is not always possible, accurate pollen counts will help alert patients who need to reduce the level of pollen exposure in their automobile and home during periods of increased airborne pollination. Closing windows, avoiding the use of window fans, and using automobile and home air conditioning units (using closed vents) are relatively simple measures that can reduce the risk for pollen–sensitive asthmatic patients.

It must be recognized, however, that complex interpersonal relationships at home and at work may prevent complete compliance with such recommendations. If so, asthmatic control with medications and/or allergen immunotherapy may be necessary for the patient to function normally.

Mold allergy. As are house dust, animal allergen and pollens, molds, and fungi are aeroallergens that can trigger significant exacerbations of asthma. All molds belong to the phylum thallophyte (lacking stems, roots, or leaves). Because they lack chlorophyll, most molds are saprophytes, but unlike pollens, there are no well–defined seasonal peaks and valleys for airborne mold spores. Only in the northernmost areas of the United States is there a consistent seasonal increase in mold counts starting in May or June and ending in October or November, having peaked in July or August. In southern areas of this country, atmospheric molds are present throughout the winter, with a peak in summer or early fall. Although molds are classified anatomically, for the purposes of discussing their role in asthma, they are usually divided into outdoor ("field fungi") or indoor ("storage fungi") types.

The two most common outdoor molds are *Alternaria* and *Cladosporium* (often incorrectly referred to in the literature as *Hormodendrum*). Additional common outdoor molds include *Helminthosporium*, *Spondylcladium*, and *Fusarium*. These outdoor molds grow on plants and in decaying vegetation. Outdoor mold comes from soil and is more predominant in rural farm communities, settling in large quantity on hay. Mold levels are affected by temperature, wind, rainfall, and humidity. Rain or high humidity levels will lower mold spore counts temporarily, but counts rise rapidly when the rainy period ends. Generally, a late summer–autumn peak is seen for common fungal spores. A spring peak may be seen in some areas, where late melting snow cover produces so–called snow mold.

Staying indoors as much as possible and keeping home and automobile windows closed reduce exposure to mold spores. The importance of minimizing mold exposure in mold–sensitive asthmatic patients cannot be overemphasized. From observation of such phenomena as New Orleans asthma and from recent articles, it is clear that inhalation of large quantities of mold can produce severe, life–threatening asthma in some patients.[97] Possibly this is in part because mold spores generally are smaller than pollen grains and therefore are more likely to penetrate the lower airways.

The most important indoor molds are *Aspergillus* and *Penicillium* (the green mold in wet cellars known as mildew), although indoor *Alternaria* levels have received attention recently.[97] The amount of indoor mold in any dwelling will depend on several factors, including the age of the structure, insulation materials, heating system, and use of humidifiers and air conditioners. Dark, humid, and poorly ventilated basements are ideal sites for mold growth. The next most common sites of mold growth are the bathroom and the kitchen. Home heating, cooling, and humidification systems are also potential sources of fungal growth, although air conditioning generally reduces indoor humidity and hence discourages mold growth. Most fungal spores in an indoor environment are nonviable spores that will be found in house dust reservoirs such as carpeting, bedding, and furniture. Implementing precautions used to reduce levels of dust mites is the best way to eliminate mold spores for the home. Levels of viable indoor mold spores can be reduced by use of dehumidifiers in the basement and air conditioners in the bedroom or family room. Home humidifiers should be used with caution and cleaned frequently because of the potential for mold and *Actinomyces* growth. Bathrooms and kitchens should be well ventilated.

Electronic air filters also lower the level of mold spores within a dwelling. When the major source of molds within a home is a wet or damp cellar, the basement should be kept free of carpeting, immediately dried out after a rainstorm, and, whenever possible, protected with a drainage system or sump pump.

Nonallergenic indoor triggers. Nonallergenic indoor triggers of asthmatic symptoms should be carefully eliminated or avoided. Passive cigarette smoke, consisting of very small particles that remain in the air for long periods, is a risk factor for all asthmatic patients. Studies in children, in particular, have demonstrated a worsening of asthma or increase in airway responsiveness to passive smoke.[98, 99] It also has been suggested that passive exposure to cigarette smoke may increase the risk for the development of asthma.[100] Smoke from wood-burning heating stoves also has been reported to produce a negative effect on the lower respiratory tract.[101, 102] In addition, fumes and strong odors (e.g., paint fumes, household sprays, insect sprays, cooking fumes, and cosmetics) may initiate or exacerbate asthmatic symptoms in some patients.

REFERENCES

1. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin test reactivity to allergens. N Engl J Med 1989;320:271-7.
2. Dodge R, Cline MG, Burrows B. Comparisons of asthma, emphysema, and chronic bronchitis: diagnosis in a general population sample. Am Rev Respir Dis 1986;133:981-6.
3. Lehrer SB, Lopez M, Burcher BT, Olson J, Reed M, Salvaggio JE. Basidiomycete mycelia and spore allergen extracts: skin test reactivity in adults with symptoms of respiratory allergy. J ALLERGY CLIN IMMUNOL 1986;78:479.
4. Pollart SM, Chapman MD, Fiocco GP, Rose G, Platts-Mills TAE. Epidemiology of acute asthma: IgE antibodies to common inhalant allergens as a risk factor for emergency room visits. J ALLERGY CLIN IMMUNOL 1989;83:875-82.
5. Peat JK, Britton WJ, Salome CM, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian school children, III: effect of exposure to environmental allergens. Clin Allergy 1987;17:291-300.
6. Reid MJ, Moss RB, Hsu YP, Kwasnicki MJ, Commerford TM, Nelson BL. Seasonal asthma in Northern California: allergic causes and efficacy of immunotherapy. J ALLERGY CLIN IMMUNOL 1986;78:590-9.
7. Chapman MD, Heymann PW, Wilkins SR, Platts-Mills TAE. Monoclonal immunoassays to measure allergens from house dust mites [Abstract]. J ALLERGY CLIN IMMUNOL 1986;77:204.
8. Warner JO, Price JA. Aero-allergen avoidance in the prevention and treatment of asthma. Clin Exp Allergy 1990;20:15-9.
9. Hamilton RG, Chapman MD, Platts-Mills TAE, Adkinson NF. House dust aeroallergen measurements in clinical practice: a guide to allergen-free home and work environments. Immunol Clin Pract 1992;15:96-112.
10. Van Asperen PP, Kemp AS, Mukhi A. Atopy in infancy predicts the severity of bronchial hyperresponsiveness in later childhood. J ALLERGY CLIN IMMUNOL 1990;85:700-5.
11. Sporik R, Holgate ST, Platts-Mills TAE, Cogswell J. House dust mite allergen (*Der p I*) exposure and the development of sensitization and asthma in childhood: prospective study. N Engl J Med 1990;323:502-7.
12. Voorhorst R, Spieksma FThM, Varekamp H, Leupen MJ, Lyklema AW. The house dust mite *(Dermatophagoides pteronyssinus)* and the allergen it produces: identity with the house dust allergen. J Allergy 1967;39:325.
13. Platts-Mills TAE, Thomas WR, Aalberse RC, et al. Dust mite allergens and asthma: report of a second international workshop. J ALLERGY CLIN IMUNOL 1992;89:1046-60.
14. Korsgaard J. Mite asthma and residency: a case-control study on the impact of exposure to house dust mites in dwellings. Am Rev Respir Dis 1983;128:231.
15. Witt C, Stuckey MS, Woolcock AJ, Dawkins RL. Positive allergy prick tests associated with bronchial histamine responsiveness in an unselected population. J ALLERGY CLIN IMMUNOL 1986;77:698-702.
16. Sears MR, Herbison GP, Holdaway MD, Hewitt CJ, Flannery EM, Silva PA. The relative risks of sensitivity to grass pollen, house dust mite, and cat dander in the development of childhood asthma. Clin Exp Allergy 1989;19:419-24.
17. Peat JK, Woolcock AJ. Sensitivity to common allergens: relation to respiratory symptoms and bronchial hyperresponsiveness in children from three different climatic areas of Australia. Clin Exp Allergy 1991;21:573-81.
18. Smith TF, Kelly LB, Heymann PW, Wilkins SR, Platts-Mills TAE. Natural exposure and serum antibodies to house dust mite of mite- allergic children with asthma in Atlanta. J ALLERGY CLIN IMMUNOL 1985;76:782-91.
19. Platts-Mills TAE, Hayden ML, Chapman MD, Wilkins SR. The seasonal variations in dust mite and grass pollen allergens in dust from the houses of patients with asthma. J ALLERGY CLIN IMMUNOL 1986;79:781-91.
20. Platts-Mills TAE, Ward GW, Sporik R, Gelber LE, Chapman ND, Heymann PW. Epidemiology of the relationship between exposure to indoor allergens and asthma. Int Arch Allergy Appl Immunol 1991;15:21-4.
21. Dowse GK, Turner KJ, Stewart GA, Alpers MP, Woolcock AJ. The association between *Dermatophagoides* mites and the increasing prevalence of asthma in village communities with in the Papua New Guinea highlands. J ALLERGY CLIN IMMUNOL 1985;75:75.
22. Chur V, Lau S, Wahn U. *Dermatophagoides pteronyssinus*: an important allergen source in Guatemala. J ALLERGY CLIN IMMUNOL 1989;83:198.
23. Arlian LG, Bernstein IL, Geis GP, Vyszenski-Moher DL, Gallagher JS, Martin B. Investigations of culture medium-free house dust mites, III: antigens and allergens of body and fecal extract of *Dermatophagoides farinae*. J ALLERGY CLIN IMMUNOL 1987;79:457-66.
24. Hamilton RG, Chapman MD, Platts-Mills TAE, Adkinson NF. House dust aeroallergen measurements in clinical practice: a guide to allergen-free home and work environments. Immunol Clin Pract 1992;15:96-112.
25. Hart BJ, Whitehead L. Ecology of house dust mites in Oxfordshire. Clin Exp Allergy 1990;20:203-9.
26. Green WF, Woolcock AJ, Stuckey M, Sedgwick C, Leeder

SR. House dust mites and skin tests in different Australian localities. Aust NZ J Med 1986;16:639-43.
27. Wharton GW. House dust mites. J Med Entomol 1976; 12:557.
28. Arlian LG. Humidity as a factor regulating feeding and water balance of the house dust mites *D. farinae* and *D. pteronyssinus* (acari: *Pyroglyphidae*). J Med Entomol 1977;14:484-8.
29. Charpin D, Kleisbauer JP, Lanteaume A, et al. Asthma and allergy to house dust mites in populations living at high altitudes. Chest 1988;93:758-61.
30. Charpin D, Burnbaum J, Haddie E, Genard G, Toumi M, Vervolet D. Altitude and allergy to house dust mites: an epidemiologic study in primary school children. J ALLERGY CLIN IMMUNOL 1990;85:185.
31. Haddi E, N'Guyen A, Toumi M, van der Brempt X, Charpin D, Vervloet D. Mites allergen content at sea level and at high altitude. J ALLERGY CLIN IMMUNOL 1989;83:198.
32. Report of an International workshop. Dust mite allergens and asthma a worldwide problem. J ALLERGY CLIN IMMUNOL 1989;83:416-25.
33. Trudeau W, Fernandez-Caldas E, Fox R, Lockey R. Mite aeroallergen concentrations before, during, and after vacuum cleaning. J ALLERGY CLIN IMMUNOL 1989; 83:264.
34. Kersten W, Musken H, Moers FRG. A clinical study on the effectiveness of the acaricide Acarosan in treating house-dust mite allergy. J ALLERGY CLIN IMMUNOL 1989;28:263.
35. Vervloet D, Penaud A, Razzouk H, et al. J ALLERGY CLIN IMMUNOL 1982;69:290.
36. Korsgaard J. Preventative measures in house dust allergy. Am Rev Respir Dis 1982;125:80-4.
37. Burr ML, Dean BV, Merrett TG, Neale E, Leger AS, Verrier-Jones ER. Effects of antimite measures on children with mite- sensitive asthma: a controlled trial. Thorax 1980;35:506-12.
38. Murray AB, Ferfuson AC. Dust-free bedrooms in the treatment of asthmatic children with house dust mite allergy: a controlled trial. Pediatrics 1983;71:418.
39. Walshaw MJ, Evans CC. Allergen avoidance in house dust mite-sensitive adult asthma. Q J Med 1986;58:199-215.
40. Sarsfield JK, Gowland G, Toy R, Norman AL. Mite-sensitive asthma of childhood: trial of avoidance measures. Arch Dis Child 1974;49:771-6.
41. Platts Mills TAE, Chapman MD. Dust mites: immunology, allergic disease, and environmental control. J ALLERGY CLIN IMMUNOL 1987;80:755-77.
42. Platts-Mills TAE, Tovey ER, Mitchell EB, Moszoro H, Nock P, Wilkins SR. Reduction of bronchial hyperreactivity during prolonged allergen avoidance. Lancet 1982: 1:675-8.
43. Vervloet D, Penaud A, Razzouk H, et al. Altitude and house dust mites. J ALLERGY CLIN IMMUNOL 1982;69:290.
44. Own S, Morganstern M, Hepworth J, Woodcock A. Control of house dust mite antigen in bedding. Lancet 1990;335:396-7.
45. Mosbech H, Jensen J, Heinig JH, Schou C. House dust mite allergens on different types of mattresses. Clin Exp Allergy 1991;21:351-5.
46. Tovey ER, Chapman MD, Wells CW, Platts-Mills TAE. The distribution of dust mite allergen in the houses of patients with asthma. Am Rev Respir Dis 1981;124: 630-5.
47. LeMao J, Pauli G, Tekaia F, Hoyet C, Bischoff E, David B. Guanine content and *Dermatophagoides pteronyssinus* allergens in house. J ALLERGY CLIN IMMUNOL 1989;83:926.
48. LeMao J, Dandeau JP, Rabillon J, Lux M, David B. Comparison of antigenic and allergenic composition of two partially purified extracts from *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* mite cultures. J ALLERGY CLIN IMMUNOL 1983;71:588.
49. Green WF, Nicholas NR, Salome CM, Woolcock AJ. Reduction of house dust mites and mite allergens: effects of spraying carpets and blanket with Allersearch DMS, an acaracide combined with an allergen reducing agent. Clin Exp Allergy 1989;19:203-7.
50. Lau S, Rusche A, Weber A, Bischoff E, Wahn U. Short term efficacy of benzylbenzoate on mite allergen concentrations in house dust. J ALLERGY CLIN IMMUNOL 1989; 83:263.
51. Dietemann A, Hoyet C, Bessot JC F, Blay DE, Pauli G. Effects of acaricide application on mite allergen levels and on symptoms of *Dermatophagoides pteronyssinus*. J ALLERGY CLIN IMMUNOL 1989;83:263.
52. Kersten W, Musken H. A clinical study on the effectiveness of the acaricide Acarosan in treating house-dust mite allergy. J ALLERGY CLIN IMMUNOL 1989;83:263.
53. Brown HM, Merrett TG. Effectiveness of an acaracide in management of house dust mite allergy. Ann Allergy 1991;67:25-31.
54. Kniest FM, Young E, Van Praag CG, et al. Clinical evaluation of a double-blind dust-mite avoidance trial with mite-allergic rhinitic patients. Clin Exp Allergy 1991; 21:39-47.
55. Hayden ML, Rose G, Diduch KB, et al. Benzyl benzoate moist powder: investigation of acaracil activity in cultures and reduction of dust mite allergens in carpets. J ALLERGY CLIN IMMUNOL 1992;89:536-45.
56. Kang B, Sulit N. A comparative study of prevalence of skin hypersensitivity to cockroach and house dust antigens. Ann Allergy 1978;41:333.
57. Kang B, Vellody D, Homburger H, Yunginger JW. Cockroach cause of allergic asthma: its specificity and immunologic profile. J ALLERGY CLIN IMMUNOL 1979; 63:80.
58. Kang B. Study on cockroach antigen as probable causative agent in bronchial asthma. J ALLERGY CLIN IMMUNOL 1976;58:365.
59. Shulaner FA. Sensitivity to the cockroach in three groups of allergic children. Pediatrics 1970;45:465.
60. Mendoza J, Synder FD. Cockroach sensitivity in children with bronchial asthma. Ann Allergy 1970;28:159.
61. Bernton HS, Brown H. Insect allergy: preliminary studies of the cockroach. J ALLERGY CLIN IMMUNOL 1964;35:506.
62. Bernton HS, McMahon TF, Brown H. Cockroach asthma. Br J Dis Chest 1972;66:61.
63. Lehrer SB, Horner WE, Menon PK, Oliver J, Hauck P. Cockroach allergenic activity: analysis of commercial cockroach and dust extracts. J ALLERGY CLIN IMMUNOL 1991;88:895-901.
64. Lan JL, Lee DT, Wu CH, Chang CP, Yeh CL. Cockroach hypersensitivity: preliminary study of allergic cockroach asthma in Taiwan. J ALLERGY CLIN IMMUNOL 1988;82: 736-40.
65. Kang B, Jones J, Johnson J, Kang IJ. Analysis of indoor environment and atopic allergy in urban populations with bronchial asthma. Ann Allergy 1989;62:30-4.

66. Linna O. Environmental and social influences in skin test results in children. Allergy 1983;38:513.
67. Murray AB, Ferguson AC, Morrison BJ. The frequency and severity of cat allergy vs dog allergy in atopic children. J ALLERGY CLIN IMMUNOL 1983;72:145.
68. Ohman JL, Kendall S, Lowell FC. IgE antibody to cat allergens in an allergic population. J ALLERGY CLIN IMMUNOL 1977;60:317.
69. Sarsfield JK, Boyle AG, Rowell EM, Moriarty SC. Pet sensitivities in asthmatic children. Arch Dis Child 1976;51: 186.
70. Wood RA, Eggleston PA, Lind P, et al. Antigenic analysis of household dust samples. Am Rev Respir Dis 1988;137: 358.
71. Lind P, Norran PS, Newton M, Lowestein H, Schwartz B. The prevalence of indoor allergens in the Baltimore area: house dust mite and animal dander antigens measured by immunochemical techniques. J ALLERGY CLIN IMMUNOL 1987;80:541.
72. Tai E, Chinn S, Forgacs P. Skin tests and clinical features of asthma. Br J Dis Chest 1975;69:125.
73. Friedhoff LR, Meyers DA, Marsh DG. A genetic–epidemiologic study of human immune responsiveness to allergens in an industrial population, II: the association among skin sensitivity, total serum IgE, age, sex, and the reporting of allergies in a stratified random sample. J ALLERGY CLIN IMMUNOL 1984;73:490.
74. Lutsky I, Neuman I. Laboratory animal dander allergy: an occupational disease. Ann Allergy 1975;35:201.
75. Cockcroft A, Edwards–McCathy P, Anderson N. Allergy in laboratory animal workers. Lancet 1981;1:827.
76. Platts–Mills TAE, Longbottom J, Edwards J, Cockcroft A, Willeins S. Occupational asthma and rhinitis related to laboratory rats: serum IgG and IgE antibodies to the rat urinary allergen. J ALLERGY CLIN IMMUNOL 1987; 79:505.
77. Findlay SR, Stotsky E, Leiterman K, Hemady Z, Ohman JL. Allergens detected in association with airborne particles capable of penetrating into the peripheral lung. Am Rev Respir Dis 1983;128:1008.
78. Van Metre TE, Marsh DG, Adkinson NF, et al. Dose of cat allergen (Fel d 1) that induces asthma. J ALLERGY CLIN IMMUNOL 1986;78:62.
79. Swanson MC, Agarwal M, Reed CE. An immunochemical approach to indoor aeroallergen quantitation with a new volumetric air sampler: studies with mite, roach, cat, mouse, and guinea pig antigens. J ALLERGY CLIN IMMUNOL 1985;76:724.
80. Platts–Mills TAE, Heymann PW, Longbottom JL, Wilkins SR. Airborne allergens associated with asthma: particle sizes carrying dust mite and rat allergens measured with a cascade impactor. J ALLERGY CLIN IMMUNOL 1986;77:850.
81. Swanson MC, Campbell AR, Klauchk MJ, Reed CE. Correlations between levels of mite and cat allergens in settled and airborne dust. J ALLERGY CLIN IMMUNOL 1989;83:776-83.
82. Charpin C, Mata P, Charpin D, Lavaut MN, Allasia C, Vervolet D. *Fel D 1* allergen distribution in cat fur and skin. J ALLERGY CLIN IMMUNOL 1991;88:77-82.
83. Hamilton RG, Chapman MD, Platts–Mills TAE, Adkinson NF. House dust aeroallergen measurements in clinical practice: a guide to allergen–free home and work environments. Immunol Clin Pract 1992;15:96-112.
84. Pollart SM, Chapman MD, Platt–Mills TAE. Allergen levels inside homes: risk factors for acute asthma attacks [Abstract]. J ALLERGY CLIN IMMUNOL 1988;82:242.
85. Wood RA, Chapman MD, Adkinson FN Jr, Eggleston PA. The effect of cat removal on allergen content in household–dust samples. J ALLERGY CLIN IMMUNOL 1989; 83:730-4.
86. Wood RA, Mudd KE, Eggleston PA. The distribution of cat and dust mite allergens on wall surfaces. J ALLERGY CLIN IMMUNOL 1992;89:126-30.
87. Vanto T, Koivikko A. Dog hypersensitivity in asthmatic children: a clinical study with special reference to the relationship between the exposure to dogs and the occurrence of hypersensitivity symptoms. Acta Paediatr Scand 1983;72:571-5.
88. Ford AW, Alterman L, Kemeny DM. The allergens of dog, I: identification using crossed radio–immunoelectrophoresis. Clin Exp Allergy 1989;19:183-90.
89. Wood RA, Chapman MD, Adkinson FN Jr, Eggleston PA. The effect of cat removal on allergen content in household–dust samples. J ALLERGY CLIN IMMUNOL 1989; 83:730-4.
90. Platts–Mills TAE. Allergen avoidance at home: what really works? J Respir Dis 1989;10:53-5.
91. deBlay F, Chapman MD, Platts–Mills TAE. Airborne cat allergen (*Fel d I*): environmental control with the cart in situ. Am Rev Resp Dis 1991;143:1334-9.
92. Tovey ER, Marks GB, Matthews M, Green WF, Woolcock AJ. Changes in mite allergen *Der P I* in house dust following spraying with a tannic acid/acaracide solution. Clin Exp Allergy 1992;22:67-74.
93. Solomon WR. Aerobiology and inhalant allergens, I: pollens and fungi. In: Middleton E Jr, Reed CE, Ellis EF, eds. Allergy principles and practice. St Louis: Mosby, 1978:899-945.
94. Solomon WR. Aerobiology and inhalant allergens. In: Middleton E Jr, Reed CE, Ellis EF, eds. Allergy principles and practice. St Louis: Mosby, 1978.
95. Busse WW, Reed CE, Hoehne JH. Where is the allergic reaction in ragweed asthma? J ALLERGY CLIN IMMUNOL 1972;50:289-93.
96. Dolovich J, Zimmerman B, Hargreave FE. Allergy in asthma. In: Clark TJH, Godfrey S, eds. Asthma. London: Chapman & Hall, 1983;132-57.
97. O'Hollaren MT, Yunginger JW, Offord KP. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. N Engl J Med 1991;324:359-63.
98. Evans D, Levison MJ, Feldman CH, et al. The impact of passive smoking on emergency room visits of urban children with asthma. Am Rev Respir Dis 1987;135:567-72.
99. Murray AB, Morrison BJ. Passive smoking and the seasonal difference of severity of asthma in children. Chest 1988;94:701-8.
100. Honicky RE, Osborne JS, Akpom CA. Symptoms of respiratory illness in young children and the use of wood–burning stoves for indoor heating. Pediatrics 1985;75:587-93.
101. Morris K, Morganlander M, Coulehan JL, et al. Wood–burning stoves and lower respiratory tract infections in American Indian children. Am J Dis Child 1990;144: 105-8.
102. Forastiere F, Agabit N, Conbo GM, et al. Passive smoking as a determinant of bronchial responsiveness in children. Am J Respir Crit Care Med 1994;149:365.

Food hypersensitivity and asthma

Summary statements

- Allergies to foods can induce wheezing in a small number of patients with asthma.
- Evaluation of food hypersensitivity should be considered in patients with chronic symptoms, especially those in the pediatric age group with a history of atopic dermatitis.
- A positive prick test to suspected foods may suggest specific food allergens that require further study.
- A definitive diagnosis of food allergy is based on a double-blind, placebo-controlled oral challenge. Under certain circumstances a presumptive diagnosis based on less stringent criteria may suffice.

The association of food allergy and various allergic symptoms, including asthma, was first described in the early part of the twentieth century. Subsequently, many reports linked food allergy with asthma in both children and adults. However, because these were uncontrolled anecdotal reports, confirmation could not be established until more objective methods of evaluation were available (i.e., double-blind, placebo-controlled food challenge [DBPCFC]).[1-3] Recent studies using DBPCFCs indicated that food hypersensitivity is responsible for wheezing in a small subset of patients with asthma.[4, 5] In one study[4] of 300 asthmatic patients (7 months to 80 years of age) monitored at a respiratory diseases clinic, wheezing was provoked by DBPCFCs in 6 (2%) of 300 patients. In another study[5] involving 140 children with asthma, wheezing was induced in 8 (5.7%) of 140 patients by use of blinded oral food challenge. These studies noted that isolated asthma resulting from food allergy was extremely rare and that most cases involved children with a history of active atopic dermatitis. In another study[6] 212 patients referred because of severe atopic dermatitis and possible food allergy were evaluated by use of DBPCFC. Approximately 50% of these patients had asthma at the time of the initial evaluation. In this select population 22 patients (10%) experienced wheezing in response to the oral food challenge; 3 of 22 patients had no history of asthma.

As noted in the aforementioned studies, food hypersensitivity may exacerbate wheezing in a small percentage of asthmatic patients. Evaluation for food hypersensitivity should be considered in patients with chronic asthma, especially in the pediatric patient with a strong history of food allergy or active atopic dermatitis. As with other IgE-mediated food allergic symptoms, skin prick testing to a panel of properly prepared suspect food extracts may suggest specific foods to which the patient is allergic or not allergic. A positive skin test (or RAST) result does not always indicate that the test-positive food causes symptoms. Nor does a negative skin test (or RAST) result reflect the inability of a food to produce symptoms. In one study in children 15% of clinically significant reactions would have been missed had a diagnosis been based on a positive skin test result alone.[7] Use of a positive RAST result alone resulted in 23% missed reactions. Despite this, a negative skin test result alone can be useful in excluding potential food allergens in children. However, a strong history indicative of food allergy suggests the need for further evaluation by DBPCFC. If DBPCFC is done, foods suspected because of positive skin test (or RAST) results or a strong history should be completely eliminated from the diet for 1 to 2 weeks. DBPCFC should be performed in an appropriate setting[8] (including equipment available to treat potential anaphylactic reactions).

FOOD ALLERGY RESOURCES

- Allergy Information Association. *The Food Allergy Cookbook: Diets Unlimited for Limited Diets*. St. Martin's Press, 175 Fifth Ave., New York, NY 10010; $6.95.
- Autry GD, Allen TD. *The Color-Coded Allergy Cookbook*. The Bobbs-Merril Co. Inc.
- Bock S. *Food Allergy: A Primer for People*. Vantage Press, Inc., New York, NY 10001; $8.95.
- Colorado State University. *Wheat, Gluten, Egg, and Milk-Free Recipes for Use at High Altitudes and at Sea Level*. Bulletin 530-A, CSU Cooperative Extension Service, Fort Collins, CO 80523; $2.75 plus $1 shipping.
- Food items/recipes for people with special dietary needs. Ener-G Foods, Inc., PO Box 84487, Seattle, WA 98124-5787, phone 1(800)331-5222.
- Hamrick B, Wiesenfeld SL. *The Egg-Free, Milk-Free, Wheat-Free Cookbook*. Harper & Row, 1982; $16.50.
- Jacobson M. *The Fast Food Guide*. Workman Publishing Co., New York, NY 10018; $4.95.
- Taylor F, Latta S. *Special Diets and Kids*. Dodd, Mean and Co., Inc., 71 Fifth Ave., New York, NY 10003; $16.95.
- Williams L. *Cooking Without Recipes for the Allergic Child (and His Family)*. Tricor, Inc., PO Box 386, Blue Bell, PA 19422-0939.

The patient's asthma should be stable, wheezes should be absent on auscultation, or FEV_1 should be greater than 70% of predicted. Inhaled corticosteroids and theophylline may be continued, but cromolyn and β–adrenergic agonists should be discontinued for at least 12 hours before challenge is initiated. Antihistamines should be discontinued for an appropriate time period before challenge is begun. In adults, double–blind challenges may be more of a problem because of difficulty in masking larger quantities of foods necessary for the challenge.[9] If no wheezing occurs (or decrease in FEV_1 is less than 20% of baseline), the patient may be fed *openly* to confirm the negative result of blinded challenge. If the reaction is positive the challenge should be repeated in double–blind fashion, if possible, giving incremental doses with an appropriate placebo control to rule out the effects of drug withdrawal, unstable baseline, and unintentional observer bias.[8] Food elimination diets should not be prescribed for all adult patients with asthma who report a food reaction or have positive prick test or RAST results to food allergens. DBPCFC may be particularly beneficial and reassuring in the patient whose history is positive but whose skin test/RAST results are negative. Patients with a history of anaphylaxis to foods generally should be excluded from direct challenge with the suspected food.

REFERENCES

1. Bock SA, Buckley J, Hobst A, May CD. Proper use of skin tests with food extracts on diagnosis of hypersensitivity to food in children. Clin Allergy 1977;7:375-83.
2. May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children. J ALLERGY CLIN IMMUNOL 1976;58:500.
3. Bock SA, Lee WY, Remigio LK, May CD. Studies of hypersensitivity reactions to foods in infants and children. J ALLERGY CLIN IMMUNOL 1978;62:327-34.
4. Onorato J, Merland N, Terral C, Michel BF, Bousquet J. Placebo–controlled double–blind food challenge in asthma. J ALLERGY CLIN IMMUNOL 1986;78:1139-46.
5. Novembre E, de Martino M, Vierucci A. Foods and respiratory allergy. J ALLERGY CLIN IMMUNOL 1988;81:1059-65.
6. Sampson HA, Scanlon S. Natural history of food hypersensitivity in children with atopic dermatitis. J Pediatr 1989;115:23-7.
7. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double–blind placebo controlled food challenges in children with atopic dermatitis. J ALLERGY CLIN IMMUNOL 1984;74:26.
8. Bock SA, Sampson HA, Atkins FM. Double–blind placebo–controlled food challenge as an office procedure: a manual. J ALLERGY CLIN IMMUNOL 1988;82:986-97.
9. Bernstein M, Day JH, Welsh A. Double–blind food challenge in the diagnosis of food sensitivity in the adult. J ALLERGY CLIN IMMUNOL 1982;70:205.

Other nutritional considerations in the asthmatic patient

Summary statement

- Adequate nutrition is an essential part of the general treatment plan for asthmatic patients and should be emphasized, especially when there are dietary restrictions related to food sensitivities or blunted appetite caused by medications.

Adequate nutrition is essential for all age groups. For patients with acute and chronic lung disease, nutrition is an essential part of the general treatment plan. Inadequate growth in asthmatic children or inappropriate weight control in asthmatic patients of any age can be an important sign of uncontrolled asthma and improper nutrition. Adequate nutrition is essential despite (1) possible dietary restrictions caused by food hypersensitivity, (2) decreased appetite caused by medications, (3) need for cautious caloric intake in patients taking oral corticosteroids, and (4) patient involvement in popular diets and dietary supplements.

Adults as well as children with asthma may at some time be prescribed strict elimination diets for diagnostic or therapeutic purposes. Such diets must be nutritionally appropriate for age, activity, and cultural background, with provisions for adequate supplementation of specific nutrients, such as calcium in milk–restricted diets. Diets used for diagnostic purposes are usually of limited duration (approximately 2 weeks); then foods are added back into the diet individually at specific intervals. Ongoing nutritional supervision of the diet is essential. Once foods capable of producing an adverse reaction have been identified, special dietary and nutritional guidelines may help patients avoid these foods. Overdiagnosis of multiple food sensitivities may lead to malnutrition.

Effect of medications on dietary intake. Medications can directly or indirectly affect nutritional status. Oral bronchodilators, especially theophylline, can produce anorexia and other gastrointestinal symptoms. Oral β–agonists also can cause nausea in susceptible individuals. Some antihistamines can increase appetite. Oral corticosteroids also can increase appetite and cause weight gain. Salt restriction may be necessary in patients with hypertension or heart disease who are receiving corticosteroids. For patients receiving long–term,

high–dose corticosteroid therapy, adequate calcium intake must be maintained. Some authorities recommend augmenting calcium intake with vitamin D and/or fluoride. In addition, metabolic changes may be noted after use of certain types of drugs (e.g., cholesterol levels may be increased by corticosteroids and other medications).

Effect of diet on asthma and medications used to treat asthma. Dietary changes can affect the metabolism and clearance of drugs used to control asthma. For instance, theophylline levels are affected by diet (charcoal–broiled foods and fats). Various dietary supplements, such as ascorbic acid and fish oil, have been used to decrease bronchial hyperresponsiveness. Evidence of adequate improvement in controlled clinical trials is necessary before such supplementation, as well as various controversial diets, can be recommended.

Summary. In summary, knowledge of an asthmatic patient's nutritional intake, medications being taken, the individual effect of both, and the timing of medication intake in relation to a meal (see Section VI E, Pharmacotherapy, Theophylline) is essential to provide quality care. Absorption of other drugs can also be affected by dietary intake.

E. PHARMACOTHERAPY

Introduction

Successful pharmacologic management of asthma should incorporate two major strategies: reversal of acute and chronic airway obstruction and long–term attenuation and prophylaxis of the intrabronchial sequelae of inflammatory cells and their mediators. Treatment of airway obstruction usually requires the use of antagonists of smooth muscle contraction and occasionally the use of agents that counteract neurogenic imbalance (cholinergic overload), bronchial edema, and hypersecretion of mucus. In a sense, the long–term use of anti–inflammatory drugs also ameliorates airway obstruction by decreasing the exudative reaction within epithelial and submucosal tissues and by providing a favorable milieu for regeneration of bronchial epithelium.

Apart from their specific activities in various components of bronchial obstruction, the effects of some therapeutic agents may be discerned by the patient soon after administration, either on an acute or chronic basis, whereas the effects of other agents (e.g., cromolyn, corticosteroids) may become apparent only after long–term prophylactic use. Both physician and patient must understand that less readily apparent effects of anti–inflammatory agents are just as important as the short–term symptomatic relief afforded by bronchodilator drugs.

The effects of specific medications may encompass both strategic categories. Thus β–agonists and theophylline not only are well–established bronchodilators but also, when used on a long–term basis, may contribute an anti–inflammatory effect by inhibiting mediator release from intraluminal and tissue mast cells. In contrast, the classic anti–inflammatory agents, cromolyn and corticosteroids, do not exert significant bronchodilator effects.

Therapeutic decision analysis concerning when and how long to use specific medications should be based on the clinical severity of the patient's asthma, as stressed in the preceding section on stepwise management (see Section VI A, Classification of Asthma Severity). For example, occasional and isolated episodes of asthma rarely require more than inhalation of a β_2–agonist. Recurrent seasonal asthma with daily symptoms might require β–agonists, inhaled corticosteroids, theophylline, and/or cromolyn. This combined treatment offers the advantage of both bronchodilator and anti–inflammatory effects. In chronic asthma, other pharmacotherapeutic options are available, including inhaled and systemic corticosteroids.

Finally, this section will include a discussion of acceptable management techniques that will maximize the benefit from pharmacotherapeutic management. Possible adverse reactions induced by, as well as potential advantages of, polypharmacy will be discussed in a later section (see Section VI, Pharmacotherapy, Other Considerations, Polypharmacy).

β–Adrenergic agonist bronchodilators

Summary statements

- Treatment of the asthmatic patient must be individualized.
- β–agonist bronchodilators vary in their degree of selectivity, ranging from nonselective (e.g., isoproterenol) to relatively β_2–selective (e.g., albuterol).
- It is preferable to use a β_2–agonist rather than a nonselective β–agonist because β_2–agonists have a longer duration of action and are less likely to produce cardiovascular side effects.
- The use of sustained–release oral β_2–agonists may be appropriate and indicated for some asthmatic patients, especially in situations where

a long duration of effect is desired or the patient does not tolerate inhaled β_2–agonists. Otherwise, *inhaled* β_2–agonists are preferable to *oral* drugs of this type in the treatment of chronic asthma because they have a rapid onset of action, are generally more effective than other routes of administration, and infrequently produce adverse reactions.

- *Inhaled* β_2–agonists may be more effective when administered on an as–needed basis rather than a regular basis in the treatment of many patients with chronic asthma. If more than eight inhalations per day (or approximately one canister per month) are needed, the addition of cromolyn, nedocromil, or inhaled corticosteroids should be considered.
- *Inhaled* β_2–agonists are generally the safest and most effective treatment for acute asthma. In general, *oral* β_2–agonists should not be administered for the treatment of acute severe asthma.
- The administration of β_2–agonists in the treatment of acute or chronic asthma is not a substitute for the early use of anti–inflammatory drugs.
- Patients must be carefully instructed, often more than once, in the use of inhaled β_2–agonists because a large percentage of patients fail to use inhaler devices correctly. Spacers attached to inhaled β_2–agonists improve drug delivery in patients who are not correctly using inhalers.
- Inhaled β_2–agonists, when administered 15 to 30 minutes before exercise, prevent exercise–induced bronchospasm in many patients. Inhaled β_2–agonists generally are considered the agent of choice for this purpose.
- Tolerance to β_2–agonists, which usually is reversible after administration of corticosteroids, may develop after continued use of these drugs and may be associated with an unrecognized decrease in efficacy and delay in seeking medical attention.
- Bronchial hyperresponsiveness may increase in patients who have been receiving inhaled β_2–agonists on a regular basis. This possibility should be considered in patients whose asthma is worsening on a regimen that includes the regular use of these drugs.
- Tremor and central nervous system effects are minimized by inhalation of β_2–agonists, although hypokalemia and significant cardiovascular effects can occur when these drugs are administered by this route.
- Serious adverse effects from the administration of β_2–agonists, when administered in recommended doses, are uncommon when given orally and extremely uncommon when administered by inhalation.
- Both β_2–agonists and nonselective β–agonists, when administered by inhalation, can produce a sudden paradoxical increase in bronchospasm in some asthmatic patients, which may be life–threatening.
- Salmeterol is a long–acting, highly β_2–selective β–agonist bronchodilator.
- Well–controlled studies have shown that the duration of action of salmeterol is 12 hours or longer in most patients.
- Pretreatment with single doses of salmeterol also prevents bronchospasm from histamine, methacholine, and cold–air challenge.
- Salmeterol can protect patients against exercise–induced bronchospasm for up to 12 hours after administration.
- Because salmeterol is inherently different from short–acting inhaled β–agonists, there are special recommendations that must be considered when salmeterol is prescribed for patients. In this regard, salmeterol metered–dose inhaler (1) should not be initiated in patients with significantly worsening or acutely deteriorating asthma, (2) should not be used to treat acute symptoms, and (3) should not be considered a substitute for inhaled or oral corticosteroids.

β–Adrenergic agonists are used widely in the management of asthma to produce bronchodilation and to prevent bronchoconstriction.[1] These agents reduce airway obstruction not only by producing bronchodilation but also by stimulating mucociliary clearance and by inhibiting mediator release from mast cells,[2] thereby preventing bronchoconstriction. The development of β_2–selective agents and longer–acting drugs and the availability of inhaled forms of β_2–agonists represent recent advances designed to improve the safety and efficacy of this class of drugs.[3]

Pharmacology. Naturally occurring catecholamines such as epinephrine have both α– and β–adrenoreceptor–stimulating properties. Substitution at the *N*–alkyl position of the basic catecholamine structure determines the relative α– and β adrenoreceptor–stimulating activity. Differentiation of β–agonists into relatively β_2–specific agonists with increasing selectivity for respiratory tissues is based on further modification of the

catecholamine moiety. In addition, longer duration of action and the effectiveness of the drug in an oral formulation are achieved by modification of hydroxyl groups on the benzene ring of the catecholamine nucleus. It is through such substitution that a variety of different β–adrenergic agents have come into pharmacologic use.[4]

Although epinephrine, ephedrine, and isoproterenol are all effective bronchodilators, their use in the treatment of asthma is limited by the occurrence of unwanted cardiovascular effects and/or a short duration of action. On the other hand, β–adrenergic agonists that selectively stimulate β_2–receptors with relatively little stimulation of β_1–receptors produce significant bronchodilation with less adverse cardiovascular effects when administered at recommended doses. However, these relatively β_2–selective agonists still possess substantial β_1–activity, especially in higher doses. Furthermore, whereas β_2–receptors predominate in the lung and β_1–receptors predominate in the heart, up to 50% of the β–receptors in some areas of the heart are of the β_2–type.[5] Relatively β_2– selective agonists therefore could produce adverse cardiac effects directly by stimulating β_1– or β_2–receptors in the heart and also indirectly through stimulation of peripheral β_2–receptors on peripheral blood vessels. Thus, cardiovascular side effects are reduced, but not eliminated, by the use of relatively β_2–selective agonists.[6-16] The inhaled route of delivery is probably more important, in fact, than receptor specificity in the reduction of cardiovascular effects because of the lower doses that are needed to produce similar degrees of efficacy.[17]

Specific β_2–agonists. In the United States *terbutaline* can be administered parenterally, orally, or by the inhaled route. *Metaproterenol* and *albuterol* are administered by the oral and inhaled routes, whereas *bitolterol* and *pirbuterol* are available for administration only by the inhaled route. Unlike the other specific β_2–agonists, bitolterol is an inactive prodrug that is hydrolyzed in vivo to an active metabolite. It is essential to recognize the potential for significant variability in patient response to different β–agonists. Even the same β–agonist given by different routes of administration, or at different times, may produce different clinical effects.

Inhalation of a single dose of a β_2–agonist results in clinically significant bronchodilation (defined as a 15% or greater increase in FEV_1 above baseline after drug administration) within 5 minutes in most patients, peak bronchodilation 30 to 60 minutes after drug administration, and persistent bronchodilation for 3 to 6 hours after drug administration in many patients. Aerosolized isoproterenol, by comparison, produces peak bronchodilation within 5 minutes but has a duration of action of only about 2 hours or less.

Adverse effects. Most of the important adverse effects of β–agonists relate directly to their pharmacologic (adrenergic) effects, whereas the frequency and intensity of these effects depend on the route of administration. Oral preparations produce, in general, more unwanted adrenergic effects than inhaled drugs, and parenteral administration of β–agonists causes the most adverse effects. At conventional doses, inhalation of drugs by means of metered–dose inhaler produces fewer side effects than inhalation by nebulization. However, this is probably related to the total dose delivered to the patient.

Cardiovascular adverse effects. The potential for β–agonists to produce significant increases in blood pressure and pulse rate, clinically significant hemodynamic changes,[14] and, in some patients, arrhythmias and myocardial necrosis makes careful monitoring of patients who are receiving these medications essential.[8-14, 18] This is especially true of elderly patients or patients with underlying cardiac disease. Intravenous isoproterenol has produced myocardial necrosis in asthmatic patients with previously normal cardiac status.[18] There are also data indicating that the frequency of cardiac arrhythmias is increased in asthmatic patients receiving both methylxanthines and β–agonists.[19] It should be emphasized, however, that serious adverse effects resulting from the administration of β_2–selective drugs in conventional doses are rare with oral administration and even more rare with inhalation. Although palpitations or tachycardia may limit the dose that can be administered in some patients, they rarely progress to more serious cardiac events, and tolerance to these effects may develop with continued treatment.[20]

Tremor and central nervous system effects. Stimulation of β_2–receptors on skeletal muscle can produce tremor. Tremor is not an uncommon side effect of β–agonist administration, especially when administration is by the oral route, but patient awareness often diminishes with long–term treatment.[21] Although β–adrenergic agents cross the blood–brain barrier poorly (with the exception of ephedrine), headache and irritability may occur after their administration. Tremor and central nervous system effects are

minimized when selective β_2–agonists are administered by inhalation.

Paradoxical bronchospasm. Inhalation of β–agonists or drugs with both α– and β–adrenergic–stimulatory effects (e.g., epinephrine) can produce a paradoxical increase in airway obstruction in some asthmatic patients. Furthermore, in the 1960s there was concern about metabolites of isoproterenol producing this type of effect. Although the cause of drug–induced paradoxical bronchospasm is unknown in most cases, sulfites and other preservatives, propellants, and emulsifying agents used in inhaled β–agonist products have been implicated in some cases.[22-24] Sulfites have received the most attention in this regard.[25-27] They are used effectively as antioxidants in some β–agonist solutions for nebulization and adrenergic agents intended for parenteral use. Inhalation or injection of sulfite–containing preparations may produce sudden, severe, and potentially life–threatening bronchospasm in susceptible asthmatic patients.[27] Although some inhaled and injectable adrenergic drug products still contain sulfites, there are sulfite–free nebulized solutions of albuterol, terbutaline, and metaproterenol and metered–dose inhalers do not contain sulfites. Other causes of paradoxical bronchospasm (more frequently reported after the use of metered–dose inhalers) are largely unrecognized, although these reactions frequently occur after the first use of a new canister or bottle in patients who previously have used the same product without difficulty.[28]

Hypoxemia. Isoproterenol administered by oral inhalation can decrease the arterial Po_2 in asthmatic patients as a result of ventilation/perfusion mismatching despite improvement in airway obstruction.[29, 30] The clinical significance of this relative hypoxemia is unclear and has not been reported after administration of β_2–selective agonists. Recent studies in rhesus monkeys have indicated that even β_2–selective agonists have the potential to produce hypoxemia by increasing the oxygen cost of breathing, at least when there is poor cardiac output or decreased minute ventilation.[31]

Tolerance. Chronic treatment with β–agonists at conventional doses can produce a decrease in the number of β–adrenergic receptors on peripheral blood leukocytes and possibly bronchial smooth muscle.[32, 33] A decrease in peak bronchodilating effect or duration of bronchodilation may occur after repetitive administration of oral or inhaled β–agonists.[34] The duration of clinically effective bronchodilation with β_2–selective agonists can decrease after treatment for several weeks. Although the clinical significance of the development of tolerance to β–agonists is unclear, there is concern that tolerance could lead to overuse of inhaled β–agonists, a development considered by some to be associated with epidemics of asthma–related deaths.[35] The overuse of inhaled β–agonists (e.g., more than eight inhalations per day) indicates that the patient's asthma is not adequately controlled. This is particularly likely if there is an associated failure by the patient and the physician to recognize the severity of the patient's asthma and the necessity of using corticosteroids. The patient also may experience worsening of asthma because of decreased effectiveness of β–agonist treatment without recognizing that it is based on development of tolerance. Systemic corticosteroids will rapidly restore the response of β–agonists.[36, 37] It is not clear whether downregulation of β–adrenergic receptors is responsible for increases in bronchial hyperresponsiveness seen after repetitive administration of inhaled β–agonists.[38-41] Tolerance often develops more rapidly to adverse effects (such as tremor) caused by β–agonists than to the therapeutic effects of these agents. The development of tolerance with chronic use of β–agonists does not mitigate against their use during an acute exacerbation of asthma.

Metabolic effects. β–Agonists can elevate blood sugar and free fatty acids and can produce hypokalemia, even when administered by the inhalation route.[42, 43] These metabolic effects are of little clinical importance in most patients with asthma but may be relevant in individual cases. This may be particularly true of hypokalemia, which can potentially lead to cardiac arrhythmias, especially in elderly patients, who may be receiving corticosteroids and/or non–potassium–sparing diuretics. Children, however, also may be at significant risk for the development of hypokalemia.[44]

Increased bronchial hyperresponsiveness. Studies have shown that statistically significant increases in bronchial hyperresponsiveness may occur after repetitive administration of inhaled β–agonists.[32-35] Although it is not clear whether these changes are of clinical significance, destabilization of asthma from the repetitive administration of inhaled β–agonists reported in some studies suggests that they are clinically relevant.[45-48]

Increased antigen load. Decreased exposure to aeroallegens has been associated with decreases in bronchial hyperresponsiveness.[49] β–agonists, as do other bronchodilators, theoretically allow in-

creased allergen deposition in the lower respiratory tract. It has been demonstrated that increasing the antigen load in asthmatic patients may change the pattern of their response to allergens and increase the likelihood of late-phase responses.[50-52] It is therefore essential that patients receiving β–agonists adopt strict measures to minimize exposure to allergens or other triggers.

Acute asthma in adults. Adrenergic agents are considered first–line therapy for the treatment of acute asthma in adults.[53] Inhalation therapy with a nebulized β_2–selective agonist produces bronchodilation equivalent to parenteral therapy with epinephrine and terbutaline but with fewer side effects,[45, 54-58] and therefore inhaled β_2–agonists should be considered the treatment of choice for most patients with acute asthma. Recent studies suggest that inhalation of a β_2–selective agent by means of metered–dose inhaler in sufficient dosage may be as effective as a nebulized β_2–agonist in treatment of acute asthma.[59] However, efficacy depends on proper inhalation technique by the patient, which may be especially difficult in the acute setting.[60, 61] Aerosol delivery by nebulization requires no technical skills on the part of the patient, and high doses of the drug can be effectively delivered if necessary. On the other hand, the amount of the drug that will be delivered to the lower bronchial passages by nebulized devices is impossible to determine when airway obstruction is present. Nevertheless, nebulized β_2–agonists are effective and generally well tolerated in the treatment of acute asthma. Some studies have suggested that there is a role for continuous nebulization with β_2–selective agonists in adults, although patients may need to be monitored more carefully for adverse effects.[62, 63]

Clinical studies have shown that inhalation of β_2–specific agonists is superior to intravenous aminophylline in the treatment of acute asthma.[19] However, the concomitant use of an adrenergic agonist and aminophylline may be effective in some patients and is under continued study.[64]

Subcutaneous administration of epinephrine produces peak bronchodilation in approximately 5 minutes, and efficacy persists for 30 minutes or longer. Available data indicate that subcutaneous terbutaline and epinephrine produce similar bronchodilatation and adverse effects. Parenteral administration of adrenergic agonists requires careful monitoring of the patient for adverse cardiovascular events, especially elderly patients or patients with suspected or proven cardiovascular disease, and is not, in many cases, an acceptable substitute for treatment with an inhaled β–agonist.[65, 66]

The degree of improvement in pulmonary function after initial treatment of acute asthma with adrenergic agonists is inversely correlated with asthma relapse and need for hospitalization.[67, 68] Patients with acute asthma who do not demonstrate significant bronchodilation after treatment with adrenergic agonists require systemic corticosteroids and may need to be admitted for close observation. Although multiple administrations of subcutaneous or inhaled bronchodilators usually are necessary to help resolve an acute asthmatic attack, overtreatment with adrenergic agonists should be avoided, especially because response to treatment may be compromised already by airway inflammation.

Patients who are being treated for acute asthma require careful monitoring, including spirometry and peak flow measurements if possible. Evaluation should include electrocardiographic monitoring in patients at high risk. Monitoring of serum potassium along with other metabolic measurements including blood gases should be considered during the management of the patient.

Acute asthma in children. Inhaled β–agonists are the preferred treatment for acute exacerbation of asthma in children as well as adults.[69-72] In addition, some degree of bronchodilation after administration of inhaled β–agonists in infants with acute bronchospasm has been demonstrated.[73] In older children, as in adults, it has been shown that β_2–selective agonists produce more bronchodilation and fewer cardiovascular side effects than nonselective β–agonists.[74] No studies have demonstrated that one β_2–selective agonist delivered by means of metered–dose inhaler is significantly better than any other for the treatment of acute bronchospasm in children. Metaproterenol, terbutaline, bitolterol, pirbuterol, and albuterol can be used to relieve acute bronchospasm without much apparent difference in onset or duration of effectiveness. Further information is needed regarding differences in peak effect and duration of action of these drugs, as well as the frequency with which they should be administered to children during the acute episode. Although the usual treatment of acute asthma in children is the nebulized form of these drugs, some data indicate that 6 to 10 inhalations of albuterol delivered by metered–dose inhaler attached to a spacer may be as effective as 2.5 to 5 mg of albuterol administered by jet nebulizer.[75] However,

this assumes, at least, adequate cooperation on the part of the patient.

Nebulized solutions of isoproterenol, isoetharine, metaproterenol, albuterol, and terbutaline are available, although doses have not been clearly established in the management of acute attacks of asthma in children less than 6 years of age. The use of β–agonists in the treatment of acute bronchospasm in infants has produced mixed results. Some of these data need to be considered in light of the difficulty in measuring the response to bronchodilators in small children.[73] The amount of medication administered may be significantly different if β–agonist solutions are administered via face mask or mouthpiece and if they are administered by open or closed nebulizers.[76]

It has been demonstrated that inhaled β_2–agonists, when administered by continuous or intermittent nebulization, can be used safely and effectively in the management of an acute attack of asthma, and may prevent intubation and mechanical ventilation in patients with impending or acute respiratory failure.[77] Little data are available to support the administration of β–agonists by other routes of administration in the acute setting. In addition, the chance of adverse reactions after administration of inhaled β–agonists is less than after oral β–agonists. It should be remembered that the dose of nebulized solutions is greater than the dose delivered from metered–dose inhalers. Substantial amounts of inhaled drugs may be swallowed and absorbed, producing systemic side effects in some patients. Therefore cardiovascular parameters need to be monitored closely in this situation. In patients with cyanosis or history of cardiovascular disease, special precautions must be taken and careful monitoring is necessary when nebulized β–agonists are administered. There is a limited role for the use of oral β–agonists in the treatment of acute severe asthma in children. The onset of action is relatively slow, and the risk of systemic effects is greater than with inhaled β–agonists. (See Section VII N, Asthma in children.)

Chronic asthma in adults

Proper use of metered–dose inhalers. Besides providing the opportunity to deliver small amounts of drug directly to the area producing symptoms, metered–dose inhalers are convenient and portable. One disadvantage, however, is the difficulty many patients have in mastering the proper inhalation technique. It has been established that up to 75% of patients use metered–dose inhalers improperly.[78] Repeated observation and careful instruction are necessary to overcome errors in hand–lung coordination.[79] Proper use of a pressurized inhaler involves either holding the inhaler 4 cm from the open mouth or placing the lips around the inhaler orifice, actuation just after inhalation through the mouth, and slow inhalation over 5 to 6 seconds from the end of a normal expiration to full inhalation (i.e., inspiration from functional residual capacity to total lung capacity at flow rates of 25 to 30 L/min) followed by breath–holding for 10 seconds to allow small particles to sediment.

Under ideal conditions, only about 8% to 12% of the inhaled dose is deposited in the lower airways.[80, 81] In an attempt to increase the dose delivered to this area, spacer devices have been developed for those patients unable to use metered–dose inhalers properly even after careful instruction. Some studies have demonstrated increased bronchodilation with the use of spacer devices, whereas other studies have shown equivalent efficacy.[82-85] Alternative approaches for patients who do not effectively use a metered–dose inhaler are administration of the drug as a dry powder formulation or use of a flow–activated device.[86]

Mild asthma. When only occasional pharmacologic intervention is necessary, administration of a β–agonist by means of metered–dose inhaler on an as–needed basis is appropriate. Prophylactically, β_2–agonists delivered via metered–dose inhaler are also highly effective in preventing immediate bronchospasm, which can occur after allergen exposure or after exercise. In many patients it appears that change in pulmonary function is no greater after two inhalations than after one inhalation. Therefore one or two inhalations may be appropriate for different patients.

Moderate asthma. Patients who require regular maintenance medication for control of symptoms and optimal pulmonary function can be treated with an inhaled β_2–specific agonist on an as–needed basis or on a regular basis up to eight inhalations per day, or with an oral β_2–agonist. β_2–agonists can be used alone or concomitantly with theophylline, inhaled corticosteroids, anticholinergic agents, or cromolyn. It should be emphasized that the use of β_2–specific agonists or other bronchodilators does not lessen the need for routine use of anti–inflammatory drugs such as cromolyn sodium or inhaled corticosteroids. Therapeutic success with this program requires proper inhaler technique and good compliance. One disadvantage of relying on use of currently available inhaled β_2–selective agonists is their relatively short duration of bronchodilation when compared

with sustained-release theophylline or oral β_2-agonists, especially if the patient has nocturnal asthma. It should be recognized that albuterol and other shorter-acting inhaled β-agonists produce bronchodilatation for a period of only 3 to 6 hours in most patients and therefore cannot be expected to protect patients from nocturnal asthma. Patients with nocturnal asthma may benefit from regular use of anti-inflammatory drugs and an evening dose of oral β_2-agonist or theophylline.[87] A long-acting inhaled β-agonist (salmeterol) may also be effective in preventing nocturnal asthma. Many patients with moderate asthma may require a combination of medications for effective control of symptoms and maintenance of pulmonary function. Concomitant treatment with a β_2-specific agonist and theophylline is frequently used in patients with moderate asthma, although some data suggest that adverse cardiovascular effects may be increased with this approach.[88-91] Most studies, however, have not demonstrated any increase in adverse cardiovascular events associated with the administration of these drugs in conventional doses to patients with stable asthma.[92-96]

Some studies have demonstrated an additive effect when inhaled β-agonists and ipratropium bromide are administered concomitantly, whereas other studies have not.[97-100]

Severe asthma. Inhaled β_2-agonists can be used concomitantly with inhaled corticosteroids and theophylline in the management of more severe asthma. These patients are particularly vulnerable to overuse of inhaled β-agonists, often at the expense of other important therapy, most notably corticosteroids. Therefore, use of an inhaled β_2-specific agonist must be monitored carefully in these patients in conjunction with assessment of changes in asthma severity by daily recording of peak flow and frequent evaluation of the patient. If the need for inhaled β_2-selective agonists increases, the patient with severe asthma may require prompt treatment with oral corticosteroids or even hospitalization.

Chronic asthma in children

Inhaled β-agonists. The use of inhaled β-agonists is an acceptable approach to the management of chronic asthma in children, provided patients do not become so dependent on them that the patient or the patient's parents fail to recognize the severity of the asthma. Nebulized solutions of β-agonists also can be administered to patients requiring chronic therapy, recognizing that the dose of the nebulized solution is greater than the dose delivered from a metered-dose inhaler and therefore can be associated with increased systemic side effects.

Oral β-agonists. Oral β-agonists are used more widely for the treatment of chronic asthma in young children than are inhalational β-agonists. β_2-Specific agonists are preferred because of their longer duration of action. The primary side effect of oral β-agonists is tremor, which is seen less frequently and is less pronounced after administration of inhaled β_2-agonists. Oral β_2-selective agonists available for use in children are metaproterenol, terbutaline, and albuterol, although only the sustained-action albuterol has been demonstrated to have a 12-hour duration of action in children.

Parenteral β-agonists. There is no basis for the use of parenteral β-agonists in the treatment of chronic asthma because they have only a short duration of action and are associated with an increased risk of adverse effects.

Recent concerns. It has been reported recently that asthma may be controlled more poorly by the regular use of inhaled β-agonists than by their use on an as-needed basis.[45, 46] The reason for this is not clear, but it has been speculated that it could be based on the fact that (1) inhaled β-agonists increase bronchial hyperresponsiveness to a significant degree[38-41]; (2) inhaled β-agonists, and probably other bronchodilators as well, increase antigen load to the lower respiratory tract[50-52]; (3) specific β_2-agonists decrease heparin release from mast cells, thereby eliminating heparin's ability to limit the inflammatory process and the destructive/reparative process that follows antigen deposition in the lower respiratory tract[101]; and/or (4) inhaled β-agonists produce paradoxical bronchospasm, which in some cases could be subclinical.[28] Therefore it has been suggested that use of short- acting inhaled β-agonists administered on an as-needed basis may be more effective and possibly safer than regular administration,[102, 103] although reviews of this issue have raised questions about the data that support this contention.[104, 105] Other studies have shown that control of symptoms was poorer with as-needed albuterol.[106, 107] If more than eight inhalations per day are needed (approximately one canister per month), cromolyn or inhaled corticosteroids probably are indicated.

Salmeterol. Salmeterol is a long-acting, highly β_2-selective β-agonist bronchodilator. Salmeterol is highly lipophilic and therefore is taken up rapidly by the cell membrane, with the saligenin molecule directly attaching to the active side on the β-adrenoreceptor on the cell surface and the

long flexible side chain attaching to a hydrophobic core domain of the receptor, termed the *exosite*. Binding of the side chain to the exosite fixes the molecule within the β-receptor protein itself, which then allows the head of the molecule to repeatedly engage and disengage the active site, presumably accounting for salmeterol's long duration of action.[108, 109]

Well-controlled studies have shown that the duration of action is 12 hours or longer in most patients.[110-112] In this regard it has been shown to be effective for the prevention of nocturnal asthma, and it will inhibit both the early- and late-phase reactions that occur in some patients with asthma after allergen challenge.[113, 114] The median onset of action is 23 minutes.

Salmeterol also prevents bronchospasm induced by histamine, methacholine, and cold air challenge.[115-117] However, there are data in the literature that show that after repetitive administration of salmeterol for 8 weeks, there is less protection against methacholine challenge than there was on the first day of salmeterol administration.[118] Although there was a decrease in PC_{20} after repetitive administration of salmeterol for 8 weeks, the increase seen on the first day of treatment had been of such magnitude that the PC_{20} after administration for 8 weeks was still substantially above the baseline value. This finding is therefore of uncertain clinical significance.[119]

As with other inhaled β-agonists, there is the potential for paradoxical bronchospasm, overuse, and cardiovascular effects in patients receiving salmeterol.

There has been concern about the number of deaths in patients who received salmeterol in the United Kingdom.[120] However, the data do not clearly implicate salmeterol as a cause of such deaths. Subsequently, as reflected in the reporting of spontaneous adverse drug reactions, serious acute respiratory events, including fatalities, have been noted, both in the United States and worldwide in patients receiving salmeterol. Although it is not possible from these reports to determine whether salmeterol contributed to these adverse events or simply failed to relieve significantly worsening or acutely deteriorating asthma, salmeterol should not be initiated in these settings.

It must be recognized that salmeterol is not simply another inhaled β-agonist. The following need to be considered before this medication is prescribed: (1) salmeterol should not be administered more often than approximately every 12 hours. (2) salmeterol is not indicated for symptoms that can be managed by occasional use of short-acting inhaled β_2-agonists. (3) salmeterol is intended for regular, not as-needed use. (4) salmeterol is not recommended for the treatment of acute exacerbations of asthma. (5) Patients should be prescribed a short-acting inhaled β-agonist for treatment of acute exacerbations of asthma. (6) After starting salmeterol, if the patient had already been using a short-acting inhaled β-agonist on a regular basis, he or she should be instructed to use short-acting β-agonists only as needed for symptomatic relief. (7) If the patient finds that, after starting salmeterol, he or she is using more than four inhalations per day of short-acting inhaled β-agonists or more than one canister every 2 months, he or she should be instructed to seek medical advice as soon as possible. (8) salmeterol is not a replacement for oral or inhaled corticosteroids; therefore corticosteroids should not be stopped or reduced when salmeterol is initiated, even if the patient's symptoms improve with salmeterol.

Salmeterol can protect patients from exercise-induced bronchospasm for up to 12 hours after administration.[101] To protect against exercise-induced bronchospasm, salmeterol should be taken at least 30 minutes before exercise. There are data that suggest that protection against exercise-induced bronchospasm may be diminished in some patients with regular administration of salmeterol for 4 weeks. If regular use of salmeterol does not protect against exercise-induced bronchospasm, additional doses should not be used. In this situation treatment should be directed at better control of the patient's asthma in general, especially bronchial inflammation.

Conclusions. β-agonists have a wide therapeutic range with a favorable side effect profile compared with other bronchodilator drugs. Inhaled β-agonists are effective bronchodilators for use in the treatment of chronic asthma and are the treatment of choice for acute asthma. Although this class of drugs has the potential for life-threatening cardiovascular and pulmonary side effects, they are safe in most patients. Electrocardiographic monitoring is recommended when β-agonists are used in the treatment of high-risk patients with acute asthma. Because of the favorable benefit/risk ratio of β_2-selective agonists and their rapid onset of action, use of inhaled β_2-selective agonists on an as-needed basis should be considered part of the daily management of patients with chronic asthma.[82, 83, 121, 122] The use of β-agonists does not obviate the need for the early use of drugs for control of airway inflammation.

REFERENCES

1. Ahrens RC, Harris JB, Milavetz G, et al. Use of bronchial provocation with histamine to compare the pharmacodynamics of inhaled albuterol with metaproterenol in patients with asthma. J ALLERGY CLIN IMMUNOL 1987;79:876-82.
2. Church MK, Hiroi J. Inhibition of IgE-dependent histamine release from human dispersed lung mast cells by anti-allergy drugs and salbutamol. Br J Pharmacol 1987; 90:421-9.
3. Nelson HS. Adrenergic therapy of bronchial asthma. J ALLERGY CLIN IMMUNOL 1986;77:771-85.
4. Reed CE. Beta agonists: adrenergic bronchodilators: pharmacology and toxicology. J ALLERGY CLIN IMMUNOL 1985;76(2 pt 2):335-41.
5. Robberecht P, Delhaye M, Taton G, et al. The human heart beta-adrenergic receptors. I: heterogeneity of the binding sites; presence of 50% beta-1 and 50% beta-2 adrenergic receptors. Mol Pharmacol 1983;24:169.
6. Hudson LD, Pierson DJ, Stark K. Cardiac rhythm and pulmonary function changes in COPD patients with terbutaline and a combination bronchodilator. [Abstract]. Chest 1977;72:401.
7. Kendall MJ, Dean S, Bradley D, et al. Cardiovascular and metabolic effects of terbutaline. J Clin Hosp Pharmacol 1982;7:31-6.
8. Kinney EL, Trautlein JJ, Harbaugh CV, Gibson R, Worthington DJ. Ventricular tachycardia after terbutaline. JAMA 1978;240:2247.
9. Santo M, Sidi Y, Pinkhas Y. Acute myocardial infarction following intravenous salbutamol. S Afr Med J 1980;58:394.
10. Windom HH, Burgess CD, Siebers RWL, et al. The pulmonary and extrapulmonary effects of inhaled β-agonists in patients with asthma. Clin Pharmacol Ther 1990;48:296.
11. Shovlin CL, Tami FWK. Salbutamol nebulizer and precipitation of critical cardiac ischaemia. Lancet 1990;336: 1258.
12. Wong CS, Pavord ID, Williams J, et al. Bronchodilatation, cardiovascular, and hypokalemic effects of fenoterol, salbutamol, and terbutaline in asthma. Lancet 1990;336:1396.
13. Neville E, Corris PA, Vivian J, Nariman S. Nebulized salbutamol and angina. BMJ 1982;285:796.
14. Cookson W, Lane DJ, John SM, McCarthy GL, McCarthy ST. Cardiac arrhythmias caused by nebulized beta-agonist therapy. Lancet 1987;2:863.
15. Lulich KM, Goldie RG, Ryan G, et al. Adverse reactions to beta$_2$-agonist bronchodilators. Med Toxicol 1986;1: 289-99.
16. Chapman KR, Smith DL, Rebuck AS, et al. Hemodynamic effects of an inhaled beta-2 agonist. Clin Pharmacol Ther 1984;35:762.
17. Lipworth BJ. Risks versus benefits of inhaled β_2-agonists in the management of asthma. Drug Safety 1992;7:59.
18. Kurland G, Williams J, Lewiston NJ. Fatal myocardial toxicity during continuous infusion of intravenous isoproterenol therapy of asthma. J ALLERGY CLIN IMMUNOL 1979;63:407.
19. Siegel D, Shephard D, Gelb A, Weinberg PF. Aminophylline increases the toxicity but not the efficacy of an inhaled beta-adrenergic agonist in the treatment of acute exacerbations of asthma. Am Rev Respir Dis 1985;132:283.
20. Lipworth BJ, Struthers AD, McDevitt DG. Tachyphylaxis to systemic but not to airway responses to prolonged therapy with high dose inhaled salbutamol in asthmatics. Am Rev Respir Dis 1989;140:586-92.
21. Jenne JW, Valearenghi G, Druz WS, Starkey PW, Yu C, Shaughnessy TK. Comparison of tremor responses to orally administered albuterol and terbutaline. Am Rev Respir Dis 1986;134:708-13.
22. Beasley CRW, Rafferty P, Holgate ST. Bronchoconstrictive properties of preservatives in ipratropium bromide (Atrovent) nebulizer solution. BMJ 1987;294: 1197.
23. Malish DM. Possible allergic reactions to inert ingredients in Alupent metered dose inhaler, sorbitan trioleate. Immunol Allergy Pract 1985;7:31.
24. Koepke JW, Selner JC, Dunhill AL. Presence of sulfur dioxide in commonly used bronchodilator solutions. J ALLERGY CLIN IMMUNOL 1983;72:504.
25. Koepke JW, Christopher KL, Chai H, Selner JC. Dose-dependent bronchospasm from sulfites in isoetharine. JAMA 1984;251:2982.
26. Twarog FJ, Leung DYM. Anaphylaxis to a component of isoetharine (sodium bisulfite). JAMA 1982;248:2030.
27. Schwartz HJ, Chester EH. Bronchospastic responses to aerosolized metabisulfite in asthmatic subjects: potential mechanisms and clinical implications. J ALLERGY CLIN IMMUNOL 1985;74:511.
28. Nicklas RA. Paradoxical bronchospasm associated with the use of inhaled beta agonists. J ALLERGY CLIN IMMUNOL 1990;95:959-64.
29. Sly RM, Anderson JA, Bierman CW, et al. Position statement: adverse effects and complications of treatment with beta-adrenergic drugs. J ALLERGY CLIN IMMUNOL 1985;75:443-9.
30. Alliot RJ, Lang BD, Rawson DRW, Leckie WJH. Effects of salbutamol and isoprenaline/phenylephrine in reversible airways obstruction. BMJ 1972;1:539-42.
31. Newth CJ, et al. The ventilatory and oxygen costs in the anesthetized rhesus monkey of inhaled drugs used in therapy and diagnosis of asthma. Am Rev Respir Dis 1991;143:766-71.
32. Reed CE. Pharmacologic basis of the treatment of the allergic patient. Immunol Allergy Clin North Am 1991;11: 1-15.
33. Sterk PJ, Bel EH. The shape of the dose-response curve to inhaled bronchoconstrictor agents in asthma and in chronic obstructive pulmonary disease. Am Rev Respir Dis 1991;143:1433-7.
34. Tattersfield AE, Britton JR. β-Adrenoceptor agonists. In: Barnes PH, Rodger IW, Thomson NC, eds. Asthma: basic mechanisms and clinical management. 2nd ed. London: Academic Press, 1992:527-54.
35. Beasley R, Pearce N, Crane J, Windom H, Burgess C. Asthma mortality and inhaled beta agonist therapy. Aust N Z J Med 1991;21:753-63.
36. Holgate ST, Baldwin CJ, Tattersfield AE. Beta-adrenergic resistance in normal human airways. Lancet 1977;2: 375.
37. Ellul-Michallef R, French FF. Effect of intravenous prednisolone in asthmatics with diminished adrenergic responsiveness. 1975;2:1269.
38. Kraan J, Koeter GH, Vander Mark TW, Sluiter HJ, de Vries K. Changes in bronchial hyperreactivity induced by four weeks of treatment with antiasthmatic drugs in patients with allergic asthma: a comparison between budesonide and terbutaline. J ALLERGY CLIN IMMUNOL 1985;76:628-36.

39. Kerrebijn KF, Van Essen–Sanduliet EE, Neijens HJ. Effect of long–term treatment with inhaled corticosteroids and beta–agonists on the bronchial hyperresponsiveness in children with asthma. J ALLERGY CLIN IMMUNOL 1985;76:628-36.
40. Van Schayck CP, Graafsma SJ, Visch MV, Dompelding E, Van Weel C, Van Herwaarden CLA. Increased bronchial hyperresponsiveness after inhaling salbutamol during one year is not caused by subsensitization to salbutamol. J ALLERGY CLIN IMMUNOL 1990;86:793.
41. Vathenen AS, Knox AJ, Higgins RG, Britton JR, Tattersfield AE. Rebound increase in bronchial responsiveness after treatment with inhaled terbutaline. Lancet 1988;1: 554-8.
42. Clifton GD, Hunt BA, Patel RC, Burki NK. Effect of sequential doses of parenteral terbutaline on plasma levels of potassium and related cardiopulmonary response. Am Rev Respir Dis 1990;41:575.
43. Crane J, Burgess C, Beasley R. Cardiovascular and hypokalemic effects of inhaled salbutamol, fenoterol, and isoprenaline. Thorax 1989;44:136.
44. Massannari M, Geller D, Howenstine M, Francis R, Everett P. Safety of continuously nebulized high dose albuterol in children with acute asthma [Abstract]. J ALLERGY CLIN IMMUNOL 1992;89:154.
45. Sears MR, Taylor DR, Print CG, et al. Regular inhaled beta–agonist treatment in bronchial asthma. Lancet 1990; 336:1391-6.
46. van Schayck CP, Dompeling E, van Herwaarden CLA, et al. Bronchodilator treatment in moderate asthma or chronic bronchitis: continuous or on demand? A randomised controlled study. BMJ 1991;303:1426-31.
47. Hargreave FH, Dolovich J, Newhouse MT. The assessment and treatment of asthma: a conference report. J ALLERGY CLIN IMMUNOL 1990;88:1098-111.
48. Wahenda I, Wisniewski A, Wong C, et al. Airway effects of regular broxaterol and salbutamol treatment in asthmatic subjects. Thorax 1991;46:770P.
49. Platts–Mills TAE, Mitchell EB, Moszoro H, Wilkins SR, Tovey ER. Reduction of bronchial hyperreactivity during prolonged allergen avoidance. Lancet 1982;2:675-8.
50. Lai CKW, Twentman OP, Holgate SR. The effect of an increase in inhaled allergen dose after rimiterol hydrobromide on the occurrence and magnitude of the late asthmatic response and the associated change in nonspecific bronchial responsiveness. Am Rev Respir Dis 1989;140: 917-23.
51. Sanjar S, Aoki S, Kristersson A, Smith D, Morley J. Antigen challenge induces pulmonary airway eosinophil accumulation and airway hyperreactivity in sensitised guinea pigs: the effect of anti–asthma drugs. Br J Pharmacol 1990;99:679-86.
52. Larsson K, Martinsson A, Hjemdahl P. Influence of β–adrenergic receptor function during treatment on allergen sensitivity and bronchodilator response to terbutaline in asthmatic subjects. Chest 1992;101:953-60.
53. Rossing TH, Fanta CH, Goldstein DH, Snapper JR, McFaddin ER. Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. Am Rev Respir Dis 1980;122:365-71.
54. Becker AB, Nelson NA, Simon FER. Inhaled salbutamol (albuterol) vs injected epinephrine in the treatment of acute asthma in children. J Pediatr 1983;102:465.
55. Lawford P, Jones BJ, Milledge JS. Comparison of intravenous and nebulized salbutamol in initial treatment of asthma. BMJ 1978;1:84.
56. Tinkleman D. Comparison of nebulized terbutaline and subcutaneous epinephrine in the treatment of acute asthma. Ann Allergy 1983;50:398.
57. Uden DL, et al. Comparison of nebulized terbutaline and subcutaneous epinephrine in the treatment of acute asthma. Ann Emerg Med 1985;14:229.
58. Van Renterghem D. Intravenous versus nebulized terbutaline in patients with acute severe asthma: a double–blind randomized study. Ann Allergy 1987;59:313.
59. Salzman GA, Steele MT, Pribble JP, et al. Aerosolized metaproterenol in the treatment of asthmatics with severe airflow obstruction: comparison of two delivery methods. Chest 1989;95:1017-20.
60. Shim C, Williams MH Jr. The adequacy of inhalation of aerosol from canister nebulizers. Am J Med 1980;69: 891.
61. Crompton GK. Problems patients have using pressurized aerosol inhalers. Eur J Respir Dis 1982;63(suppl 119):101.
62. Lin RY, et al. Continuous versus intermittent albuterol nebulization in the treatment of acute asthma. Ann Emer Med 1993;22:1847.
63. Rudnitsky GS, et al. Comparison of intermittent and continuously nebulized albuterol for treatment of asthma in an urban emergency department. Ann Emer Med 1993;22:1842.
64. Fanta CH, Rossing TH, McFadden ER. Treatment of acute asthma: is combination therapy with sympathomimetics and methylxanthines indicated? Am J Med 1986; 85:5-10.
65. Lawford P, Jones BJM, Milledge JS. Comparison of intravenous and nebulized salbutamol in initial treatment of severe asthma. BMJ 1978;1:84.
66. Williams SJ, Winner SJ, Clark TJH. Comparison of inhaled and intravenous terbutaline in acute severe asthma. Thorax 1981;36:629-31.
67. Kelsen SG, Kelsen DP, Fleegler BF, Jones RC, Rodman T. Emergency room assessment and treatment of patients with acute asthma. Am J Med 1978;64:622-6.
68. Fanta CH, Rossing T, McFadden ER. Emergency room treatment of asthma: relationships among therapeutic combinations, severity of obstruction and time course of response. Am J Med 1982;72:416-22.
69. Becker AB, Nelson NA, Simons FER. Inhaled salbutamol (albuterol) vs injected epinephrine in the treatment of acute asthma in children. J Pediatr 1983;102:465-9.
70. Lenney W, Molner AD. At what age do bronchodilator drugs work? Arch Dis Child 1978;53:532-5.
71. Schuh S, Parkin J, Rajan A, et al. High versus low–dose frequently administered nebulized albuterol in children with severe, acute asthma. Pediatrics 1989;83:513-8.
72. Schuh S, Reider MJ, Canny G, et al. Nebulized albuterol in acute childhood asthma: comparison of two doses. Pediatrics 1990;86:509-13.
73. Bentur L, Canny GJ, Shields MD, et al. Controlled trial of nebulized albuterol in children younger than 2 years of age with acute asthma. Pediatrics 1992;89:133-7.
74. Maguire JF, O'Rourke PP, Colan SD, Geha RS, Crone R. Cardiotoxicity during treatment of severe childhood asthma. Pediatrics 1991;88:1180-6.
75. Karem, et al. Efficacy of albuterol administered by nebulizer versus spacer device in children with acute asthma [Abstract]. J Pediatr 1993;123:313.

76. Matthys H, Kohler D. Pulmonary deposition of aerosols by different mechanical devices. Respiration 1985;48:269-76.
77. Moler FW, Horwitz MC, Custer JR. Improvement in clinical asthma score and $PaCO_2$ in children with severe asthma treated with continuously nebulized terbutaline. J ALLERGY CLIN IMMUNOL 1988;81:1101-9.
78. DeBlaquiere P, Christensen DB, Carter WB, Martin TR. Use and misuse of metered dose inhalers by patients with chronic lung disease. Am Rev Respir Dis 1989;140:910-6.
79. Kemp JP, Pinnas JL, Tinkelman DG, et al. Comparison of bronchodilator responses with bitolterol mesylate solution with the use of two different nebulizer systems in asthma. J ALLERGY CLIN IMMUNOL 1986;77:509-15.
80. Chaleb JA, Kamghusoff PL, Prim FT. Effect of repeated doses of terbutaline inhalation. Curr Med Res Opin 1974;2:275.
81. Robertson CF, Smith F, Beck R, et al. Response to frequent low doses of nebulized salbutamol in acute asthma. Pediatrics 1985;106:672.
82. Crimi N, Palermo F, Capopardo B, et al. Effect of an aerosol delivery system on bronchodilator activity. Ann Allergy 1989;62:26-9.
83. Morgan MDL, Singh HBV, Fraim H, Williams SJ. Terbutaline aerosol given through pear spacer in acute asthma. BMJ 1982;285:849-50.
84. Newman SP, Millar AB, Lennard-Jones TR, Moren F, Clark SW. Improvement of pressurized aerosol deposition with Nebuhaler spacer device. Thorax 1984;39:935-41.
85. Newhouse MT, Dolovich M. Aerosol therapy of reversible airflow obstruction—concepts and clinical correlations. Chest 1987;9(suppl 5):585-645.
86. Schecker MH, et al. A device for overcoming discoordination with metered dose inhalers. J ALLERGY CLIN IMMUNOL 1993;92:783.
87. Dahl R, Pedersen B, Hagglof B. Nocturnal asthma: effect of treatment with oral sustained-release terbutaline, inhaled budesonide and the two in combination. J ALLERGY CLIN IMMUNOL 1989;79:811.
88. Nicklas RA, Balas T. Concomitant use of beta adrenergic agonists and methylxanthines. J ALLERGY CLIN IMMUNOL 1984;73:20.
89. Josephson GW, Kennedy HL, MacKenzie EJ, Gibson G. Cardiac dysrhythmias during the treatment of acute asthma. Chest 1980;78:429.
90. Banner AS, Sunderrayun EV, Agarivol MK, Addington WW. Arrhythmogenic effects of orally administered bronchodilators. Arch Intern Med 1979;139:434.
91. Coleman JJ, Vollmer, Barker AF, et al. Cardiac arrhythmias during combined use of beta-adrenergic agonist drugs and theophylline. Chest 1986;90:45-51.
92. Joad JP, et al. Extrapulmonary effects of maintenance therapy with theophylline and inhaled albuterol in patients with chronic asthma. J ALLERGY CLIN IMMUNOL 1986;78:1147.
93. Kemp JP, Chervinsky P, Orgel A, et al. Concomitant bitolterol mesylate aerosol and theophylline for asthma therapy with 24 hour electrocardiographic monitoring. J ALLERGY CLIN IMMUNOL 1984;73:32.
94. Smith JA, Weber RW, Nelson HS. Theophylline and aerosolized terbutaline in the treatment of bronchial asthma. Chest 1980;78:816.
95. Kelly HW, Menendez R, Voyles W. Lack of significant arrhythmogenicity from chronic theophylline and beta-2 adrenergic combination therapy in asthmatic subjects. Ann Allergy 1985;54:405-10.
96. Furakawa CT, Kemp JP, Simons FER, Tinkelman DG. The proper role of β_2-adrenergic agonists in the treatment of children with asthma. Pediatrics 1992;90:639-40.
97. Leahy RC, Gomm SA, Allen SC. Comparison of nebulized salbutamol with nebulized ipratropium bromide in acute asthma. Br J Dis Chest 1983;77:159.
98. Karpel JP, et al. A comparison of atropine sulfate and metaproterenol sulfate in the emergency treatment of asthma. Am Rev Respir Dis 1986;132:727.
99. Higgens RM, Stradling JR, Lane DJ. Should ipratropium bromide be added to beta-agonists in treatment of acute severe asthma? Chest 1988;94:718.
100. Rebuck AS, et al. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airways disease in the emergency room. Am J Med 1987;82:59.
101. Page C. One explanation of the asthma paradox: inhibition of natural anti-inflammatory mechanism by β_2 agonists. Lancet 1991;337:717-20.
102. Wahedna I, Wong CS, Wisniewski AP, Pavard ID, Tattersfield AE. Asthma control during and after cessation of regular beta2 agonist treatment. Am Rev Respir Dis 1993;148:707-12.
103. Ernst P, et al. Is the association between inhaled beta agonist use and life threatening asthma because of confounding by severity. Am Rev Respir Dis 1993;148:75.
104. McFadden ER. Rostrum: perspectives in B2-agonist therapy: vox clamantis in deserto vel lux in tenebris? J ALLERGY CLIN IMMUNOL 1995;95:641-51.
105. Executive Committee. Position statement: inhaled B2 adrenergic agonists in asthma. J ALLERGY CLIN IMMUNOL 1993;91:1234-7.
106. Shepherd GL, Hetzel MR, Clark TJH. Regular versus symptomatic aerosol bronchodilator treatment of asthma. Br J Dis Chest 1981;72:215-7.
107. Chapman KR, Kesten S, Szalai JP. Regular vs as-needed inhaled salbutamol in asthma control. Lancet 1994;343:1379-82.
108. Brogden RN, Faulds D. Salmeterol xinafoate: a review of its pharmacological properties and therapeutic potential in reversible obstructive airways disease. Drugs 1991;42:895.
109. Brittain RT. Approaches to a long-acting, selective beta2 adrenoceptor stimulant. Lung 1990;168(suppl):111.
110. Pearlman DS, et al. A comparison of salmeterol with albuterol in the treatment of mild-to-moderate asthma. N Engl J Med 1992;327:1420.
111. D'Alonzo GE, et al. Salmeterol xinafoate as maintenance therapy compared with albuterol in patients with asthma. JAMA 1994;271:1412.
112. Ullman A, Svedmyr N. Salmeterol, a new long acting inhaled B2 adrenoceptor agonist: comparison with salbutamol in adult asthmatic patients. Thorax 1988;43:674.
113. Fitzpatrick MF, et al. Salmeterol in nocturnal asthma: a double-blind placebo controlled trial of a long acting inhaled beta-2 agonist. BMJ 1990;301:1365.
114. Twentyman OP, et al. The long-acting B2 agonist salmeterol protects against allergen-induced inflammatory events in asthma. Lancet 1990;2:1338.
115. Derom E, Pauwels R, Van Der Strae M. Duration of the protective effect of salmeterol on methacholine challenge

of asthmatics [Abstract]. Am Rev Respir Dis 1990; 141(suppl):A469.
116. Malo JL, et al. Salmeterol, a new inhaled beta2 adrenergic agonist, has a longer blocking effect than albuterol on hyperventilation–induced bronchoconstriction. J ALLERGY CLIN IMMUNOL 1992;89:567.
117. Kemp JP, Dockhorn RJ, Busse WW, et al. Prolonged effect of inhaled salmeterol against exercise–induced bronchospasm. Am J Respir Crit Care Med 1994;150:1612-5.
118. Cheung D, Timmers MC, Zwinderman AH, et al. Long–term effects of a long–acting B2-adrenceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. N Engl J Med 1992;327:1198-203.
119. Booth H, Fishwick K, Harkawat R, et al. Changes in methacholine–induced bronchoconstriction with the long acting B2 agonist salmeterol in mild to moderate asthmatic patients. Thorax 1993;48:121-4.
120. Castle W, et al. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ 1993;306:1034.
121. British Thoracic Society. Guidelines for management of asthma in adults, I: chronic persistent asthma. BMJ 1990;301:651- 3.
122. Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute National Asthma Education Program: expert panel report. J ALLERGY CLIN IMMUNOL 1991;88:477-92.

Theophylline

Summary statements

- Theophylline is less effective than inhaled or injected β_2–selective agonists for the treatment of acute severe asthma.
- Maintenance therapy with theophylline is effective in reducing the frequency and severity of the symptoms of chronic asthma. It may be similar in effectiveness to cromolyn or β_2–agonists, and long–acting preparations allow for effective control of nocturnal symptoms.
- Mild chronic asthma may be controlled at steady–state theophylline serum concentrations less than 10 μg/ml; patients with more severe disease may require concentrations greater than 10 μg/ml for effective control of symptoms. Although patients may experience significant adverse reactions at less than 10 μg/ml, as the serum concentration increases, the frequency and severity of toxicity increases. With levels less than 15 μg/ml, severe adverse reactions are less likely to occur.
- The rate of theophylline metabolism varies greatly among patients in the same age group and is influenced by numerous medical conditions and pharmaceutical interventions.
- The rate of theophylline metabolism is reduced, thereby leading to increased serum levels and increased potential for toxicity, in the presence of such conditions as cardiac decompensation, respiratory failure, hepatic cirrhosis, sustained high fever, viral infections, and hypothyroidism and after administration of cimetidine, oral contraceptives, troleandomycin, erythromycin, ciprofloxacin, and disulfiram. In contrast, such factors as cigarette or marijuana smoking, hyperthyroidism, or use of rifampin, phenytoin, carbamazipine, and phenobarbital increases the rate of metabolism.
- Oral slow–release formulations generally provide stable serum concentrations and favor patient compliance. However, the rate and extent of absorption vary between formulations, between individuals, and possibly in the same individual from time to time. Food ingestion also may affect the rate of absorption in different ways, depending on the specific formulation.
- Dosage for chronic therapy is based on the principle of slow titration of the dose over several days to circumvent transient caffeine–like side effects. Final dosage usually is based on the peak serum concentration measurement obtained at steady state.
- Elevated blood levels may produce neurologic, gastrointestinal (including gastroesophageal reflux), or cardiovascular side effects.
- Orally administered activated charcoal or charcoal hemoperfusion dialysis should be considered to combat toxic theophylline concentrations. Intravenous phenobarbital should also be considered to prevent seizures; diazepam, but not phenytoin, should be used to terminate seizures.

Efficacy. Theophylline has been one of the most widely used and intensively studied medications for the treatment of asthma.

In a study that used meta–analysis to evaluate 13 controlled trials of aminophylline therapy in patients with severe acute asthma, it was concluded that the data are insufficient to recommend its routine use.[1] In a recent study, however, there was a threefold decrease in hospital admission rates for patients treated in the emergency room with aminophylline compared with placebo. All patients received β–agonists and corticosteroids. No differences were found between groups in pulmonary function, patient satisfaction, physician assessment, or side effects except for a trend toward nausea in the aminophylline–treated group.[2] Theophylline is a less potent bronchodilator than subcutaneous or inhaled adrenergic drugs[1, 3]; and in patients who have not been taking the drug on a regular basis, it may cause transient

adverse effects even at "therapeutic" serum concentrations.[4, 5] In patients with chronic asthma, however, theophylline effectively decreases the frequency and severity of asthmatic symptoms, including nocturnal symptoms,[6-12] reduces the need for emergency medications such as inhaled β–agonists[6, 8] and short courses of corticosteroids,[8, 11, 12] and prevents exercise–induced bronchoconstriction.[13, 14] It appears to have a corticosteroid–sparing effect when used to treat asthma,[8, 11, 12] but abrupt withdrawal of theophylline from corticosteroid–dependent asthmatic children has led to precipitation of severe and sometimes life–threatening asthmatic symptoms.[11]

Mode of action. Although the mechanism of action is not precisely delineated, theophylline: (1) increases the level of 3′,5′–cyclic adenosine monophosphate, possibly through inhibition of one or more phosphodiesterases; (2) modulates intracellular calcium transport; (3) antagonizes prostaglandins; and (4) inhibits adenosine receptors.[15] It probably decreases mucosal edema and secretions and improves mucociliary clearance, and recently has been found to have some anti–inflammatory properties at low doses,[16] immunomodulatory actions,[17, 18] and the ability to block late–phase reactions.[19, 20] Its positive inotropic effect on diaphragmatic muscle has justified its use as a stimulant in respiratory failure, and its stimulation of the diaphragm favors its consideration in the treatment of chronic obstructive pulmonary disease (COPD).[21, 22] It increases cardiac output, enhances the right ventricular ejection fraction, and reduces pulmonary vascular resistance. It also increases ventilatory drive by direct stimulation of the respiratory center.

Relationship of serum concentration to effect. Patients with mild symptoms may benefit from doses of theophylline producing a serum concentration less than 10 μg/ml.[10] In addition, lower doses have the advantage of minimal side effects.[23] However, in patients with more severe disease, a concentration exceeding 10 μg/ml may have other benefits, including preventing symptoms that interfere with sleep, reducing the need for emergency medications, and blocking exercise–induced bronchoconstriction.[6, 9, 13, 14] At concentrations within the 10 to 20 μg/ml range or even lower, transient caffeine-like side effects occur unless the dose is slowly titrated.[24, 25] Behavioral abnormalities have been reported in patients receiving theophylline.[26] However, data do not support such an adverse effect in most patients.[27-29] Although certain patients obtain additional benefit with serum concentrations exceeding 20 μg/ml, the frequency and severity of adverse effects increase progressively.[12] These include nausea, vomiting, diarrhea, headache, nervousness, tachycardia, insomnia, cardiac arrhythmias, and seizures, which can result in permanent brain damage or death. Notable side effects can occur in susceptible patients at lower theophylline levels. The number of reports of severe theophylline toxicity has increased markedly in recent years, particularly in infants[30] and in older patients with sustained fever, with influenza, or after medications such as erythromycin, ciprofloxacin, or cimetidine, which decrease the rate of theophylline metabolism.[31]

No evidence has been found that theophylline in the usual dosage range is unsafe for pregnant women, nursing mothers, or the fetus.[32] Theophylline crosses the placenta. Most infants tolerate serum theophylline levels that correspond to theophylline levels in the mother.[33] Theophylline is found in breast milk, and levels in milk approximate 70% of maternal blood theophylline levels.[34]

Metabolism. Theophylline is metabolized at varying rates by the liver; the half–life averages 3.7 hours (range 2 to 8 hours) for children more than 1 year of age[35-38] and 8.2 hours (range 6 to 13 hours) in otherwise healthy, nonsmoking adults less than 55 years of age.[4] The half–life is very long in the newborn and decreases progressively during the first year of life as the metabolic pathways mature.[39] Because the rate at which patients metabolize theophylline varies, an "average" dose will produce a wide range of steady–state serum concentrations. In patients who continue to have asthmatic symptoms or adverse effects at usual doses (i.e., <800 mg/day for adults or <20 mg/kg/day for children 1 to 9 years of age), dosage must be individualized on the basis of serum measurements to achieve maximum benefit and safety.[24] Heart failure, liver dysfunction, sepsis with multiorgan failure,[25] and sustained fever associated with viral infections, influenza, or hypothyroidism can slow theophylline metabolism and increase serum concentrations[36-38] to toxic levels.[35] Patients 55 years or older or those with COPD[36-38] also metabolize theophylline more slowly. In fact, clearance in the elderly, mostly in patients with COPD, may be 30% less than the "adult" figures used in the literature.[38] In contrast, the rate of metabolism is increased in tobacco and marijuana smokers[35] and in the presence of hyperthyroidism. Many drugs, including cimetidine, oral contraceptives, erythromycin, ciprofloxacin, and disulfiram, can slow metabolism; whereas phenytoin, carbamazepine, rifampin, and phenobarbital can increase the rate of metabolism.[31] When the former medi-

cations are given to a patient already taking theophylline, the dose may have to be reduced by 25% to 50% and blood levels followed appropriately. The various factors that can affect theophylline metabolism must be considered when one is adjusting dosage and determining how soon after initiation of therapy serum concentrations should be measured.

Formulations. Theophylline rectal suppositories are erratically absorbed and should not be used. Plain uncoated tablets, liquids, and rectal solutions are rapidly and completely absorbed but can result in wide fluctuations in serum concentrations.[35] Oral slow–release formulations provide more stable concentrations and are associated with improved compliance,[40] but there are clinically important differences found in the rate and/or completeness of absorption between the many slow–release products available.[41]

Food can affect the absorption of many formulations by either increasing or decreasing the rate and extent of absorption.[23, 42-44] For example, a large meal can cause an increase in rate and extent of absorption from Theo 24, a once–a–day product,[23] whereas it reduces the extent of absorption by 60% from Theo–Dur Sprinkle capsules.[42] Food has little effect on Theo–Dur tablets[43] or Slo–bid. Timing of the doses of slow–release theophylline to achieve maximum serum concentration in the middle of the night may decrease sleep disturbance that occurs in many patients with chronic asthma.[45]

Regardless of the formulation selected, physicians should indicate on the prescription that the pharmacist should not substitute one brand for another. Substitution of a product with a formulation that has a different rate or extent of absorption could decrease efficacy or induce theophylline toxicity.[46]

Use and dosage for acute bronchodilation. For the treatment of acute asthmatic symptoms, an inhaled β_2–agonist such as albuterol or terbutaline provides greater bronchodilation with fewer side effects than theophylline.[3] However, when the addition of theophylline is required (i.e., impending respiratory failure), intravenous delivery of aminophylline (theophylline) provides the most rapid and guaranteed delivery of medication.

On average, each milligram per kilogram (ideal body weight) of a theophylline loading dose administered as an intravenous 30-minute infusion results in an average *incremental* increase in serum concentration of 2 μg/ml ± 30%.[4] However, the initial level depends on the distribution volume, which varies unpredictably (a loading dose of 6 mg of aminophylline/kg total body weight results in a blood level of about 12 μg theophylline). When a loading dose is required in a patient who already has received theophylline in the previous 24 hours, estimation of the serum concentration based on the history is unreliable, and an immediate serum concentration measurement is indicated.[47] The loading dose can then be determined as follows:

Loading dose = (Desired concentration − Measured concentration) × (0.5 L/kg), where 0.5 L/kg is the mean volume of distribution.

The serum concentration obtained 30 minutes after an intravenous loading dose, when distribution is complete, can be used to assess the need for and size of subsequent loading doses, if clinically indicated, and for guidance of continuing therapy.[47] Recommended initial dosage is 0.4 mg/kg/hr in nonsmokers and 0.7 mg/kg/hr in smokers. Once a serum concentration of 8 to 15 μg/ml has been achieved, a constant intravenous infusion is started at a rate appropriate for age and concurrent abnormalities.[35] Because there is a large interpatient variability in theophylline clearance, serum concentrations will rise or fall when the patient's clearance is significantly different from the mean population value used to calculate the initial infusion rate. Therefore a second serum concentration is obtained 4 to 6 hours after the constant infusion is started in children and 8 hours after it is started in adults to determine whether the concentration is increasing or declining from the post–loading dose level. If the level is declining as a result of a higher–than–average clearance, an additional loading dose can be administered and the infusion rate increased. In contrast, if the second sample demonstrates a higher level, accumulation of the drug can be assumed, and the infusion rate should be decreased before the concentration exceeds 20 μg/ml. An additional sample is obtained 12 to 24 hours later to determine whether further adjustments are required, and then at 24-hour intervals to adjust for changes.

Dosage for continuous therapy of chronic asthma. In patients with chronic asthma there is no urgency to obtain a therapeutic theophylline serum concentration. Slowly increasing the dosage over a period of days can circumvent transient caffeine-like side effects such as nausea, headache, nervousness, and insomnia.[24] If the patient has no symptoms, an inhaled β_2–selective agonist alone or in combination with a short course of corticosteroids can be used during the slow titration process to relieve acute symptoms.

Serum concentration measurements. Blood samples should be collected at steady state (i.e., no doses missed in the previous 48 to 72 hours,[25] no

extra doses taken, and approximately equal intervals between doses). However, in many children and some adults there is great variation in theophylline levels from day to day, and a single determination of the theophylline level does not necessarily indicate peak or trough values or "steady state." In addition, it is emphasized that many phenomena, including vomiting, dehydration, prolonged temperature elevation, viral disease, vaccination, and concomitant medications, can significantly alter levels.[28-31, 48-51] Before low or inconsistent results are accepted as valid in ambulatory patients, compliance must be ensured by a careful history taken from a patient or parent who is informed of the consequences of improper dosage.

Dosage adjustments should be guided by an estimation of the peak concentration 2 hours after a rapid-release formulation or 4 hours after most slow-release products. (Once-a-day formulations peak about 12 hours after a fasting dose.) Repeat measurements should be considered at 6-month intervals in rapidly growing children and yearly in all others,[24] unless there is some intervening circumstance such as a sustained high fever, cardiac failure, or addition of a second drug (e.g., cimetidine or erythromycin) that might alter the metabolism of theophylline.[31]

As a result of increased physician demand and improved methodology, facilities for measuring theophylline in serum are now readily available in most communities in the United States. In addition, inexpensive office methods of measuring theophylline that are rapid and specific and that require very small amounts of serum or blood have become available recently.[52, 53]

Management of theophylline poisoning. Despite more than a decade of clinical experience with theophylline monitoring, iatrogenic overdosage continues to occur.[50, 51] In addition, there has been an increased frequency of suicide attempts by patients taking this drug. Ingestion of an excessive oral dose of theophylline requires discontinuation of the drug and prompt emergency treatment with activated charcoal dissolved in water.[54] Ipecac is ineffective if not given soon after ingestion.[55] Charcoal should be repeated at 2-hour intervals until the serum concentration decreases below 20 μg/ml. Cathartics, including sorbitol, do not increase the efficacy of activated charcoal and may increase vomiting and dehydration.[56, 57] Charcoal hemoperfusion can remove theophylline rapidly[58] and may be clinically indicated when the serum concentration is extremely high (e.g., >60 μg/ml after multiple doses or >100 μg/ml after a single overdose), *even in the absence of obvious signs of toxicity.* Seizures therefore may be prevented by prompt reduction in the serum concentration to safe levels.[59] Use of oral activated charcoal ("intestinal trapping") may double the clearance rate and speed up removal of the drug.[60] Peritoneal dialysis and other extracorporeal methods of removal, including conventional hemodialysis, do not clear theophylline rapidly enough and thus are not adequate for management of theophylline poisoning. Phenobarbital, but not phenytoin, has been shown to protect laboratory animals from theophylline-induced seizures[61] and has been recommended to treat any patient with toxic levels and evidence of central nervous system hyperreactivity (tremulousness, excitation, confusion).[62] When seizures occur they should be terminated rapidly with intravenous diazepam and/or thiopental or, if necessary, by a general anesthetic such as enflurane, while oxygenation and respiratory support are maintained. Phenytoin is ineffective in terminating theophylline-induced seizures, and halothane should be avoided because of sensitization of the myocardium to endogenous catecholamines.

REFERENCES

1. Littenberg B. Aminophylline treatment in severe, acute asthma: a meta-analysis. JAMA 1988;259:1678-84.
2. Wrenn K, Slovis CM, Murphy F, Greenberg RS. Aminophylline therapy for acute bronchospastic disease in the emergency room. Ann Intern Med 1990;115:241-7.
3. Fanta CH, Rossing TH, McFadden ER. Treatment of acute asthma: is combination therapy with sympathomimetics and methylxanthines indicated? Am J Med 1986;80:5-10.
4. Hendeles L, Weinberg M, Bighley L. Disposition of theophylline after a single intravenous infusion of aminophylline. Am Rev Respir Dis 1978;118:97-103.
5. Siegel D, Sheppard D, Gelb A, Weinberg PF. Aminophylline increases the toxicity but not the efficacy of an inhaled beta-adrenergic agonist in the treatment of acute exacerbations of asthma. Am Rev Respir Dis 1985;132:283-6.
6. Weinberger MM, Bronsky EA. Evaluation of oral bronchodilator therapy in asthmatic children. J Pediatr 1974;84:421-7.
7. Hambleton G, Weinberger M, Taylor J, et al. Comparison of cromoglycate (cromolyn) and theophylline in controlling symptoms of chronic asthma. Lancet 1977;1:381-5.
8. Nassif EG, Weinberger M, Thompson R, Huntley W. The value of maintenance theophylline in steroid-dependent asthma. N Engl J Med 1981;304:71-5.
9. Neijens HJ, Duiverman EJ, Graatsma BH, Kerrebijn KF. Clinical and bronchodilating efficacy of controlled-release theophylline as a function of its serum concentrations of preschool children. J Pediatr 1985;107:811-5.
10. Joad JP, Ahrens RC, Lindgren SD, Weinberger MM. Relative efficacy of maintenance therapy with theophylline, inhaled albuterol, and the combination for chronic asthma. J ALLERGY CLIN IMMUNOL 1987;79:78-85.
11. Brenner M, Berkowitz R, Marshall N, Strunk RC. Need for theophylline in severe steroid-requiring asthmatics. Clin Allergy 1988;18:143-50.

12. Dusdicker L, Green M, Smith GD, Ekwo EE, Weinberger M. Comparison of orally administered metaproterenol and theophylline in the control of chronic asthma. J Pediatr 1982;101: 281-7.
13. Pollock J, Kiechel F, Cooper D, Weinberg M. Relationship of serum theophylline concentration to inhibition of exercise-induced bronchospasm and comparison with cromolyn. Pediatrics 1977;60:840-4.
14. Magnussen H, Reuss G, Jorres R. Methylxanthines inhibit exercise-induced bronchoconstriction at low serum theophylline concentration and in a dose-dependent fashion. J ALLERGY CLIN IMMUNOL 1988;81:531-7.
15. Weinberger M. Pharmacology and therapeutic use of theophylline. J ALLERGY CLIN IMMUNOL 1984;73:525-40.
16. Sullivan P, Bekir S, Jaffar Z, Page C, Jeffrey P, Costello J. Anti-inflammatory effects of low dose oral theophylline in atopic asthma. Lancet 1994;343:1006.
17. Kidney JC, et al. Immune modulation by theophylline: the effect of withdrawal of chronic treatment in asthma. Am Rev Respir Dis 1993;146:A772.
18. Ward AJM, McKenniff M, Evans JM, Page CP, Costello JF. Theophylline—an immunomodulator role in asthma. Am Rev Respir Dis 1993;147:518.
19. Pauwels R, Van Renterghem D, Van Der Straeten M, et al. The effect of theophylline and Enprofylline on allergen-induced bronchoconstriction. J ALLERGY CLIN IMMUNOL 1985;76:583-90.
20. Pauwels R. The effects of theophylline on airway inflammation. Chest 1987;92:325-75.
21. Aubier M, et al. Aminophylline improves diaphragmatic contractility. N Engl J Med 1981;305:249-52.
22. Aubier M. Effect of theophylline on diaphragmatic and other skeletal muscle function. J ALLERGY CLIN IMMUNOL 1986;78:787-92.
23. Spector SL. Advantages and disadvantages of 24-hour theophylline. J ALLERGY CLIN IMMUNOL 1985;76:302-11.
24. Milavetz G, Vaughan LM, Weinberger MM, Hendeles L. Evaluation of a scheme for establishing and maintaining dosage of theophylline in ambulatory patients with chronic asthma. J Pediatr 1986;109:351-4.
25. Toft P, Heslet L, Hansen M, Klitgaard NA. Theophylline and ethylenediamine pharmacokinetics following administration of aminophylline to septic patients with multiorgan failure. Intensive Care Med 1991;17:465-8.
26. Rachelefsky GS, Wo J, Adelson J. Behavior abnormalities and poor school performance due to oral theophylline use. Pediatrics 1986;78:1133-8.
27. FDA. Theophylline and school performance. FDA Drug Bull 1988;18:32-3.
28. Lindgren S, Lokshin B, Stromquist A, et al. Does asthma or treatment with theophylline limit children's academic performance? N Engl J Med 1992;327:926-30.
29. Bender B, Milgrom H. Theophylline induced behavior change in children. JAMA 1992;267:2621-4.
30. Massanari M, Hendeles L. Potentially dangerous theophylline dose recommendations in The Harriet Lane Handbook. J Pediatr 1985;106:348-9.
31. Jonkman JHG, Upton RA. Pharmacokinetic drug interactions with theophylline. Clin Pharmacokinet 1984;9:309-34.
32. Spector SL. The treatment of the asthmatic mother during pregnancy and labor. Ann Allergy 1983;51:173-8.
33. Labovitz E, Spector SL. Placental theophylline transfer in pregnant asthmatics. JAMA 1982;247:786-8.
34. Yurchak AM, Jusko WJ. Theophylline secretion into breast milk. Pediatrics 1976;57:518-20.
35. Hendeles L, Massanari MJ, Weinberger M. Theophylline. In: Evans WE, Schentag JJ, Jusko WJ, eds. Applied pharmacokinetics. 2nd ed. San Francisco: Applied Therapeutics, 1986:1105-88.
36. Vestal RE, Cusack BJ, Mercer GD. Aging and drug reactions, I: effects of cimetidine and smoking on the oxidation of theophylline and cortisol in healthy men. J Pharmacol Exp Ther 1987;241:488-500.
37. Au WY, Dutt Ak, DeSoyze N. Theophylline kinetics in chronic obstructive airway disease in the elderly. Clin Pharmacol Ther 1985;37:472-8.
38. Jusko WJ, Gardner MJ, Mangione A, Schentag J, Koiup JR. Factors affecting theophylline clearances; age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates, and ethanol. J Pharm Sci 1979;68:1358-66.
39. Nassif EG, Weinberger MM, Shannon D, et al. Theophylline disposition in infancy. J Pediatr 1981;98:158-61.
40. Spector SL. Is your asthmatic patient really complying? Ann Allergy 1983;51:173-8.
41. Hendeles L, Iafrate P, Weinberger M. A clinical and pharmacokinetic basis for the selection and use of slow release theophylline products. Clin Pharmacokinet 1984; 9:95-135.
42. Hendeles L, Weinberger M. Selection of a slow-release theophylline product. J ALLERGY CLIN IMMUNOL 1986;78: 743-51.
43. Spector SL. Theophylline once-a-day dosage. Chest 1986; 90:623-5.
44. Milavetz G, Vaughan LM, Weinberger MW, Harris JB, Mullenix TA. Relationship between rate and extent of absorption of oral theophylline from Uniphyl brand of slow-release theophylline and resulting serum concentrations during multiple dosing. J ALLERGY CLIN IMMUNOL 1987;80:723-9.
45. Martin RJ, Cicutto LC, Ballard RD, Goldenheim PD, Cerniack RM. Circadian variation in theophylline concentrations and the treatment of nocturnal bronchospasm. Am Rev Respir Dis 1989;139:475-8.
46. Baker JR Jr, Moessner H, Gonzalez U, et al. Clinical relevance of the substitution of different brands of sustained-release theophylline. J ALLERGY CLIN IMMUNOL 1988;81:664-73.
47. Weinberg M, Matthay RA, Ginchansky EJ, Chidsey CA, Petty TL. Intravenous aminophylline dosage: use of serum theophylline measurement for guidance. JAMA 1976;235:2110-3.
48. Baker MD. Theophylline toxicity in children. J Pediatr 1986;109:538-42.
49. Klein JJ, Lefkowitz MS, Spector SL, et al. Relationship between serum theophylline levels and pulmonary function before and after inhaled beta-agonist in "stable" asthmatics. Am Rev Respir Dis 1983;127:413-6.
50. Sessler CN. Theophylline toxicity: clinical features of 116 consecutive cases. Am J Med 1990;88:567.
51. Olson KR, Benowitz NL, Woo OF, Pond SM. Theophylline overdose: acute single ingestion versus chronic repeated overmedication. Am J Emerg Med 1985;3:386.
52. Hill M, Hendeles L. Evaluation of an office method of measuring theophylline serum concentrations. J ALLERGY CLIN IMMUNOL 1988;82:30-4.
53. Milavetz G, Vaughan LM, Weinberger MM. Comparative efficiency of a laboratory and examining room assay for therapeutic drug monitoring of theophylline in ambulatory patients. Ann Allergy 1989;62:453-6.
54. Sintek C, Hendeles L, Weinberg M. Inhibition of theo-

phylline absorption by activated charcoal. J Pediatr 1979; 94:314-6.
55. Neuvonen PJ, Vactiainen M, Tokola O. Comparison of activated charcoal and ipecac syrup in prevention of drug absorption. Eur J Clin Pharmacol 1983;24:557-62.
56. Massanari M, Hendeles L, Neims A, Pohorylo E, George D. The effect of cathartics on drug absorption from a slow-release formulation [Abstract]. Drug Intell Clin Pharm 1985;19:462.
57. Massanari MJ, Hendeles L, Hill E, Neims A, George D. The efficacy of sorbitol and activated charcoal in reducing theophylline absorption from a slow release formulation [Abstract]. Drug Intell Clin Pharm 1986;20:471.
58. Park GD, Spector R, Roberts RJ, et al. Use of hemoperfusion for treatment of theophylline intoxication. Am J Med 1983;74:961- 6.
59. Woo OF, Pond SM, Benowitz NL, Olson KR. Benefit of hemoperfusion in acute theophylline intoxication. Clin Toxicol 1984;22:411-24.
60. Park GD, Radomski L, Goldberg MJ, Spector R, Johnson GF, Quee CK. Effects of size and frequency of oral doses of charcoal on theophylline clearance. Clin Pharmacol Ther 1983;34:663-6.
61. Blake KV, Massey KL, Hendeles L, Nickerson D, Neims A. Relative efficacy of phenytoin and phenobarbital for the prevention of theophylline–induced seizures in mice. Ann Emerg Med 1988;17:1024-8.
62. Hendeks L, Weinberger M. Theophylline: a "state of the art" review. Pharmacotherapy 1983;3:2-44.

Anticholinergic agents

Summary statements

- The regular use of anticholinergic bronchodilators appears to be most effective in patients with COPD who have partially reversible airflow obstruction.
- Inhaled anticholinergic medication is not sufficiently effective to be used as a single agent in the treatment of acute severe asthma but may provide benefit when combined with a β–agonist or other primary therapeutic agent.
- Inhaled anticholinergic agents such as ipratropium appear to be more effective when used to treat patients with chronic mild–to–moderate degrees of airflow obstruction.
- Inhaled anticholinergic medications such as ipratropium may be indicated in patients in whom alternative agents have not been sufficiently effective, are inappropriate because of other medical conditions, or have produced unacceptable side effects.

Naturally occurring alkaloid substances with anticholinergic activity found in jimsonweed *(Durata stramonium)* and deadly nightshade *(Atropia belladonna)* provided some of the earliest known asthma remedies. However, these agents had serious side effects that limited their use. Interest in anticholinergic drugs as a part of the therapeutic regimen for asthma has increased recently owing to the development of newer anticholinergic agents with significantly fewer side effects and a growing understanding of the role of the autonomic nervous system in normal and pathologic lung function.

Autonomic influences play a role in normal lung function and may contribute significantly to the overall pathogenesis of bronchial asthma.[1, 2] Nerve fibers from both the afferent and efferent limbs of the parasympathetic nervous system enter the lung. Parasympathetic preganglionic fibers travel through the vagus nerve and end in ganglia that are located in the walls of the large and intermediate airways. Postganglionic fibers innervate receptors on smooth muscles and submucosal glands. Stimulation of the efferent limb of the parasympathetic innervation of the lung results in constriction of bronchial smooth muscle and increased mucous gland secretion. The afferent limb of parasympathetic pulmonary innervation begins with irritant receptors located below the epithelial lining of the airways, and nervous impulses travel up neurofibers in the ascending vagal trunk. Normal resting airways bronchodilate after the administration of atropine, suggesting that persistent baseline parasympathetic activity produces mild tonic constriction of the normal airway. Parasympathetic influences appear to become even more pronounced in bronchial asthma.

The therapeutic benefits of anticholinergic drugs in asthma are derived from both bronchodilator activity and, in some patients, from inhibition of cholinergically stimulated mucous gland secretion. However, atropine has been shown to mildly depress both ciliary activity and mucus transport of particles.

The neurotransmitter of the parasympathetic nervous system is acetylcholine. Acetylcholine interacts with two types of cholinergic receptors called *muscarinic* (stimulated by the alkaloid muscarine) and *nicotinic* (stimulated by nicotine) *receptors*. The anticholinergic agents that are the subject of this section are those that antagonize acetylcholine action at muscarinic sites.

All anticholinergic drugs are either tertiary or quaternary ammonium compounds. Of these, the tertiary compound, atropine, and the quaternary ammonium compounds, ipratropium bromide and glycopyrrolate, are clinically important, although glycopyrrolate has not been approved for use as a bronchodilator. The tertiary and quaternary ammonium compounds differ markedly in their pharmacologic properties. Atropine is well absorbed from the gastrointestinal tract and easily crosses

the blood–brain barrier. In contrast, neither ipratropium bromide nor glycopyrrolate is absorbed from the gastrointestinal tract in appreciable quantities and neither is capable of crossing the blood–brain barrier.

When atropine is used as an aerosolized bronchodilator, the initial effects can be seen within 15 minutes of administration, and the maximal response generally occurs within 100 to 200 minutes. In adults the duration of action ranges from 3 to 5 hours. The usual dose is 25 to 50 μg/kg or 1 to 2 mg in the adult. Doses exceeding 2 mg may be more effective; however, adverse side effects are noted at these doses.

The major side effects of atropine include bradycardia and dry mouth, which can be seen with doses of atropine as low as 0.5 mg. At higher levels (2 to 5 mg) tachycardia, mydriasis, urinary retention, dry flushed skin, difficulty with speech, dysphagia, excitement, and fever may appear. The signs of true poisoning with atropine are delirium and coma.

Both ipratropium bromide and glycopyrrolate have been shown to have significant bronchodilatory effects. Ipratropium bromide, the *N*-propyl derivative of atropine, is available in the form of a metered-dose inhaler (Atrovent), which delivers 20 μg per activation. The usual dose is one to four inhalations (20 to 80 μg) four times a day. Ipratropium also is available for administration by nebulizer. It is prepared in individual unit dose vials containing 500 μg in a volume of 2.5 ml. The recommended dose is nebulization of a unit dose (0.02% ipratropium) three to four times a day. In addition, it also may be used as a single dose under appropriate clinical conditions. In the inhaled form ipratropium bromide attains negligible serum levels. Although more than 90% of the drug is swallowed, it is minimally absorbed from the gastrointestinal tract. Ipratropium bromide, unlike atropine sulfate, has no effect on mucus production, mucus transport, or ciliary activities. Glycopyrrolate has significant bronchodilator effects in both atopic and nonatopic asthmatic patients when administered by inhalation.[3, 4] Doses of 480 μg provide maximal bronchodilation with no side effects and a significantly prolonged duration of action that may last as long as 12 hours.[4]

Many studies have examined the effect of anticholinergic agents on bronchospasm induced by a variety of mechanisms.[5, 6] In a dose-related fashion, anticholinergics offer excellent protection from bronchospasm caused by cholinergic agents such as methacholine. Bronchospasm provoked by a variety of irritating stimuli, including sulfur dioxide, carbon dust, citric acid, and tobacco smoke, is prevented only partially by anticholinergic agents. Anticholinergic agents are also only partially protective when given before histamine challenge. At high doses, ipratropium bromide has a modest effect on bronchospasm induced by prostaglandin $F_{2\alpha}$ or prostaglandin D_2.[7] In contrast, no consistent effect of pretreatment has been seen in challenges with serotonin, bradykinin, or ultrasonically nebulized distilled water. Anticholinergic medications may be particularly useful in patients who require β-blockers.

The effect of anticholinergic agents on allergen-induced bronchospasm has been studied in some detail. More than half of the studies currently available show no protection at any dose of anticholinergic drug given, whereas others show variable protection. The late-phase response after allergen challenge is unaffected.[8]

The effect of anticholinergic agents on exercise-induced asthma has been highly variable. Most studies have demonstrated a significant improvement in baseline pulmonary function and no consistent change in the absolute fall in FEV_1 after exercise. Subgroups of patients whose exercise-induced asthma was partially protected by anticholinergics have been described. In general these patients had less severe asthma and a milder response to exercise. All of the studies done to date have demonstrated that β-adrenergic agonists and cromolyn sodium are superior to anticholinergics in protecting against exercise-induced asthma. Thus anticholinergic agents are not the drugs of choice for prevention of exercise-induced asthma; they nevertheless may be useful in some patients.

Many studies have examined the role of atropine or ipratropium bromide in the treatment of patients with acute asthma.[9, 10] These studies have demonstrated that neither agent is effective alone in most patients with acute asthma. When compared with β-adrenergic agonists, such as albuterol, metaproterenol, or fenoterol, ipratropium bromide is significantly less effective. Therefore this drug is not indicated as a primary therapeutic modality in the emergency setting, although some studies have suggested that ipratropium bromide may be beneficial in combination with β-adrenergic agonists.[9]

Studies examining the effectiveness of one or more doses of ipratropium bromide in patients with chronic asthma have shown optimal bronchodilation after 40 to 80 μg. Most clinical trials in adults show no additional bronchodilation at

higher doses, although in some studies an increased duration of action was noted.

After a single dose of ipratropium bromide (two inhalations; i.e., 40 μg), most responders will show an effect within 15 minutes; by 30 minutes 75% to 85% of the maximal bronchodilation will have been attained, with the peak effect usually occurring within 1 to 2 hours. The duration of effect varies from 4 to 6 hours. When compared with β_2–specific adrenergic agonists, ipratropium bromide in general has a slower onset and a longer duration of action; however, the area under the time–response curve, a measure of overall drug effectiveness, is generally greater for β–adrenergic agonists than for ipratropium bromide.

When used as a single agent, ipratropium bromide was an effective bronchodilator over 45- to 90-day periods.[11] When compared with metaproterenol, for example, on the first day of drug administration, ipratropium bromide had a smaller area under the time–response curve than had metaproterenol. By 45 days of use the area under the curve was identical for both drugs; and at the end of the 90-day study period, ipratropium bromide appeared to be slightly, but not statistically, more effective than a β–adrenergic agonist.

A small subset of asthmatic patients appears to respond better to ipratropium bromide than to β–adrenergic agonists. In general, responders have mild–to–moderate asthma; patients with an FEV_1 less than 50% of predicted show little or no response. Other than overall severity of asthma, there are no characteristics that allow the physician to distinguish those individuals who respond well to anticholinergic agents. Thus a therapeutic trial or a test dose with spirometry repeated at 30 and 60 minutes would be necessary to select patients who are within the "responder" group.

Ipratropium bromide also has been studied in combination with variety of other therapeutic agents for treatment of asthma.[12-15] These include the combination of ipratropium bromide with β–adrenergic agonists, theophylline, cromolyn sodium, or cromolyn sodium plus corticosteroids. These studies demonstrate that perhaps the most effective use of anticholinergic agents occurs when they are combined with a β–agonist, the effects of the combination being equal to the combined effects of the drugs administered separately. In some studies the effect of this combination is greater than the individual effects.

Several studies have examined the effect of ipratropium bromide when combined with methylxanthines. A single dose of oxytriphylline (400 mg) produced a peak improvement in FEV_1 within 2 hours of administration. Ipratropium bromide (40 μg) alone was slightly less effective. When both drugs were combined, the bronchodilation was additive during the first 2 hours. Beyond this time, however, the additive effect was lost, with the combination appearing to offer no advantage over theophylline alone.

A number of studies have attempted to examine the effectiveness of ipratropium bromide in treatment of different types of asthma. Most studies have demonstrated that ipratropium bromide is equally effective in both allergic and nonallergic asthma. The best predictor of ipratropium bromide effectiveness is the severity of the asthma rather than its type. Differences in ipratropium bromide effectiveness do appear, however, when compared with alternative asthma therapies. For example, a number of studies have shown that in allergic asthmatic patients β–adrenergic agonists provide better bronchodilation than do ipratropium bromide, whereas in so–called intrinsic asthmatic patients the drugs are generally equally potent.

Other conditions are worthy of note because they appear to be particularly responsive to anticholinergic therapy. These include the bronchospasm seen with β–blockade, anxiety–induced asthmatic episodes, cough–variant asthma syndrome, and cough associated with asthma.

Studies in children have produced conflicting results.[16, 17] Several studies have shown that young asthmatic patients show significant improvement after treatment with inhaled ipratropium bromide, although other studies have demonstrated limited responsiveness. In selected instances the response to ipratropium bromide in young children was superior to the response of aerosolized albuterol. In older children, as in adults, response to β–agonists generally was better than that to ipratropium bromide.

Studies in adults have suggested that asthmatic patients older than 40 years of age may respond better to ipratropium bromide than to β–agonists. This is particularly true in patients with longer histories of asthma or patients who have long smoking histories. However, it is difficult, in this age group, to differentiate those patients with pure asthma from those who have a reversible component associated with COPD.

A large number of studies have clearly demonstrated the effectiveness of anticholinergic agents in general and ipratropium bromide in particular in patients with COPD.[18, 19] Indeed, ipratropium

bromide or glycopyrrolate is the most effective single therapy in COPD.

Currently ipratropium bromide administered via metered-dose inhaler is the anticholinergic drug of choice. Although atropine and glycopyrrolate can be given in a nebulized form, the inconvenience of this delivery system limits their use. Ipratropium bromide may have a significant role when combined with a β-agonist.

Because most studies have suggested that ipratropium bromide is not effective in patients with acute asthma, this drug should not be relied on as the sole or major therapeutic agent in the emergency treatment of the patient with acute asthma.

REFERENCES

1. Barnes PJ. Cholinergic control of airway smooth muscle. Am Rev Respir Dis 1985;132:S42-5.
2. Barnes PJ. Neural control of human airways in health and disease. Am Rev Respir Dis 1986;134:1289-314.
3. Walker FB, Kaiser DL, Kowal MB, Suratt PM. Prolonged effect of inhaled glycopyrrolate in asthma. Chest 1987;91: 49-51.
4. Schroeckenstein DC, Bush RK, Chervinsky P, Busse WW. Twelve-hour bronchodilation in asthma with a single dose of the anticholinergic compound glycopyrrolate. J ALLERGY CLIN IMMUNOL 1988;82:115-9.
5. Morris HG. Review of ipratropium bromide in induced bronchospasm in patients with asthma. Am J Med 1986;81: 36-44.
6. Schlueter DP. Ipratropium bromide in asthma. Am J Med 1986;81:55-60.
7. Beasley R, Varley J, Robinson C, Holgate ST. Cholinergic-mediated bronchoconstriction induced by prostaglandin D_2, its initial metabolite 9a, 11B-PGF_2, and $PGF_{2\alpha}$ in asthma. Am Rev Respir Dis 1987;136:1140-4.
8. Paggiaro F, Bacci E, Talini D, et al. Atropine does not inhibit late asthmatic responses induced by toluene-diisocyanate in sensitized subjects. Am Rev Respir Dis 1987; 136:1237-41.
9. Rebuck AS, Chapman KR, Abboud R, et al. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airways disease in the emergency room. Am J Med 1987;82:59-64.
10. Guill MF, Maloney MJ, DuRant RH. Comparison of inhaled metaproterenol, inhaled atropine sulfate, and their combination in treatment of children with acute asthma. Ann Allergy 1987;59:367-71.
11. Storms WW, Bodman SF, Nathan RA, et al. Use of ipratropium bromide in asthma. Am J Med 1986;81:61-6.
12. Chervinsky P. Concomitant bronchodilator therapy and ipratropium bromide. Am J Med 1986;81:67-73.
13. Rayner RJ, Cartlidge PHT, Upton CJ. Salbutamol and ipratropium in acute asthma. Arch Dis Child 1987;62: 840-1.
14. Huhti E, Poukkula A. Comparison of fenoterol, ipratropium bromide, and their combination in patients with asthma or chronic airflow obstruction. Respiration 1986;50:298-301.
15. Boushey HA. Combination therapy with anticholinergic agents for airflow obstruction. Postgrad Med J 1987;63:69-74.
16. Milner AD. Ipratropium bromide and airways obstruction in childhood. Postgrad Med J 1987;63:53-6.
17. Reisman JM, Galdes-Sebalt M, Kazim F, Canny G, Levison H. Frequent administration by inhalation of salbutamol and IB in the initial management of severe acute asthma in children. J ALLERGY CLIN IMMUNOL 1988;81:16-20.
18. Gross NJ. Anticholinergic agents in chronic bronchitis and emphysema. Postgrad Med J 1987;63:29-34.
19. Gross NJ. Anticholinergic agents in COPD. Chest 1987;91: 52S-7S.

Antihistamines

Summary statements

- Antihistamines can be used safely in most patients with asthma.
- Antihistamines may be effective in the treatment of asthma because histamine, acting through H_1 receptors, produces smooth muscle contraction, an increase in vascular permeability, and stimulation of parasympathetic nerves, all of which are pathophysiologic features of asthma.
- Based on their ability to partially attenuate late-phase responses, newer antihistamines may play a greater role in the future treatment of asthma.
- Antihistamines may alleviate asthma somewhat through their direct effect on the bronchial passageways.
- There is a strong clinical impression that improvement of upper respiratory symptoms by antihistamines in patients who have concomitant allergic rhinitis and asthma may facilitate the treatment of lower respiratory symptoms.
- Although antihistamines are not the treatment of choice for exercise-induced bronchospasm, pretreatment may attenuate exercise-induced bronchospasm in some patients.
- Histamine is not the only mediator responsible for asthma symptoms, and therefore antihistamines, if used, should be considered adjunctive therapy in the treatment of asthma.

Pathophysiology of asthma. Asthma is characterized by inflammation and bronchospasm, resulting in reduction in airway caliber and bronchial hyperresponsiveness.[1] Bronchoconstriction occurs in response to mediators released from airway mast cells.[2, 3] In regard to inflammation, examination of bronchoalveolar lavage fluid after allergen challenge in asthmatic patients indicates that mast cells release inflammatory mediators (including histamine) not only early after challenge but also up to 48 hours after challenge.[4] Both preformed and actively generated mediators are released

from mast cells in response to challenge. Prostaglandins, thromboxanes, leukotrienes, and platelet–activating factor are actively generated, whereas chemotactic factors and histamine represent preformed inflammatory mediators.[5]

Role of histamine in asthma. Histamine release and resultant bronchoconstriction after allergen exposure have been appreciated as a feature of asthma for 40 years.[6, 7] Furthermore, histamine delivered by inhalation is one of the agents used to quantify the degree of airway hyperresponsiveness in asthmatic patients.[8] The importance of histamine in the induction of clinical asthma is supported also by the ability of antihistamines to diminish allergen–induced bronchoconstriction. However, H_1 receptor antagonists such as chlorpheniramine[9, 10] and clemastine[11, 12] are limited in their ability to prevent allergen–induced bronchoconstriction because of their sedative or anticholinergic effects at higher doses. The recent development of nonsedating antihistamines, which can produce bronchodilation, has revived interest in the potential role for new H_1 blocking agents in the treatment of asthma.

Recent studies with terfenadine and astemizole suggest that histamine accounts for significant airflow obstruction after allergen exposure.[13] Pretreatment with terfenadine or azelastine (not currently marketed in the United States) confers partial protection against allergen in dose–response bronchoprovocation tests.[14, 15] Recently developed antihistamines also can prevent nonallergen–mediated bronchoconstriction such as that produced by cold air,[16] ultrasonic nebulized water,[16] adenosine monophosphate,[17] benzalkonium chloride,[18] and exercise.[19] In addition, analysis of bronchoalveolar lavage fluids after bronchial instillation of hypertonic saline has shown increased levels of histamine and prostaglandin D_2.[20, 21] Pretreatment with higher than recommended doses of some H_1 antagonists also will partially inhibit exercise–induced asthma.[22, 23]

Late–phase reactions. Allergen challenge produces late–phase bronchial obstruction in many asthmatic patients. The role of histamine in late–phase reactions is, however, unclear. Inhibition studies with first–generation H_1 antagonists (chlorpheniramine) have demonstrated some efficacy in attenuation of late–phase responses, but it is uncertain whether this is a specific antihistamine effect or caused by other pharmacologic properties, such as anticholinergic or antiserotonin activity.[24, 25]

Use of antihistamines in asthma. About 50 years ago Herxheimer[26] reported that chlorpheniramine produced clinically significant bronchodilation.[26] Single–dose studies done recently with terfenadine, as well as cetirizine and azelastine (not currently marketed in the United States), have demonstrated that such drugs produce bronchodilation.[27–29] Studies of longer duration suggest that terfenadine and astemizole are effective clinically in the treatment of pollen–induced asthma.[30, 31] These H_1 antagonists improve asthmatic symptoms by two postulated mechanisms: direct inhibition of histamine–induced bronchoconstriction and inhibition of histamine–induced increase in nasal resistance. Other pharmaceutical agents that have antihistamine effects but are not currently marketed in the United States have been demonstrated to have anti–inflammatory properties. Such products could have a beneficial effect on both acute and late–phase asthmatic reactions.

Some early clinical trials that were carried out to determine the effects of oral H_1 antihistamines in asthma showed that these agents had little benefit and even seemed to provoke bronchospasm in certain individuals.[32, 33] This led to the warning printed on virtually all of the package inserts for these products that antihistamines should not be used in patients with asthma because their condition could deteriorate. Some studies have shown, however, that asthmatic patients can actually benefit from the use of antihistamines because certain antihistamines are also bronchodilators. At present, therefore, there is no general contraindication to the use of antihistamines in asthmatic patients; in fact, antihistamines may be useful adjuncts to asthma therapy. In addition, there has been concern that antihistamines may have a drying effect on bronchial mucus, presumably through anticholinergic activity. Perhaps of more concern has been recent data related to the ability of terfenadine and astemizole to produce prolongation of the QTc interval on electrocardiographic monitoring.[34–36] These effects have been reported after overdosage of these drugs or when they are used in combination with ketaconazole or certain macrolide antibiotics.

REFERENCES

1. Holgate ST, Beasley R, Twenbyman OP. The pathogenesis and significance of bronchial hyperresponsiveness in airway disease. Clin Sci 1987;73:561-72.
2. Flint KC, Leung KBP, Hudspith BN, Brostoff J, Pearce FL, Johnson N. Bronchoalveolar mast cells in extrinsic asthma: a mechanism for the initiation of antigen–specific bronchoconstriction. BMJ 1986;291:923-6.
3. Leung KBP, Flint KC, Brostoff J, Hudspith BN, Johnson

N, Pearce FL. Some properties of mast cells obtained by human bronchoalveolar lavage. Agents Actions 1986;18: 100-12.
4. Metzger WJ, Zavala D, Richerson HW, et al. Local allergen challenge and bronchoalveolar lavage of allergic asthmatic lungs: description of the model and local airway inflammation. Am Rev Respir Dis 1987;135:433-40.
5. Henderson WR Jr. Lipid-derived and other chemical mediators of inflammation in the lung. J ALLERGY CLIN IMMUNOL 1987;79:543-53.
6. Herxheimer HGJ. Antihistamine in bronchial asthma. BMJ 1949;2:901.
7. Schild HO, Hawkins DF, Mongave JL, Herxheimer H. Reactions of isolated human asthmatic lung and bronchial tissue to a specific antigen. Lancet 1951;2:376.
8. McFadden ER. Pathogenesis of asthma. J ALLERGY CLIN IMMUNOL 1984;73:413.
9. Popa VT. Bronchodilating activity of an H_1-blocker chlorpheniramine. J ALLERGY CLIN IMMUNOL 1977;59:54.
10. Groggins RC, Milner AD, Stokes GM. The bronchodilator effects of chlorpheniramine in childhood asthma. Br J Dis Chest 1979;73:297.
11. Nogrady SG, Bevan C. Inhaled antihistamines—bronchodilation and effects on histamine and methacholine-induced bronchoconstriction. Thorax 1978;33:700.
12. Partridge MR, Saunders KB. Effect of an inhaled antihistamine (clemastine) as a bronchodilator and as maintenance treatment in asthma. Thorax 1979;34:771.
13. Rafferty P, Beasley CR, Holgate ST. The contribution of histamine to bronchoconstriction produced by inhaled allergen and adenosine 5'-monophosphate in asthma. Am Rev Respir Dis 1987;136:369-73.
14. Thomson NC, Kerr JW. Effect of inhaled H_1- and H_2-receptor antagonists in normal and asthmatic subjects. Thorax 1980;35:428.
15. Phillips MJ, Ollier S, Gould CAL, Davies RJ. Effect of antihistamines and antiallergic drugs on response to allergen and histamine provocation tests in asthma. Thorax 1984;39:345-51.
16. Townley RG, Hopp RJ, Bewtra AK, Nabe M. Effects of terfenadine on pulmonary function, histamine release, and bronchial challenges with nebulized water and cold air hyperventilation. Ann Allergy 1989;63:455-60.
17. Phillips GD, Holgate ST. Effect of oral terfenadine alone and in combination with flurbiprofen on adenosine 5'-monophosphate-induced bronchoconstriction in non-atopic asthma. Thorax 1987;42:939-45.
18. Miszkiel KA, Beasley R, Rafferty P, Holgate ST. The influence of ipratropium bromide and sodium cromoglycate on benzalkonium chloride-induced bronchoconstriction in asthma. Br J Clin Pharmacol 1988;26:295-301.
19. Patel KR. Terfenadine in exercise-induced asthma. BMJ 1984;288:1496.
20. Smith CM, Anderson SD. Hyperosmolarity as the stimulus to asthma induced by hyperventilation. J ALLERGY CLIN IMMUNOL 1986;77:729-36.
21. Gravelyn TR, Pan PM, Eschenbacher WL. Mediator release in an isolated airway segment in subjects with asthma. Am Rev Respir Dis 1988;137:641-6.
22. Patel JR. Terfenadine in exercise-induced asthma. BMJ 1984;288:1496-7.
23. Finnerty JP, Holgate ST. Role of histamine and prostaglandins in exercise-induced asthma. J ALLERGY CLIN IMMUNOL 1988;81:240.
24. De Monchy JG, Keyzer JJ, Kauffman HF, Beaumont F, de Vries K. Histamine in late asthmatic reactions following housedust mite inhalation. Agents Actions 1985;16:252-5.
25. Holgate ST, Finnerty JP. Recent advances in understanding the pathogenesis of asthma and its clinical implications. Q J Med 1988;149:5-9.
26. Herxheimer H. Antihistamines in bronchial asthma. BMJ 1949;2:901-5.
27. Patel KR. Effect of terfenadine on methacholine-induced bronchoconstriction in asthma. J ALLERGY CLIN IMMUNOL 1987;79:355-8.
28. Kemp JP, Meltzer EO, Orgel HA, et al. A dose response study of the bronchodilator action of azelastine in asthma. J ALLERGY CLIN IMMUNOL 1987;79:893-9.
29. Tashkin DP, Brik A, Gong H. Cetirizine inhibition of histamine-induced bronchospasm. Ann Allergy 1987;59: 49-52.
30. Holgate ST, Emanuel MB, Howarth PH. Astemizole and other H_1-antihistaminic drug treatment of asthma. J ALLERGY CLIN IMMUNOL 1985;76:375-80.
31. Rafferty P, Holgate ST. Terfenadine (Seldane) is a potent and selective H_1 histamine receptor antagonist in asthmatic airway. Am Rev Respir Dis 1987;135:181-4.
32. Schuller D. The spectrum of antihistamines adversely affecting pulmonary function in asthmatic children. J ALLERGY CLIN IMMUNOL 1983;71:147.
33. Levy LI, Seabury JH. Spirometric evaluation of Benadryl in asthma. J Allergy 1947;18:244-50.
34. Kemp JP. Editorial: antihistamines—is there anything safe to prescribe? Ann Allergy 1992;69:276-80.
35. Monahan BP, Ferguson CL, Killeavy S, et al. Torsades de pointes occurring in association with terfenadine use. JAMA 1990;264:2788-90.
36. Simons FER, Kesselman MS, Giddins NG, et al. Astemizole-induced torsades de pointes. Lancet 1988;2:264.

Cromolyn and nedocromil

Summary statements

- Cromolyn can be effective in many patients, alone or in conjunction with bronchodilators, in preventing the symptoms of mild-to-moderate asthma.
- Cromolyn has been demonstrated to be extremely safe, although serious adverse effects, such as bronchospasm, have been reported.
- Cromolyn can be effective in preventing or diminishing exercise-induced asthma when given 15 to 30 minutes before exercise.
- Overall there is similar effectiveness whether delivered via metered-dose inhaler, Spinhaler, and solution for nebulization, although individual response must be considered in the choice of the product.
- Cromolyn has the ability to attenuate both early- and late-phase IgE-mediated reactions.
- Nedocromil sodium is a topically active anti-inflammatory agent (pyranoquinoline) that also has mast cell-stabilizing properties.

- Nedocromil sodium possesses a number of putative mechanisms of action, as suggested by both in vivo experiments in animals and in vitro effects on a variety of animal and human cell preparations.
- Nedocromil sodium is indicated primarily as a preventive drug in the management of asthma–associated chronic inflammation. If used appropriately in this manner, it is effective in improving symptom scores and reducing use of bronchodilators and, in some cases, other concomitant medications such as inhaled corticosteroids or cromolyn sodium.
- Clinical dosing of nedocromil sodium is based on its long– term preventive effects. Because it is not a bronchodilator, it is not indicated in the treatment of acute asthma.
- Long–term use of nedocromil sodium is generally safe.
- Nedocromil sodium is clinically useful in the preventive treatment of mild and moderate asthma.

Cromolyn sodium was first introduced in this country for the treatment of asthma by oral inhalation as a powder (a capsule for delivery by a Spinhaler). In recent years cromolyn also has been marketed for use in a metered–dose inhaler and as a nebulized aqueous solution. All three products are still available for clinical use, although most patients and physicians find the metered–dose inhaler more convenient to use and less likely to produce irritation of the respiratory tract. The Spinhaler formulation does not contain propellants and can be an alternative to the metered–dose inhaler in patients who have difficulty coordinating use of the metered–dose inhaler. A recent double–blind, controlled, multicenter study found that the metered–dose inhaler was as effective as the Spinhaler or the nebulized solution.[1]

Pharmacokinetics. Conventional pharmacokinetics of cromolyn are difficult to assess, because it is eliminated rapidly from the serum and because its distribution and elimination phases are almost identical.[2] The mean percentage of inhaled cromolyn absorbed by asthmatic patients is about 10%, although absorption varies depending on inhalation technique and the severity of the airway obstruction. Peak plasma levels may be detected within 5 to 30 minutes after inhalation. The duration of action is considered to be 4 to 6 hours, but clinical studies have demonstrated a substantial "carryover" effect after the drug was administered for several weeks.[3]

Mechanism of action. The precise pharmacologic activity of cromolyn sodium has not been determined fully, and its action at the cellular level is not understood completely, although it is thought to exert an anti–inflammatory effect through the inhibition of mediator release from a variety of cells, especially mast cells. The most unique effect in humans is its ability to suppress both immediate and late–onset asthmatic responses after allergen bronchoprovocation. The protective effect of cromolyn also can be demonstrated in patients naturally exposed to aeroallergens during pollen seasons.[4] Several short– and long–term clinical trials of allergic asthma clearly demonstrated that pretreatment with cromolyn prevented the rise of histamine–induced hyperresponsiveness during the pollen season.[5]

The ability of cromolyn to prevent the development of asthmatic symptoms from different triggers suggests an ability of the drug to act through different mechanisms. For example, cromolyn prevents not only exercise–induced asthma in most asthmatic patients with this condition[6] but also several types of reflex–induced asthma, such as sulfur dioxide–induced bronchospasm.[7] Cromolyn possibly affects "nonspecific bronchial hyperresponsiveness," which correlates with the clinical severity of asthma, and it may diminish diurnal swings in bronchial lability.[8] Long–term cromolyn use also may attenuate methacholine–induced hyperresponsiveness.[8]

Clinical use. Efficacy data from many clinical studies now provide convincing evidence that cromolyn is an effective prophylactic agent for the treatment of mild–to–moderate asthma in some patients[9] and is comparable to theophylline in efficacy.[10] Extensive clinical experience with cromolyn has not shown evidence of serious side effects.[11] Most of the side effects that have been described were minor, such as irritation of the throat, hoarseness, dryness of the mouth, and other signs of local irritation. However, inhaled cromolyn has the potential rarely to produce life–threatening bronchospasm associated with acute cough, chest tightness, and/or other symptoms of bronchospasm that occurs immediately after use.[11]

Nevertheless, critical assessment of the benefit/risk ratio indicates that cromolyn should be considered to be important in the treatment of chronic asthma. The long–term efficacy of cromolyn has been demonstrated by both symptomatic and physiologic improvement in some patients. It has been demonstrated to be effective in both allergic and

nonallergic asthma and may be especially useful in preventing cough–variant asthma. It often is effective in attenuating or abrogating exercise–induced asthma if given 15 minutes before the exercise period, either alone or in combination with an inhaled β–agonist. In the opinion of many, cromolyn can be most effective if it is given for 1 week before anticipated allergen exposure, such as before a pollen season, or 30 minutes before brief antigen exposures, such as visiting homes that have a cat or dog.

As noted herein, cromolyn is available in three different forms: an encapsulated powder for use with a Spinhaler, a metered–dose inhaler, and a solution for nebulization. The usual starting dose is administered three to four times a day for long–term management. There is evidence that increased number of pretreatment inhalations from the metered–dose inhaler can improve its effectiveness in preventing exercise–induced asthma.[12, 13] Regardless of the delivery system preferred for an individual patient, it is essential that the patient be properly instructed about the prophylactic nature of cromolyn, because lack of continuous administration of the drug is probably an important reason for failure to demonstrate efficacy. Therefore, it is necessary that the initial phases of projected long–term cromolyn treatment be carefully supervised. In the opinion of many, cromolyn should be administered for 8 weeks before it is concluded that it is not effective in an individual patient; if the results are equivocal, the trial period could be extended to 12 weeks, with the dose doubled during the final 6 weeks. Special consideration should be given to long–term use of cromolyn in patients with reflex–mediated asthma or in patients with recognized dual or late asthmatic responses.

Nedocromil. Nedocromil sodium is a water–soluble synthetic disodium salt. Its more rigid structural configuration differs from that of cromolyn sodium, and it is structurally different from other available antiasthma drugs such as β–adrenergic agonists, methylxanthines, and corticosteroids.[14-16] Pharmacokinetic data for inhaled nedocromil sodium demonstrate a mean plasma concentration of 3.3 μg/L, with a half–life of 2.3 hours, after inhalation of 4 mg. It has low bioavailability, and it does not accumulate in tissue compartments. No metabolites of the parent drug have been identified. The pharmacokinetic profile for nedocromil sodium is similar in normal and asthmatic subjects.[17]

Animal in vivo experiments demonstrate that nedocromil sodium is as effective as the chromone, cromolyn sodium in diminishing both early and late airway responses by modulating cellular inflammatory responses.[18] Studies in rabbits suggest that nedocromil sodium exerts its inhibitory anti–inflammatory effect on neutrophils by blocking protein kinase C.[19] Another postulated mechanism of action is its effect on bronchial sensory C nerve endings, resulting in the inhibition of tachykinin release from collateral branches of surrounding sensory nerves. One of its primary in vitro effects is inhibition of anti–IgE–induced histamine release from rat peritoneal mast cells and human pulmonary mast cells.[20] Other in vitro studies have demonstrated that nedocromil sodium inhibits mediator release from a variety of inflammatory cells (eosinophils, platelets, neutrophils, monocytes, macrophages) and epithelial cells.[2] It also antagonizes the chemotactic effect of platelet–activating factor on neutrophils and eosinophils.

Nedocromil sodium effectively blocks both early– and late–phase asthmatic airway responses.[18, 21] This effect is accentuated if the drug is given before the onset of asthma. It also inhibits bronchospasm induced by a variety of specific and nonspecific stimuli such as allergens, adenosine, sulfur dioxide, metabisulfites, and exercise.[22-24] Nedocromil sodium is more effective than cromolyn sodium in preventing sulfur dioxide, adenosine, and cold–induced asthma. In contrast to cromolyn sodium, it is effective in attenuating citric acid–induced cough. For this reason a trial of nedocromil sodium is warranted in all cases of refractory cough associated with increased bronchial hyperresponsiveness and/or asthma. Medium– and long–term studies have shown consistently that the drug reduces bronchial hyperresponsiveness.[16] Studies evaluating nedocromil sodium in children have been promising, but further data are needed in this patient population.[25]

Nedocromil sodium is delivered by inhalation via a metered–dose inhaler that provides 4 mg per inhalation. Some reports refer to a 3.5 mg dose, which is the dose at the mouthpiece as opposed to that at the valve. The recommended dose of nedocromil sodium is 4 mg two to four times a day. Controlled[26] clinical studies have shown that the drug is effective with both dosage regimens.[27] However, in more severe cases the maximal therapeutic effects are obtained when it is given four times a day.[2, 17] When this occurs, gradual tapering of dosage to two times a day may be attempted. For patients who have difficulty in coordinating inhalation via a metered–dose inhaler and for those who experience a bad taste or a

transient cough, the drug should be administered through a spacer apparatus.

The most significant side effects include bad taste (in about one in eight patients), occasional headaches, nausea, vomiting, and dizziness.[27] Regarding its use during pregnancy, nedocromil is classified as a category B medication.[27] Animal studies have not demonstrated mutagenicity, developmental problems, or carcinogenicity, even after exposure to supraphysiologic doses of nedocromil sodium.

The chief clinical advantage of nedocromil sodium lies in its ability to attenuate inflammation and bronchial hyperresponsiveness in mild and moderate asthma. Improvement in symptoms may occur within a few days, but a clinical trial of at least 2 weeks should be undertaken for determination of clinical efficacy. After institution of nedocromil sodium therapy, symptomatic improvement may be maintained after reduction of concurrent inhaled corticosteroids.[28] In several studies it was equivalent to beclomethasone (≥400 μg/day) in improving symptoms and bronchial hyperresponsiveness.[29, 30] Because it is classified as a preventive antiasthmatic agent, nedocromil sodium should be considered in early phases (mild and moderate asthma) of the stepwise management of asthma. In addition, a therapeutic trial of nedocromil sodium is justified in patients already receiving high-dose inhaled steroids, with the aim of achieving control while reducing the total daily steroid dose.[31]

REFERENCES

1. Blumenthal MN, Selcow J, Spector S, Zeiger RS, Mellon M. A multicenter evaluation of the clinical benefits of cromolyn sodium inhaled by metered-dose inhaler in the treatment of asthma. J ALLERGY CLIN IMMUNOL 1988;81: 681-7.
2. Cox JSG, Beach JE, Blair AM, et al. Disodium cromoglycate (Intal). Adv Drug Res 1970;5:115-96.
3. Bernstein IL, Siegel SC, Brandon ML, et al. A controlled study of cromolyn sodium sponsored by the Drug Committee of the American Academy of Allergy and Immunology. J ALLERGY CLIN IMMUNOL 1972;50:235-45.
4. Engstrom I. Evaluation of Lomudal treatment in children. Scan J Respir Dis 1977;101(suppl):49-56.
5. Dickson W, Cole M. Severe asthma in children: a 10-year followup. In: Pepys J, Edwards AM, eds. The mast cell: its role in health and disease. Tunbridge Wells, England: Pitman, 1979:343- 52.
6. Ben-Dov I, Bar-Yishay E, Godfrey S. Heterogeneity in the response of asthmatic patients to pre-exercise treatment with cromolyn sodium. Am Rev Respir Dis 1983; 127:113-6.
7. Myers DJ, Geffroy B, Boushey H. Inhibition of sulfur dioxide induced bronchoconstriction in asthmatic subjects is dose dependent [Abstract]. Clin Res 1985;33:107A.
8. Altounyan REC. Review of clinical activity and mode of action of sodium cromoglycate. Clin Allergy 1980;10: 481-9.
9. Eigen H, Reid JJ, Dahl R, et al. Evaluation of the addition of cromolyn sodium to bronchial maintenance therapy in the long-term management of asthma. J ALLERGY CLIN IMMUNOL 1987;80:612-21.
10. Furakawa CT, Shapiro GG, Kraemer MJ, Pierson WE, Bierman CW. A double-blind study comparing the effectiveness of cromolyn sodium and sustained-release theophylline in childhood asthma. Pediatrics 1984;74: 453-9.
11. Settipane GA, Klein DE, Boyd GK. Adverse reactions to cromolyn. JAMA 1979;241:811-3.
12. Tullett WM, Tan KM, Wall RT, Patel KR. Dose response effect of sodium cromoglycate pressurized inhaled in exercise induced-asthma. Thorax 1985;40:41.
13. Schoeffel RE, Anderson SD, Lindsay DA. Sodium cromoglycate as a pressurized inhaled (Vicrom) in exercise induced asthma. Aust N Z J Med 1983;13:157.
14. Brogden RN, Sorkin EM. Nedocromil sodium: an updated review of the pharmacologic properties and therapeutic efficacy in asthma. Drugs 1993;45:693-715.
15. Lee TH, ed. Airway inflammation in asthma. Am Rev Respir Dis 1992;145:S1.
16. Ayres JG. Nedocromil sodium: respiratory agent. Br J Clin Pract 1987;41:971.
17. Gonzalez JP, Brogden RN. Nedocromil sodium: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of reversible obstructive airways disease. Drugs 1987;34:560.
18. Abraham WM, Stevenson JS, Sielczak MS. Preliminary report on the effect of nedocromil sodium on antigen-induced early and late reactions in allergic sheep. Eur J Respir Dis 1986;69:192.
19. Rubin RP. On the mode of action of the anti-asthmatic drug nedocromil sodium on neutrophil function. Einstein Q J Biol Med 1991;9:4.
20. Leung KBP, Flint KC, Brostoff J, et al. Effects of sodium cromoglycate and nedocromil sodium on histamine secretion from human mast cells. Thorax 1988;43:756.
21. Crimi E, Brusasco V, Crimi P. Effect of nedocromil sodium on the late asthmatic reaction to bronchial antigen challenge. J ALLERGY CLIN IMMUNOL 1989;3:985.
22. Crimi N, Palermo F, Oliveri R, et al. Comparative study of the effects of nedocromil sodium (4 mg) and sodium cromoglycate (10 mg) in adenosine-induced bronchoconstriction in asthmatic subjects. Clin Allergy 1988;18:367.
23. Dixon CMS, Philip W. Inhaled sodium metabisulfite induced bronchoconstriction: inhibition by nedocromil sodium and sodium cromoglycate. Br J Clin Pharmacol 1990;30:371.
24. Shaw RJ, Kay AB. Nedocromil, a mucosal and connective tissue mast cell stabilizer, inhibits exercise-induced asthma. Br J Dis Chest 1985;79:385.
25. Armenio L, Baldini G, Bardare M, Boner A, et al. Double-blind, placebo-controlled study of nedocromil in asthma. Arch Dis Child 1993;68:193-7.
26. van As A, Chick TW, Bodman SF, et al. A group comparative study of the safety and efficacy of nedocromil sodium (Tilade) in reversible airways disease: a preliminary report. Eur J Respir Dis 1986;69(suppl 147):143-8.
27. Foulds RA. An overview of human safety data with nedocromil sodium. J ALLERGY CLIN IMMUNOL 1993;92: 202-4.

28. Lal S, Malhotra S, Gribben D, et al. An open assessment study of the acceptability, tolerability and safety of nedocromil sodium in long-term clinical use in patients with perennial asthma. Eur J Respir Dis 1986;69:136.
29. Orefice U, Struzzo P, Dorigo R, Peratoner A. Long-term treatment with sodium cromoglycate, nedocromil sodium and beclomethasone dipropionate reduces bronchial hyperresponsiveness in asthmatic patients. Respiration 1992;59: 97-101.
30. Bel EH, Timmers MC, Hermans J, Dijkman JH, Stark P. The long-term effects of nedocromil sodium and beclomethasone dipropionate on bronchial responsiveness to methacholine in nonatopic asthmatic subjects. Am Rev Respir Dis 1990;141:21-8.
31. Svendsen UG, Jorgensen H. Inhaled nedocromil sodium as additional treatment to high dose inhaled corticosteroids in the management of bronchial asthma. Eur Respir J 1991; 4:992-9.

Corticosteroids

Summary statements

- With renewed awareness of the importance of airway inflammation in the pathogenesis and chronicity of asthma, it is generally believed that inhaled corticosteroids should be used as primary therapy in patients with moderate and severe chronic asthma.
- Systemic corticosteroids should be considered in the management of acute asthma when the patient is not responding readily to bronchodilators. Early use of corticosteroids shortens the course of asthma, prevents relapses, and reduces the need for hospitalization. The early use of corticosteroids is of particular importance in patients who have a history consistent with fatality-prone asthma.
- Intravenous corticosteroids may be lifesaving in the treatment of severe intractable asthma. After episodes of severe intractable asthma, complete restoration of pulmonary function may require weeks of treatment. Therefore, after such events, corticosteroids should be continued at least until symptoms are controlled and pulmonary function is restored.
- Because of the potential for significant side effects from the prolonged use of systemic corticosteroids (and possibly high-dose inhaled corticosteroids), the need for oral corticosteroids should be monitored by pulmonary function tests, and inadequate control despite maximal use of other treatment approaches should be a prerequisite for the long-term administration of systemic corticosteroids.
- Patients receiving systemic corticosteroids on a long-term basis may need to be carefully monitored for changes in the hypothalamic–pituitary–adrenal axis, bone changes, glucose metabolism, hypertension, and other potential side effects of such therapy under certain circumstances.

The recognition that inflammation of the respiratory tract plays a major role in the pathogenesis of asthma has led to an increased understanding of the importance of corticosteroids in the treatment of asthma. The optimal choice of preparations, when and to whom they should be given, dosage, routes, and schedules of administration are still being evaluated. However, the primary importance of this medication in the treatment of asthma is well recognized. The following guidelines are based on the present clinical experience in this rapidly advancing field.

Mechanism of action. Once absorbed, corticosteroids circulate bound to transcortin, albumin, and other proteins; they enter the cells, combine with intracytoplasmic receptors (as many as 6000 to 12,000 receptors per cell), and move to the nucleus. Within the nucleus the complex binds to specific sites on DNA and modifies gene expression, messenger RNA, and protein synthesis. Alterations in the corticosteroid structure can affect binding to serum proteins, distribution to the site of action, binding and affinity for receptors within the cell, and elimination of the drug.[1, 2]

The anti-inflammatory effects of corticosteroids have made them important in the treatment of asthma. These actions include effects on the number of β-receptors; effects on cell number (neutrophils, monocytes, eosinophils, basophils, and T cells) and function; effects on cell influx, activation, and adhesion; T cell activation; cytokine gene expression; effects on IgE synthesis; vasoconstriction; inhibition of mediator release and histamine synthesis; decrease in mast cell number; effects on eicosanoid release; and decrease in mucus secretion.[3-6] Inhaled corticosteroids have also been shown clinically to have an inhibitory effect on allergen-induced mast cell degranulation.[2] Corticosteroids suppress the late-phase reaction and, with high doses given long term, may attenuate the immediate-phase asthmatic response.

Most patients with asthma respond well to corticosteroids; however, some patients with severe asthma have little change in pulmonary function and have been classified as corticosteroid resistant.[7] A poor response to corticosteroids could be related to abnormal absorption, metabolism, or a defect in cellular actions. It has been noted that patients who were more likely to break through

their corticosteroid "control" had higher peripheral blood eosinophil and monocyte counts and lower baseline pulmonary functions.

With further information about the action of different corticosteroids and further information concerning clinical response, dosing can be better defined for an individual patient.

Systemic corticosteroids

Acute intractable asthma—status asthmaticus. Intravenous corticosteroids are very important, even lifesaving, in the treatment of severe asthma unresponsive to bronchodilators. In some studies performed in adult patients to evaluate "high-dose" versus "low-dose" therapy in status asthmaticus, investigators have been unable to determine any advantage from the higher doses. However, in one double-blind study in 24 patients, high doses of corticosteroids (125 mg intravenously every 6 hours) produced significantly greater improvement in airway obstruction than medium doses (40 mg every 6 hours), and both doses were more effective than low doses (15 mg every 6 hours).[9] In children a single dose of 1 to 2 mg/kg of intravenous methylprednisolone, followed by 1 mg/kg every 6 hours has been recommended[10-14] during the acute phase followed by prednisone, 1 to 2 mg/kg/day, for the subsequent 3 to 7 days.[15] In addition, there is some information that methylprednisolone is distributed better to the lung tissue than prednisone and prednisolone.[13, 14] Oral corticosteroids along with other appropriate medications should be continued until symptoms are controlled and pulmonary function is restored to the patient's predicted normal or the best attainable value. If this course of corticosteroids is less than 6 days, gradual dose reduction to allow for adrenal recovery is unnecessary. Longer courses may require gradual dose reduction over weeks. It often is possible to substitute inhaled corticosteroids and other medications for control over this period of time. Patients receiving long-term corticosteroid therapy should have Medic Alert identification because of the risk of adrenal suppression and should be monitored closely for signs of side effects. Fatal varicella has been reported with high-dose corticosteroid therapy. Children and adults who are taking corticosteroids and are exposed to chicken pox or measles should be carefully monitored. There may be similar concerns about measles and other viruses. Treatment with varicella zoster immune globulin or pooled intravenous immunoglobulin may be indicated. Treatment with antiviral agents may be considered.[16]

Acute asthma. Although the optimal dose and schedule of administration in ambulatory patients has not been defined, a common practice is to administer up to 2 mg/kg in divided doses of prednisone or prednisolone orally for 3 to 5 days. The absolute dose, duration of treatment, and tapering schedule must be individualized on the basis of the severity of the attack and the patient's previous history. More studies are needed comparing the relative benefits of once a day versus divided dosing.[15] However, administration of the entire dose in the morning to minimize suppression of the hypothalamic-pituitary-adrenal axis is considered advisable. Short-acting preparations, such as prednisone, prednisolone, or methylprednisolone, are preferred for the same reason. The longer half-life of corticosteroids such as dexamethasone make these preparations less desirable from a safety standpoint. Some physicians favor prednisolone over prednisone because prednisone must first be metabolized to prednisolone by the liver. Theoretically, patients with liver disease may have unpredictable levels of prednisone. For most patients, however, prednisone appears to be as effective as prednisolone. As the systemic corticosteroids are tapered, inhaled corticosteroids can be used to supplement and eventually replace the oral preparation.[17]

Corticosteroids should be considered when patients are not responding readily to bronchodilators. Recent studies have shown that the early administration of corticosteroids shortens the course, prevents relapses, and reduces the need for hospitalization.[18-20] For acute episodes related to environmental exposures, treatment can often be restricted to a short course resulting in less potential for adverse side effects. Although it is true that most patients recover from acute attacks of asthma without the use of corticosteroids and that the mortality rate from asthma has not decreased with their availability, most authorities agree that they are effective and potentially lifesaving in individual patients who are refractory to standard bronchodilator therapy. Experts have speculated that fatalities have occurred that could have been prevented by early administration of corticosteroids. Therefore, it would seem prudent to initiate corticosteroid therapy early in those patients who have a history of recurrent severe episodes of wheezing, previous hospitalizations, respiratory failure, excessive use of β-adrenergic inhalers, or any other features of their illness that places them at increased risk of dying because of asthma (see Section VI C, Identification of the Fatality-Prone

Asthmatic Patient). Therefore, it may be prudent to initiate oral corticosteroid therapy early in these patients according to a predetermined plan. Aerosolized corticosteroids may be helpful if given at the first sign of pulmonary deterioration[21]; however, oral corticosteroids are necessary if the symptoms are not controlled. Aerosolized corticosteroids may be beneficial in the recovery stages to help decrease inflammation and control bronchial hyperresponsiveness.

Chronic asthma. The prolonged use of systemic corticosteroids for the treatment of chronic asthma can be associated with serious side effects especially if the doses are high. Accordingly, the lowest therapeutically effective dose for the shortest duration of time should be used. No patient should be permanently labeled "corticosteroid dependent" and left (indefinitely) receiving a fixed dose. The need for systemic corticosteroids should be monitored with objective pulmonary function tests such as FEV_1, PEFR, or both. Maximal use of bronchodilators, cromolyn, inhaled corticosteroids, or a combination of these drugs and other treatment measures should be a prerequisite to consideration of long-term oral corticosteroid therapy. Earlier consideration of the use of oral corticosteroids may be appropriate in certain patients who are unable to comply with the use of the above medications. The entire dose should be administered in the early morning to mimic normal circadian variation in endogenous production. Alternate-day therapy with short-acting preparations may be beneficial in minimizing hypothalamic-pituitary-adrenal suppression, as well as other side effects, and should be attempted in all patients who require continued administration.

Despite the above caveats, approximately 10% of patients with chronic asthma require long-term systemic corticosteroid therapy, which is frequently accompanied by a characteristic spectrum of adverse effects. In addition to hypothalamic-pituitary-adrenal axis suppression, central nervous system complications (pseudotumor cerebri, psychiatric reactions), posterior subcapsular cataracts, glaucoma, myopathy, osteoporosis, aseptic necrosis of bone, nephrocalcinosis, nephrolithiasis, hypertension, aggravation of congestive heart failure, enhancement of certain viral or bacterial infections, growth retardation (particularly in infants younger than 2 years of age or at puberty), hyperglycemia (steroid diabetes), hypercalciuria, hyperlipidemia, and various cutaneous and subcutaneous manifestations (acne, redistribution of subcutaneous fat, hirsutism, and skin thinning) may be encountered. Although any of these occurrences may constitute a major problem in individual patients, management of eye conditions, growth retardation, and steroid-induced osteoporosis can be major dilemmas for the supervising clinician. Therefore, in patients requiring long-term systemic corticosteroids, yearly eye examinations should be recommended if the patient has no symptoms or more frequent evaluation if eye symptoms develop. Growth retardation in children may be expected at daily doses of 10 mg of prednisone or more. Wherever possible, therefore, the daily dose of prednisone should be reduced to less than 10 mg per day or patients should be switched to the minimal alternate day dosage that controls symptoms. Infants under two years of age or children during the prepubertal or pubertal years are particularly vulnerable to irreversible steroid-induced growth retardation. There is considerable controversy about optimal management of steroid-induced osteopenia. This complication is a major problem in menopausal women, during the postmenopausal years and in the elderly. It is particularly troublesome because trabecular bone is preferentially involved and vertebral collapse, often multiple, is a common event. An increase in oral calcium may, in fact, aggravate hypercalciuria because the primary steroid effect is blockage of gastrointestinal absorption of calcium. Vitamin D_3 should be added only if blood levels are low. Estrogen supplements are indicated in the menopausal woman, but there is no clear-cut evidence that such treatment prevents the decrease in bone mass associated with steroid therapy. Preliminary reports indicate that diphosphonates may help naturally occurring osteoporosis in postmenopausal women, but the effects of these agents in steroid-induced osteoporosis are as yet unknown.

Inhaled corticosteroids. The use of parenteral and oral corticosteroids has traditionally been reserved for patients failing to respond to bronchodilator, cromolyn, theophylline, and other therapeutic measures. The recent recognition that inflammation of the respiratory tract plays an important role in the pathogenesis of asthma and the introduction of topically active inhaled corticosteroids with high topical effectiveness has stimulated interest in the use of corticosteroids earlier in the treatment of chronic asthma.[22] Recent concern about inhaled β-agonists, as well as recognition of the role of inflammation in asthma, has made inhaled corticosteroids one of the primary drugs for the treatment of asthma.

Three inhaled corticosteroid preparations are available in the United States: beclomethasone

dipropionate (Vanceril, Beclovent), flunisolide (Aerobid), and triamcinolone acetonide (Azmacort). The ideal preparation has a high degree of topical anti-inflammatory activity with minimal systemic side effects. Clinical efficacy has been established in children and adults with the available preparations.[23-26]

Information in this field is rapidly expanding, and the current dosing recommendations are based on clinical experience and interpretation of the literature. The recommended doses vary with different preparations because differences exist in the amount of medication delivered per actuation. The following dosages have been recommended in the *Physicians' Desk Reference*. Beclomethasone dipropionate inhalers dispense 42 μg per actuation with a recommended maximum for adults of 20 inhalations per day or 0.84 mg and for children 10 inhalations per day or 0.42 mg. Flunisolide inhalers dispense 250 μg per inhalation, and the recommended maximum dose for adults is 8 inhalations per day or 2 mg/day and for children 4 inhalations per day or 1 mg/day. Triamcinolone inhalers dispense 100 μg per inhalation with a recommended maximum adult dose of 16 inhalations per day, or 1.6 mg/day and for children 12 inhalations per day or 1.2 mg/day. Higher doses may be indicated if the patient's condition is not well controlled despite optimal use of other asthma medications, environmental controls, and good inhalation technique. Several parameters should be monitored in patients using inhaled corticosteroids, including appropriate dose, pulmonary function tests, linear growth (in children), weight gain, and blood pressure. For patients receiving high doses of inhaled corticosteroid, some experts recommend measurement of serum cortisol level twice a year for detection of possible adrenal cortical suppression and before any scheduled surgery.[27] A 24-hour measurement of urinary free cortisol, although more accurate, is a more demanding test.

At the currently recommended doses, the effect of inhaled corticosteroids on the hypothalamic pituitary-adrenal axis is considered minimal. However, data suggest a dose-related effect on the hypothalamic-pituitary-adrenal axis with the use of inhaled beclomethasone dipropionate and inhaled budesonide at higher than recommended doses.[28] With the three presently available inhaled corticosteroid preparations, a small dose is delivered and the breakdown is rapid. However, the preparations do vary in their plasma half-life and conversion rate to inactive metabolites. The plasma half-life of flunisolide is 1.8 to 2 hours, that of triamcinolone is approximately 2 to 5 hours, and that of beclomethasone dipropionate is 5 to 15 hours. At the recommended dose and appropriate dosing interval systemic side effects are rare. Higher doses have been used, and in other countries higher-dose metered dose inhalers are available. As the dose is increased, concern has been raised about possible side effects, including loss of bone mass. Osteocalcin levels have been used as an index of bone formation in patients taking inhaled budesonide at intermediate and high doses (1.2 to 2.4 mg/day). At these levels, a decrease in serum osteocalcin levels was noted.[30] The possibility of clinically significant bone "complications" with long-term use in children and the elderly remains to be determined. Studies with recommended doses of inhaled corticosteroids[30] have suggested an effect on growth rate and onset of puberty, although this effect has been more commonly encountered after administration of high-dose inhaled corticosteroids. Concern has been raised over the risk of corticosteroid-induced cataracts from inhaled corticosteroids, but no evidence to date substantiates this risk.[31]

To maximize delivery and decrease local side effects of inhaled corticosteroids, a spacer is recommended.[16] The spacer minimizes the amount of drug delivered to the oropharynx, reducing the occurrence of thrush, and decreases the unpleasant taste experienced by some. It is also recommended that patients rinse their mouths well after use of these preparations. Nebulized corticosteroid solutions are not available in the United States at this time, but children can often effectively use metered-dose inhalers with the aid of a spacer. It is essential to monitor the patient's inhalation technique during the use of inhaled corticosteroids.

Inhaled corticosteroids do not replace oral corticosteroids for the treatment of acute asthma.[32]

REFERENCES

1. Boudinot FD, D'Ambrosio R, Jusko WJ. Receptor-mediated pharmacodynamics of prednisolone in the rat. J Pharmacokin Biopharm 1986;14:469-93.
2. Persson K, Kaliner MA, Barnes P, eds. Asthma pathology and treatment: corticosteroids in the treatment of asthma and allergic disorders. New York: Marcel Dekker, 1991.
3. Morris HG. Mechanism of action and therapeutic role of corticosteroids in asthma. J ALLERGY CLIN IMMUNOL 1985; 75:1-3.
4. Kaliner M. Inhaled corticosteroids for chronic asthma. Am Fam Physician 1990;42:1609-16.
5. Wilson JW, Djukanovic R, Howarth PH, Holgate ST. Inhaled beclomethasone dipropionate downregulates airway lymphocyte activation in atopic asthma. Am J Respir Crit Care Med 1994;149:86-90.

6. Robinson D, et al. Prednisolone treatment in asthma is associated with modulation of bronchoalveolar lavage cell interleukin–4, interleukin–5 and interferon–gamma cytokine gene expression. Am Respir Crit Care Med 1994;148: 401.
7. Carmichael J, Paterson JC, Diaz P, Compton GK, Kay AB, Grant IWB. Corticosteroid resistance in chronic asthma. BMJ 1981;282:1419-22.
8. Toogood JH, Baskerville J, Jenning B, Lefcoe NM, Johansson SA. Bioequivalent doses of budesonide and prednisone in moderate and severe asthma. J ALLERGY CLIN IMMUNOL 1989;84:688-700.
9. Ratto D, Alfaro C, Sipsey J, Glovsky MM, Sharma OP. Are intravenous corticosteroids required in status asthmaticus: a comparison of two dosages. JAMA 1988;260: 527-9.
10. Haskell RJ, Wong BM, Hansen JE. A double–blind, randomized clinical trial of methylprednisolone and status asthmaticus. Arch Intern Med 1983;143:1324-7.
11. Harris JB, Weinberger MM, Nassife, et al. Early intervention with short courses of prednisone to prevent progression of asthma in ambulatory patients incompletely responsive to bronchodilators. J Pediatr 1987;110: 627-33.
12. Braude AC, Rebuck AS. Prednisone and methylprednisolone disposition in the lung. Lancet 1983;2:995-7.
13. Vichyanond P, Irvin CG, Larsen GL, Szefler SJ, Hill MR. Penetration of corticosteroids in the lung: evidence for a difference between methylprednisolone and prednisolone. J ALLERGY CLIN IMMUNOL 1989;84:867-73.
14. Greos LS, Vichyanoud P, Bleodow DC, et al. Methylprednisolone achieves greater concentrations in lungs than prednisolone. Am Rev Respir Dis 1991;144:586-92.
15. Szefler SJ. Glucocorticoid therapy for asthma: clinical pharmacology. J ALLERGY CLIN IMMUNOL 1991;88:147-65.
16. Revised label warns of severe viral problems with corticosteroids. FDA Medical Bulletin, December 1991:3.
17. Woolcock AJ. Use of corticosteroids in treatment of patients with asthma. J ALLERGY CLIN IMMUNOL 1989;84: 975-8.
18. Fiel SB, Swartz MA, Glanz K, Francis ME. Efficacy of short term corticosteroid therapy in outpatient treatment of acute bronchial asthma. Am J Med 1983;75:259-62.
19. Littenberg B, Gluck EH. A controlled trial of methylprednisolone in the emergency treatment of acute asthma. N Engl J Med 1986;314:150-2.
20. Brunette MG, Lands L, Thibodeau LP. Childhood asthma: prevention of attacks with short term corticosteroid treatment of upper respiratory tract infections. Pediatrics 1988; 81:624-9.
21. Beasley R, Cushley M, Holgate ST. A self–management plan of treatment of adult asthma. Thorax 1989;44:200-4.
22. Clark TJH. Inhaled corticosteroid therapy. A substitute for theophylline as well as prednisolone? J ALLERGY CLIN IMMUNOL 1985;76:330.
23. Szefler SJ. A comparison of aerosol glucocorticoids in the treatment of chronic bronchial asthma. Pediatr Asthma Allergy Immunol 1991;5:227-35.
24. Dry J, Sors C, Gervais P, et al. A comparison of flunisolide inhaler and beclomethasone dipropionate inhaler in bronchial asthma. J Int Med Res 1985;13:289-93.
25. Slavin RG, Izu AE, Bernstein IL, et al. Multicenter study of flunisolide aerosol in adult patients with steroid dependent asthma. J ALLERGY CLIN IMMUNOL 1980;66:379-85.
26. Meltzer EO, Kemp JP, Orgel HA, et al. Flunisolide aerosol for treatment of severe chronic asthma in steroid dependent children. Pediatrics 1982;69:340-5.
27. Patient information for use of inhaled steroids. Denver: National Jewish Hospital, 1992.
28. Prahl P, Jensen T, Bjerregaard–Andersen H. Adrenocortical function in children on high dose steroid aerosol therapy. Allergy 1987;42:541-4.
29. Toogood JH, Hodsman AB. Effects of inhaled oral corticosteroids on bone. Ann Allergy 1991;67:87-8.
30. Tinkelman D, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline in primary treatment of chronic mild to moderately severe asthma in children. Pediatrics 1993;92:64-77.
31. Dyson D, Toogood JH, McCormick DS. Prevalence of posterior subcapsular cataracts in an asthmatic population undergoing long term surveillance of adverse effects of inhaled steroid therapy. J ALLERGY CLIN IMMUNOL 1991;85:258.
32. Toogood JH. High dose inhaled steroid therapy for asthma. J ALLERGY CLIN IMMUNOL 1989;83:528.

Hydration and pharmacomucolytic agents

Summary statements

- Adequate hydration is recommended for patients with asthma, but overhydration must be prevented by careful monitoring of fluid and electrolyte balance, especially in infants, severely ill patients, and the elderly. Dehydration may occur with severe asthma and should be corrected. However, fluid overload may have adverse pulmonary and circulatory effects and must be prevented by careful monitoring of fluid and electrolyte balance.
- Guaifenesin and potassium iodide may be worth a trial in some asthmatic patients, although the mechanisms of action are unclear.

Traditionally the severely asthmatic patient has been advised to receive generous amounts of water either orally or parenterally for prevention of mucus impaction. This recommendation has not been supported by controlled studies. Indeed, there are reasons to be cautious about overenthusiastic use of oral and parenteral fluids, especially in the very young and very old where fluid overload is more likely to occur[1] along with hypokalemia or hyponatremia.

Acetylcysteine induces expectoration mainly through an irritant effect on the bronchial mucosa, which causes bronchorrhea and stimulates coughing. Pretreatment with β–adrenergic inhalation is usually necessary to protect against bronchospasm.[2] Nebulized acetylcysteine has an unpleasant sulfurous odor and taste that can produce gagging, nausea, and vomiting. The benefit/risk assessment precludes its general use in asthma. However, in intubated patients with refractory mucoid impaction, direct installation combined with a β–agonist may be helpful.[3]

Guaifenesin at the usually recommended dose is of doubtful value for asthma. Its use in higher doses requires further study.

Iodides are often listed under the category of "expectorants." Just as this inclusive category is controversial, so are iodides themselves as prescribed for expectoration or any other purpose in the treatment of asthma. Currently available forms include saturated solution of potassium iodide, potassium iodide solution (Pima), or sodium iodide solution (for intravenous use, 500 mg/500 ml fluid).

Although the exact mode of action of iodides is unknown, it is believed that they act by stimulating the production of watery mucus and proteolytic liquefaction and may improve mucociliary clearance. However, iodides seem effective in only some asthmatic subjects, and it is not possible to differentiate responders from nonresponders in advance. A multitude of side effects have been described.[4] Nevertheless, there are favorable reports in the literature suggesting a significant response to iodides in some patients.[5-7]

In one study, 10 of 200 asthmatic patients showed an exceptionally good response to potassium iodide, 300 to 600 mg four times a day.[8] Therefore iodine may be worth a trial for a limited period of time in some asthmatic patients. The American Academy of Pediatrics has recommended that the use of iodides be limited to those children with chronic disease who have a reproducible, clear amelioration with its use.[9] The dosage should be as low as possible and used for the shortest required time in this age group.

REFERENCES

1. Stalcup SA, Melins RB. Mechanical forces producing pulmonary edema in acute asthma. N Engl J Med 1977; 297:592-6.
2. Bernstein IL, Ausdenmoore RW. Iatrogenic bronchospasm in asthmatic patients following the use of n-acetylcysteine. Dis Chest 1964;46:469-73.
3. Millman M, Goodman AH, Goldstein IM, Millman FM, Van Campen SS. Status asthmaticus: use of acetylcysteine during bronchoscopy and lavage to remove mucous plugs. Ann Allergy 1983;50:85-93.
4. Hendeles L, Weinberg M. A time to abandon the use of iodides in the management of pulmonary diseases. J ALLERGY CLIN IMMUNOL 1980;66:177-8.
5. Falliers CJ, McCann WP, Ellis EF, et al. Controlled study of iodotherapy for childhood asthma. J Allergy 1966;38:183-92.
6. Repsher LH, Glassman JM, Soyka JP. Evaluation of iodoprophylidene glycerol as adjunctive therapy in stable, chronic asthmatic patients on theophylline maintenance. Todays Ther Trends 1983;1:77-89.
7. Petty TL. The National Mucolytic Study: results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. Chest 1990;971:75-83.
8. Siegal S. The asthma-suppressive action of potassium iodide. J Allergy 1964;35:252-70.
9. Committee on Drugs for the American Academy of Pediatrics. Evidence of efficacy of iodides as an expectorant. Pediatrics 1976;57:272.

Other considerations

Alternative therapy for the treatment of severe asthma

Summary statements

- Whatever the reasons for failure to respond to corticosteroids, several treatment regimens for asthmatic patients who have not responded to systemic corticosteroids now exist.
- Corticosteroid-sparing agents or alternatives to systemic corticosteroid therapy, including troleandomycin, methotrexate, gold, and intravenous γ-globulin therapy, may be effective in some patients with asthma.
- Certain of these regimens are contraindicated in some patients and/or may be associated with significant adverse effects.

The physician should first assess whether nonresponsiveness in patients receiving long-term corticosteroid therapy is due to noncompliance. Asthma in some patients may be inadequately controlled despite high-dose systemic corticosteroid therapy. Questions have been raised about whether these patients are truly "steroid resistant."[1] It is not clear whether poor clinical response represents a true cellular resistance, inadequate corticosteroid dose, type of corticosteroid (e.g., methylprednisolone compared with prednisone), uncontrolled disease (e.g., continued exposure to significant allergens or irritants), or concurrent airway disease.[2,3] Apart from the fact that the use of these drugs is restricted to patients with severe asthma, the prevalence, long-term management, and clinical response of patients who appear to require daily oral corticosteroids are not precisely defined. The treatment regimen should be carefully evaluated for potential inducers of corticosteroid metabolism, such as phenytoin, carbamazepine, phenobarbital, and rifampin, or diseases associated with increased corticosteroid metabolism, such as hyperthyroidism.[4] Discontinuation or replacement with alternative medications may improve response to corticosteroids. Measurement of total eosinophil counts, morning plasma cortisol concentrations, and direct measurement of plasma corticosteroid concentration may be useful for assessment of compliance and drug interactions in the management of pharmacokinetic anomalies such as

poor absorption or rapid elimination of corticosteroid medications.[4]

A recent study suggests that the distribution of methylprednisolone to lung tissue is better than that of prednisone and prednisolone.[2] Pharmacokinetic studies indicate that methylprednisolone has a lower clearance and more extensive tissue distribution than prednisolone.[3] These reports suggest that methylprednisolone may offer some therapeutic advantages to prednisone in patients with respiratory disease.

Whatever the reasons for failure to respond to corticosteroids, several treatment regimens are proposed as corticosteroid–sparing or alternatives to systemic glucocorticoid therapy; these include troleandomycin, methotrexate, gold, and intravenous γ–globulin therapy. Patients requiring chronic systemic corticosteroid therapy (e.g., >10 mg prednisone per day or equivalent), those with significant adverse corticosteroid effects, or both should be considered for alternative therapy. The choice of these or future alternative therapies depends on the experience of the physician, as well as specific problems presented by the patient.

Corticosteroid–sparing agents

TROLEANDOMYCIN. Troleandomycin (TAO) was first introduced as an antibiotic in the 1950s and was studied as a potential treatment for "infectious asthma." Asthmatic patients taking troleandomycin had decreased sputum production and reduced need for medications, but these effects did not appear to be related to antibiotic action.[5,6] Further studies noted clinical improvement when troleandomycin was added to the treatment regimen of severely asthmatic patients who did not respond to high–dose daily corticosteroids.[7] Troleandomycin's corticosteroid–sparing effect was recognized when it was combined with methylprednisolone in corticosteroid–dependent asthmatic patients. On the basis of observations of relatively better response with combined administration of troleandomycin and methylprednisolone than with troleandomycin and prednisone, it was recommended that troleandomycin be combined with methylprednisolone.[8] Pharmacokinetic studies show that methylprednisolone and theophylline elimination are significantly impaired in the presence of troleandomycin.[9-12] In contrast, prednisolone elimination is not altered. When considering the use of troleandomycin, the physician should first switch the patient to methylprednisolone.

When first introduced, troleandomycin was used in doses up to 1 gm/day (for adults) and produced significant hepatotoxic effects and exacerbation of corticosteroid–related adverse effects. Lower doses of troleandomycin may reduce asthma severity and produce fewer side effects.[13] Use of troleandomycin even in lower doses requires careful monitoring of liver function (at least every other week initially) and theophylline levels (troleandomycin administration may increase levels of theophylline by 25% to 50% within the first 12 hours of administration). Suggested monitoring schemes should be consulted.[13-15]

The aggressive use of inhaled corticosteroids, especially in higher doses, has reduced the need for this medication. It is possible that the dosing scheme for inhaled corticosteroids, specifically two to four times per day, provides the same benefit as the altered methylprednisolone pharmacokinetics induced by troleandomycin therapy. The potential risk of enhancing corticosteroid adverse effects should be carefully considered before beginning troleandomycin.

METHOTREXATE. Methotrexate has been proposed as treatment for severe, steroid–dependent asthma. A double–blind placebo–controlled clinical trial indicated efficacy in facilitating corticosteroid dose reduction with consequent reduction in risk of adverse corticosteroid effects.[16] It is postulated that methotrexate allows for corticosteroid reduction through its own anti–inflammatory properties.

Methotrexate is usually administered in doses of 7.5 mg the first 2 weeks. If improvement is not evident during this initial period, the dose may be increased to 15 mg weekly. This amount may be given orally in divided doses at 12-hour intervals or as a single weekly intramuscular dose. The parenteral route may be preferred in some patients who do not respond to the orally administered drug, presumably because more complete bioavailability is obtained by this route of administration. Before initiating methotrexate therapy, asthmatic patients should be carefully evaluated for other forms of respiratory disease because methotrexate can produce interstitial pneumonitis. Methotrexate is contraindicated in patients with significant abnormalities in renal function or liver chemistry, pregnancy, liver disease, alcohol consumption, severe blood dyscrasias, immunodeficiency, or active infectious disease. In addition, patients who are unreliable in complying with a treatment program should not be included.

Beneficial effects are not immediately apparent, and it may take several months to observe significant corticosteroid dose reduction. Consultation with a hepatologist to consider a liver biopsy is recommended after a cumulative dose of 2 gm has been reached. It is also important to monitor laboratory tests, including blood chemistries, complete blood cell count with differential, and platelet counts every 4 weeks. These tests should be obtained more often

during periods when doses are increased. In addition, assays of liver function, such as prothrombin time and serum albumin, should be performed and evaluated every 3 to 6 months.

Adverse effects are minimal with the low-dose protocol but must be monitored carefully. The most frequent adverse effects include gastrointestinal symptoms, stomatitis, and hematologic effects with leukopenia. These are usually dose related and may be alleviated by temporarily reducing or discontinuing the dose. Patients should also be advised against alcohol consumption and pregnancy. Certain medications may increase the risk for methotrexate toxicity by decreasing renal elimination (salicylates, sulfonamides, penicillins).[17]

A recent double-blind controlled study failed to show a significant difference in corticosteroid reduction between patients treated with methotrexate and those given placebo.[18] Therefore, a large multicenter controlled trial is needed to establish methotrexate's efficacy and safety in asthmatic patients. Other issues concerning methotrexate therapy must also be resolved: (1) guidelines for obtaining liver biopsy specimens, (2) the risk of pulmonary toxic effects in asthmatic patients, (3) the effect of methotrexate on airway reactivity with special emphasis on its ability to induce asthma, and (4) the mechanism of action.[19]

GOLD. Similar to methotrexate, gold therapy is used to treat rheumatoid arthritis, and several reports suggest that gold may be beneficial in the treatment of patients with severe corticosteroid-dependent asthma. Early studies used parenteral gold and described improvement in asthmatic symptoms and reduction in mean daily dose of corticosteroids.[20] Another clinical study revealed improvement in asthmatic symptoms and diminished bronchial hyperresponsiveness to methacholine after a total mean dose of 1500 mg attained during 6 to 12 months of parenteral gold sodium thiomalate therapy.[21]

With the recent availability of auranofin, an oral gold compound, for the treatment of rheumatoid arthritis, an open clinical trial was conducted to assess its efficacy in severe asthma.[22] Oral auranofin was administered in a dose of 3 mg twice daily for 20 weeks in 20 corticosteroid-dependent asthmatic patients. Although serial spirometric measurements remained the same, the mean maintenance corticosteroid dose in this group was decreased by approximately 33%. In addition, a significant decrease in bronchial hyperresponsiveness to methacholine, which correlated with a decrease in corticosteroid requirements, was noted in the treated patients. Adverse effects were limited to mild diarrhea, dermatitis, and proteinuria and resolved with temporary discontinuation or reduction of the dose. Although this study and previous in vitro work suggested several immunologic mechanisms by which gold could affect the pathogenesis of asthma, the exact mechanism of its action is unknown. On the basis of this favorable experience in an open study, further controlled clinical trials are necessary to verify the efficacy of oral gold.[22] Experience with gold therapy for asthma has been reported only in adult patients. There is no information regarding the efficacy or safety of gold therapy in children.

INTRAVENOUS γ-GLOBULIN. Although large doses of corticosteroids may depress immunoglobulin levels, it is not clear that there is a corresponding decrement in the immune response to infection. Parenteral immunoglobulin may provide several favorable effects in the treatment of asthma. In low doses it will increase serum antibody levels and be protective for individuals with impaired immunity. High doses administered intravenously may act as an immunomodulator, providing passive protection and potentially reducing the production of specific IgE. In a limited open trial using high-dose intravenous immunoglobulin in patients with severe corticosteroid-dependent asthma, reduction of corticosteroid dose, improvement of pulmonary function, and diminution of skin test response to specific allergen was observed.[23]

Data in the literature also report benefit from the use of intravenous γ-globulin in patients with recurrent severe sinus disease and asthma associated with deficiency in one or more IgG subclasses. Because a strong association exists between chronic sinus disease and recalcitrant asthma and between chronic sinus disease and immunodeficiencies, treatment of underlying antibody deficiencies might have a desirable effect on asthma. This hypothesis requires further study.

What is more important than immunoglobulin levels in host defense is the ability of an individual to make antibody. This ability can be determined by immunizing individuals (e.g., to tetanus or pneumococcal vaccine) and noting an appropriate rise in the specific antibody titers.

OTHER ANTI-INFLAMMATORY AND IMMUNOMODULATOR AGENTS. Based on the concept that asthma, is an inflammatory disease, several additional treatments have been presented as alternative therapy for severe corticosteroid-dependent asthma, including hydroxychloroquine, dapsone, and cyclosporine. Experience with these agents in other

inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease provides the rationale for their potential efficacy in asthma.

Because of its value in the treatment of connective tissue diseases, hydroxychloroquine has been recognized as a potential alternative for severe asthma. An open-label trial conducted in 11 adult asthmatic patients showed a 50% reduction in patients taking oral glucocorticoids.[24] A reduction in the total serum IgE level was also noted. Toxic reactions to hydroxychloroquine include retinal damage, which can be monitored by ophthalmologic examination and color vision testing. Larger-scale controlled studies will be needed to confirm the findings of this pilot study.

The anti-inflammatory effects of dapsone including its ability to decrease neutrophil-reactive oxygen species, chemiluminescence chemotaxis, and its effectiveness in several rheumatoid diseases suggest a potential beneficial role in asthma. An open-label trial demonstrated a reduction in oral glucocorticoid doses over the course of 6 to 13 months in corticosteroid-requiring asthmatic patients.[25] Adverse effects noted during the study included malaise, rash, thrombocytopenia, and a psychotic episode. Nine of 10 subjects had a significant decline in hemoglobin (mean decrease of 3.6 gm/dl). Four subjects had transient increases in serum theophylline concentrations. Individuals with glucose-6-phosphate dehydrogenase deficiency are not suitable candidates for dapsone therapy because of the risk of severe hemolytic anemia. Further investigations will be needed to establish the efficacy of dapsone in asthma.

Cyclosporine inhibits T-lymphocyte immune responses by interfering with cytokine synthesis and release; moreover, it inhibits histamine and leukotriene C_4 release from human basophils and pulmonary mast cells challenged with anti-IgE. A 9-month open-label trial in a group of patients with corticosteroid-dependent asthma led to a 66% reduction in prednisone dose in half the patients, and their pulmonary function improved significantly.[26] The remaining half failed to respond. Toxic effects noted during the study included a transient ischemic attack and septic cholangitis in one individual and peripheral venopathy in another. Mild elevation of serum creatinine was common, and some individuals had worsening of preexisting hypertension. Another placebo-controlled clinical study supported these observations and identified improvement in pulmonary function with cyclosporine therapy.[27] Although promising, the use of cyclosporine in asthma may be limited by its potential toxicity and the lack of response in a proportion of subjects.

Summary

PROSPECTIVE PHARMACOLOGIC AGENTS. The treatment of asthma has changed dramatically over the past several years with the development of new medications. However, a significant number of patients still respond poorly despite currently available therapy. It is possible that with continued research and development, new medications will become an important part of our armamentarium. Some agents under active investigation include inhaled diuretic agents, bradykinin and leukotriene antagonists, platelet-activating factor antagonists, potassium channel blockers, anticytokines, cromolyn-like agents with multiple antiasthmatic actions, and other anti-inflammatory agents. Until further data are generated about safety, these agents should be used with special caution.

REFERENCES

1. Corrigan CJ, Brown P, Barnes NC, et al. Glucocorticoid resistance in chronic asthma: glucocorticoid pharmacokinetics, glucocorticoid receptor characteristics and inhibition of peripheral blood T-cell proliferation by glucocorticoid *in vitro*. Am Rev Respir Dis 1991;144:1016-25.
2. Braude AC, Rebuck AS. Prednisone and methylprednisolone disposition in the lung. Lancet 1983;2:995-7.
3. Szefler SJ, Ebling WF, Georgitis JW, Jusko WJ. Methylprednisolone versus prednisolone pharmacokinetics in relation to dose in adults. Eur J Clin Pharmacol 1986;30:323-9.
4. Szefler SJ. Glucocorticoid therapy for asthma: clinical pharmacology. J ALLERGY CLIN IMMUNOL 1991;88:147-65.
5. Buffington GA, Dominguez JH, Piering WF, Hebert LA, Kauffman HM, Lemann J. Interaction of rifampin and glucocorticoids: adverse effect on renal allograft function. JAMA 1976;236:1958- 60.
6. Frey FJ, Horber FF, Frey BM. Altered metabolism and decreased efficacy of prednisolone and prednisone in patients with hyperthyroidism. Clin Pharmacol Ther 1988;44: 510-21.
7. Kaplan MA, Goldin M. The use of triacetyloleandomycin in chronic infectious asthma. In: Welch H, Marti-Ibanez F, eds. Antibiotics annual, 1958-59. New York: Interscience Publishers, 1959:273-6.
8. Fox JL. Infectious asthma treated with triacetyloleandomycin. Penn Med J 1961;64:634-5.
9. Itkin IH, Menzel ML. The use of macrolide antibiotic substances in the treatment of asthma. J Allergy 1970;45: 146-62.
10. Spector SL, Katz FH, Farr RS. Troleandomycin: effectiveness in steroid-dependent asthma and bronchitis. J ALLERGY CLIN IMMUNOL 1974;54:367-79.
11. Szefler SJ, Rose JQ, Ellis EF, Spector SL, Green AW, Jusko WJ. The effect of troleandomycin on methylprednisolone elimination. J ALLERGY CLIN IMMUNOL 1980;66: 447-51.

12. Szefler SJ, Brenner M, Jusko WJ, Spector SL, Flesher KA, Ellis EF. Dose and time-related effect of troleandomycin on methylprednisolone elimination. Clin Pharmacol Ther 1982;32:166- 71.
13. Szefler SJ, Ellis EF, Brenner M, et al. Steroid-specific and anticonvulsant interaction aspects of troleandomycin-steroid therapy. J ALLERGY CLIN IMMUNOL 1982;69: 455-62.
14. Brenner M, Szefler SJ. Troleandomycin in the treatment of severe asthma. Immunol Allergy Clin North Am 1990;11: 92-102.
15. Wald JA, Friedman BF, Farr RS. An improved protocol for using troleandomycin (TAO) in the treatment of steroid-requiring asthma. J ALLERGY CLIN IMMUNOL 1986;78:36-43.
16. Mullarkey MF, Blumenstein BA, Andrade WP, Bailey GA, Olason I, Wetzel CE. Methotrexate in the treatment of corticosteroid-dependent asthma. N Engl J Med 1988;318: 603-7.
17. Evans WE, Christensen ML. Drug interactions with methotrexate. J Rheumatol 1985;12(suppl 12):15-20.
18. Ezurum SC, Leff JA, Cochran JE, et al. Lack of benefit of methotrexate in severe, steroid-dependent asthma: a double blind placebo-controlled study. Ann Intern Med 1991; 114:353-60.
19. Jones G, Mierins E, Karsh J. Methotrexate-induced asthma. Am Rev Respir Dis 1991;143:179-81.
20. Muranka M, Miyamatoto T, Shida T, et al. Gold salt in the treatment of bronchial asthma: a double-blind study. Ann Allergy 1978;40:132-7.
21. Muranka M, Nakajima K, Suzuki S. Bronchial responsiveness to acetylcholine in patients with bronchial asthma after long-term treatment with gold salt. J ALLERGY CLIN IMMUNOL 1981;67:350-6.
22. Bernstein DI, Bernstein IL, Bodenheimer SS, Pietrusko RG. An open study of Auranofin in the treatment of steroid-dependent asthma. J ALLERGY CLIN IMMUNOL 1988;81:6-16.
23. Mazer BD, Gelfand EW. An open-label study of high-dose intravenous immunoglobulin in severe childhood asthma. J ALLERGY CLIN IMMUNOL 1991;87:976-83.
24. Charous BL. Open study of hydroxychloroquine in the treatment of severe symptomatic or corticosteroid-dependent asthma. Ann Allergy 1990;65:53-8.
25. Berlow BA, Liebhaber MI, Dyer Z, Spiegel TM. The effect of dapsone in steroid-dependent asthma. J ALLERGY CLIN IMMUNOL 1991;87:710.
26. Szczeklik A, Nizankowska E, Dworski R, et al: Cyclosporin for steroid-dependent asthma. Allergy 1991;46:312-5.
27. Alexander AG, Barnes NC, Kay AB. Trial of cyclosporin in corticosteroid-dependent chronic severe asthma. Lancet 1992;339:324-8.

Role of antibiotics/antivirals

Summary statements

- Infections associated with asthma exacerbations are almost always viral in origin and do not require antibiotic therapy. Under these circumstances, however, reevaluation of the patient's treatment program, including bronchodilators and corticosteroids, may be important.
- Bacterial infections, such as acute and chronic sinusitis, should be treated appropriately, including the prompt and adequate use of antibiotics.
- Influenza can be associated with increased asthma. Therefore appropriate immunization is essential in patients with moderately severe or severe asthma.

Respiratory infections commonly precipitate exacerbations of asthma. The association between respiratory infections and asthma is particularly relevant in young children because 11% of respiratory illness in the first year of life, 6% in the second, and 1% throughout the remainder of the elementary school years may be associated with wheezing.

Studies in both children and adults have shown that viruses are the infectious agents most often responsible for increases in asthma.[1] Furthermore, the type of respiratory virus likely to produce exacerbations of asthma is strongly related to the age of the patient.[2] Commonly implicated viruses are respiratory syncytial virus (RSV) in children younger than 5 years of age[3] and parainfluenza, rhinovirus, and less often influenza (A, A2, and B),[4] enterovirus, or adenovirus in older children and adults.[5] Bacterial infections in the lower respiratory tract are not usually associated with exacerbations of asthma.[6]

A number of mechanisms have been proposed to explain virus- induced asthma,[7-10] including (1) injury to airways by infecting agents, (2) diminished β-adrenergic function, (3) production of virus-specific IgE antibodies, and (4) enhanced leukocyte histamine release. Children who have high titers of virus-specific IgE antibodies during infection with either RSV or parainfluenza virus are more likely to have lower respiratory tract illness (bronchiolitis or pneumonia) as opposed to upper respiratory tract symptoms alone.[9, 11] Children with virus-specific IgE antibodies may also be more prone to the development of recurrent episodes of wheezing. Yet the precise role of virus-specific IgE antibodies in the pathogenesis of airway hyperresponsiveness (asthma) has yet to be defined. It is likely, however, that immediate hypersensitivity reactions contribute to virus-induced wheezing because pulmonary mast cell mediator release can be linked to acute bronchospasm, persistent bronchial inflammation, and increased airway reactivity.

Antiviral agents. Because of the morbidity and mortality associated with viral infections, considerable research effort has been focused on the development of antiviral agents.[12] Ribavirin is currently the only agent available for the treatment of

viral infections, specifically RSV infections.[13] This drug is indicated for children at high risk for severe RSV–induced respiratory disease, such as children with underlying cardiopulmonary disease.[14] However, sufficient efficacy has not been demonstrated for more general use. Four antiviral agents (amantadine, rimantadine, ribavirin, and α–interferon)[15] have been studied for the prevention and treatment of influenza. Only amantadine is currently approved for prevention and treatment of influenza A and should be considered for administration to asthmatic patients during epidemics of influenza A.

Prevention of influenza with yearly administration of influenza vaccine is recommended for patients with asthma by the Centers for Disease Control and Prevention. Decisions to immunize against influenza should be individualized on the basis of asthma severity and history of adverse reactions to vaccines.

Use of antibiotics. Because viral agents are the most common infectious cause of asthma exacerbations, antibiotics are not usually beneficial in the treatment of infectious asthma.[16] The addition of antibiotics to asthma therapy is indicated, however, when strong laboratory or clinical evidence of upper or lower respiratory tract bacterial infection exists, in particular acute or chronic sinusitis.[17-21]

REFERENCES

1. Busse WW. The effect of viral infections on asthma and allergic disorders. Insights in Allergy 1988;3(4):1-7.
2. McIntosh K, Ellis EF, Hoffman LS, Lybass TG, Eller JJ, Fulginiti VA. The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children. J Pediatr 1973;82:578-96.
3. Minor TE, Dick EC, DeMeo AN, Ouellette JJ, Cohen M, Reed CE. Viruses as precipitants of asthmatic attacks in children. JAMA 1974;227:292-8.
4. Minor TE, Dick EC, Baker JW, Ouellette JJ, Cohen M, Reed CE. Rhinovirus and influenza type A infections as precipitants of asthma. Am Rev Respir Dis 1976;113:149.
5. Hudgel DW, Lanston L Jr, Selner JC, McIntosh K. Viral and bacterial infections in adults with chronic asthma. Am Rev Respir Dis 1979;120:393.
6. Berman SE, Mathison DA, Stevenson DD. Transtracheal cultures in "infectious" asthma. J ALLERGY CLIN IMMUNOL 1975;56:206.
7. Busse WW. The contribution of viral respiratory infection to the pathogenesis of airway hyperreactivity. Chest 1988; 93:1077- 82.
8. Lemanske RF Jr, Dick EC, Swenson CA, Vrtis RF, Busse WW. Rhinovirus upper respiratory infection increases airway hyperreactivity and late asthmatic reactions. J Clin Invest 1989;11:378-90.
9. Welliver RC. Virus induced IgE reactivity in the treatment of viral respiratory disease. Immunol Allergy Pract 1989; 11:378-90.
10. Martinez FD, Morgan W, Wright A, Helberg CJ, Russig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. N Engl J Med 1988;319:1112.
11. Veter IZ, Henry MM, Stewart PW, Henderson FW. Lower respiratory illness in early childhood and lung function and bronchial reactivity in adolescent males. Am Rev Respir Dis 1988;137:302-7.
12. Barnes DW, Whitley RJ. Antiviral therapy and pulmonary disease. Chest 1987;91:246-50.
13. Smith P, Frankel L, Mathers L, Tang ATS, Anagno RL, Probis CA. A controlled trial of inhaled ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. N Engl J Med 1991; 325:24-9.
14. MacDonald NE. RSV update and time to alter your clinical approach? J Respir Dis 1985;6(4):11-6.
15. Tominack RL, Hayden FG. Rimantadine hydrochloride and amantadine hydrochloride use in influenza A virus infections in the family environment: a controlled double–blind study. Lancet 1969;2:1026-8.
16. Shapiro GG, Eggleston A, Pierson WE, Ray CG, Bierman CW. Double–blind study of the effectiveness of a broad spectrum antibiotic in status asthmaticus. Pediatrics 1974; 53:867-72.
17. Cummings NP, Wood RW, Lere JL, Adinoff AD. Effect of treatment of rhinitis/sinusitis on asthma: results of a double–blind study. Pediatr Res 1983;17:373.
18. Adinoff AD, Wood RW, Buschman D, Cummings NP. Chronic sinusitis in childhood asthma: correlations of symptoms, x–rays, culture and response to treatment. Pediatr Res 1983;17:264.
19. Rachelefsky G, Siegel S, Kate R. Chronic sinus disease with associated induced reactive airway disease in children. Pediatrics 1984;73:526-9.
20. Businco L, Fiore I, Friediana A, et al. Clinical and therapeutic aspects of sinusitis in children with bronchial asthma. Int J Pediatr Otolaryngol 1981;3:287-94.
21. Wald ER, Milmore GJ, Bowen A, et al. Bacterial sinusitis in children. N Engl J Med 1981;304:749-54.

Immunizations in the asthmatic patient

Summary statements

- Routine vaccinations are not contraindicated in patients with asthma or other allergic conditions.
- Patients who have a history of egg sensitivity should have a skin test with the vaccination material. If the skin test response is positive, the patient may be immunized with small increasing doses by use of an established protocol.
- Short–term, low– to moderate–dose systemic corticosteroids, alternate–day corticosteroids, or topical corticosteroids are not immunosuppressive and are *not* a contraindication for immunization.
- Influenza vaccine and pneumococcal vaccine are recommended for patients with chronic pulmonary disease including asthma.

Children and adults with asthma should receive routine immunizations in accordance with the recommendations of the Immunization Practices Advisory Committee of the Centers for Disease Control and Prevention.[1] Vaccination is not contraindicated in individuals with asthma or allergic disorders or those in close contact with individuals who have such disorders.[2] Children should receive the primary series of oral polio vaccine, diphtheria–pertussis–tetanus (DPT), and measles– mumps–rubella (MMR). The 23-valent pneumococcal polysaccharide vaccine, licensed in the United States in 1983, is recommended for all persons 65 years of age or older and adults with chronic illness, including chronic pulmonary disease. Pneumococcal vaccine should also be considered for patients who have had pneumonia or who have had splenectomy. The pneumococcal vaccine is not specifically given to patients with recurrent upper respiratory tract disease, such as otitis media and sinusitis.[3] Influenza vaccination should be used primarily in high–risk populations (e.g., adults and children with chronic pulmonary disease, including asthma).[4-7]

Vaccine components, such as animal proteins, antibiotics, preservatives, and stabilizers can cause allergic reactions in some patients. Of these, the most common cause of allergic reactions is egg protein, which is found in vaccines prepared on embryonated chicken eggs or chicken embryo cell cultures.[8] These vaccines include mumps, measles, influenza, and yellow fever. Patients who are able to eat eggs without reaction, even those with a positive percutaneous skin test response to egg allergen, can receive these vaccines.[9] Patients who have a history of urticaria, angioedema, respiratory difficulty, or anaphylaxis associated with egg ingestion should have a skin test with the vaccine before its administration, by using first a percutaneous test followed by intradermal injection of 0.02 ml of a 1:100 dilution. Children who have a positive skin test response to measles vaccine may be safely immunized with increasing volumes of vaccine until a full dose is reached. A similar protocol for administering influenza vaccine to children with egg sensitivity and severe asthma has also been suggested, producing a specific antibody response similar to that in children who received routine vaccination.[10] Rubella vaccine is grown in human diploid cell cultures and can be safely given to patients with egg sensitivity.

Some vaccines contain trace amounts of antibiotics to which patients may be sensitive. This information is present in the labeling for these products. MMR, for example, contains trace amounts of neomycin, although the amount present is less than that which would be used to determine skin test sensitivity. Generally, reactions to neomycin are characterized by delayed hypersensitivity (local reactions 48 to 96 hours later) rather than anaphylaxis. This is not a contraindication for MMR.[1] Some bacterial vaccines, including those for cholera, DPT, plague, and typhoid, are associated with large local reactions such as redness and pain, or systemic reactions such as fever. Rarely, urticaria or anaphylaxis occurs. Local reactions appear to be toxic or hyperimmune rather than allergic.[11] In 740 patients with a history of adverse reaction to tetanus toxoid, the most common adverse effects were local edema and tenderness (33%), fever (15%), and anaphylactoid reactions (33%). A positive reaction to immediate skin tests was present in fewer than 1% of patients who had an adverse effect from tetanus toxoid.[12] In patients with an adverse reaction to tetanus toxoid, a history of allergy and asthma was similar to that in the normal population.[11]

Asthma medications generally should not interfere with or be influenced by routine vaccination. Asthmatic children who have influenza have a prolongation of theophylline plasma half–life. However, no significant alterations in theophylline metabolism have been observed in asthmatic children observed for up to 52 hours after influenza vaccination.[13] Short–term low– to moderate–dose systemic corticosteroids; intranasal or orally inhaled corticosteroids (at their usual doses); long–term, alternate–day treatment with low to moderate doses of short–acting systemic corticosteroids; and intraarticular, bursal, or tendon injections of corticosteroids in usual doses are not usually immunosuppressive and are not a contraindication for vaccine administration, *including live vaccine*.[10] On the other hand, generalized vaccinia has been described in patients taking high doses of corticosteroids and in immunocompromised patients. Children receiving long–term corticosteroid therapy for asthma, including those with decreased levels of IgG caused by corticosteroid therapy, respond to tetanus toxoid, pneumococcal vaccine, and influenza vaccine in a similar way to those who have never been treated with corticosteroids.[14]

REFERENCES

1. Centers for Disease Control, Immunization Practices Committee. General recommendations on immunization. MMWR 1989;38:205-27.
2. Bart KJ, Orenstein WA, Hinman AR. The current status of

immunization principles: recommendation for use and adverse reactions. J ALLERGY CLIN IMMUNOL 1987;79: 296-315.
3. Centers for Disease Control. Pneumococcal polysaccharide vaccine. MMWR 1989;38:64-76.
4. ATS statement. Prevention of influenza and pneumonia. Am Rev Respir Dis 1991;142:487-8.
5. Kawa T, Lindquist A, Karjalainer J, Lartiner A. Unchanged bronchial reactivity after killed influenza virus vaccine in adult asthmatics. Respiration 1987;51:98-104.
6. Kawa T. Acute respiratory infection, influenza vaccination, airway reactivity in asthma. J Respir Dis 1987;150(suppl):1-38.
7. Misieres J, Sallerer F, Fapani R, Escanilla R. Influenza vaccine and asthma. Allergy Immunol 1987;19:18-21.
8. Hermann JJ, Radin R, Schneiderman R. Allergic reactions to measles rubeola vaccine in patients hypersensitive to egg protein. J Pediatr 1983;102:196-9.
9. Greenberg MA, Brix DL. Safe administration of mumps–measles–rubella vaccine in egg–allergic children. J Pediatr 1988;113:504- 6.
10. Murphy KR, Strunk RC. Safe administration of influenza vaccine in patients hypersensitive to egg protein. J Pediatr 1985;106:931-3.
11. Jacobs RL, Lowe RS, Lanier BQ. Adverse reactions to tetanus toxoid. JAMA 1982;247:40-2.
12. Mansfield Lyon E, Ting S, Rawls D, Frederick R. Systemic reactions during cutaneous testing for tetanus toxoid hypersensitivity. Ann Allergy 1986;57:135-7.
13. San Joaquin VH, Reyes S, Marks MI. Influenza vaccination in asthmatic children in maintenance theophylline therapy. Clin Pediatr 1982;12:724-6.
14. Katz U, Harbeck RJ, DiMichelle D, Mitchell B, Strunk RD. Steroid–treated asthmatic patients with low levels of IgG have normal capacity to produce specific antibodies. Pediatr Asthma Allergy Immunol 1988;2:309-16.

Comparability of therapeutic products

Summary statements

- Comparability of inhaled products cannot be assumed because of potential differences in patient response to excipients or other "inactive" components in these products.
- Substitution of a theophylline product different from the one the patient was previously receiving can produce decreased efficacy or toxicity in some patients.
- Any adverse reaction that is temporally related to use of a drug product may be due to the drug product even if the patient has tolerated the same drug in another product.

It cannot be assumed that generic drugs will produce the same clinical effect as the innovator product. The comparable effectiveness of oral medications that act through distribution in the bloodstream can logically be based on determinations of serum levels. This is not true of inhaled drugs, however, where serum levels cannot be reliably measured. Of greater importance, serum levels have no relevance to drug effect at a receptor level within the bronchial passageways. In addition, inhaled products may contain propellants and excipients that are different from those in products. The potential for excipients to produce significant adverse effects in some patients is well documented.[1] Although generic equivalents are not currently available for most inhaled drugs used in the treatment of asthma, these issues will require careful consideration by those entrusted with the responsibility of establishing guidelines for the study of therapeutic equivalence of inhaled drugs.

Physicians who treat asthma are particularly affected by issues relating to therapeutic equivalence. A large proportion of the treatment armamentarium for asthma is in the form of inhaled delivery systems, often associated with different devices for delivery of the product. Most concern at this time, however, has focused on the safety of theophylline substitution because theophylline, which is still used extensively in the treatment of asthma, has a narrow therapeutic index. On the basis of individual patient response and serum theophylline levels, theophylline products are often not interchangeable. Substitution of one product for another can, therefore, lead to toxicity or decreased efficacy.[2]

This is a major issue because of laws that allow pharmacist substitution for prescribed drugs in 50 states. In this situation, the pharmacist can legally substitute another product of the same chemical composition without consulting the physician who prescribed the medication, unless the physician specifically prohibits such substitution by so writing on the prescription.[3]

A number of factors, intrinsic as well as extrinsic, can mediate response to different medications within the same class of drugs. As a result, a patient may benefit from or tolerate one β_2– selective agonist but not another, or one theophylline preparation and not another. It is now recognized that individual patient variability and subtle product differences may produce dissimilar responses to different products of the same medication.[4] A unique effect may also be observed when one medication is used with two different devices.

These unanticipated deviations in patient response to medications frequently used in the treatment of asthma require vigilance on the part of health care providers treating asthma. Assumptions about the comparability of products are no longer acceptable, and differences in patient response to different products must be anticipated in some patients.

REFERENCES

1. Koepke JW, Christopher KL, Chai H, Selner JC. Dose-dependent bronchospasm from sulfites in isoetharine. JAMA 1984;251:2982-3.
2. Baker JR Jr, Moessner H, Gonzales U, et al. Clinical relevance of the substitution of different brands of sustained-release theophylline. J ALLERGY CLIN IMMUNOL 1988;81:664.
3. Sly RM, Bierman CW, Brandon ML, et al. Pharmacist substitution of slow-release theophylline products [Letter]. J ALLERGY CLIN IMMUNOL 1989;84:131-2.
4. Nicklas RA. Paradoxical bronchospasm associated with the use of inhaled beta agonists. J ALLERGY CLIN IMMUNOL 1990;85:959-65.

Polypharmacy

Summary statements

- Polypharmacy may be necessary and, indeed, desirable in the management of patients with asthma.
- The physician must guard against the unnecessary addition of medications that could increase morbidity and mortality in asthmatic patients.

Polypharmacy may be necessary and, indeed, desirable in the management of patients with asthma. The need for inclusion of anti-inflammatory drugs in the treatment of asthma, in addition to sympathomimetic bronchodilators, is based on the recognized importance of bronchial inflammation in perpetuating symptoms of asthma. Polypharmacy may therefore be essential in reaching the goal of preventing and, if necessary, arresting the long-term sequelae of bronchial inflammation.

Patients with exercise-induced bronchospasm may require pretreatment with an inhaled β-agonist, as well as orally inhaled cromolyn sodium, in addition to more effective control of underlying airway inflammation, to obtain a desired level of activity. Use of antihistamines, decongestants, intranasal cromolyn, intranasal corticosteroids, or antibiotics may be necessary to eradicate or control rhinosinusitis and remove a source for exacerbation of lower respiratory tract symptoms. Asthma exacerbations may also be decreased by control of gastroesophageal reflux and esophageal irritation with antacids and H_2 receptor antagonists. The use of multiple medications in the same patient is often necessary to adequately prevent asthmatic symptoms.

Because bronchoconstriction is often the end result of different pathophysiologic events, optimal control may require concomitant use of bronchodilators that act through different pathways (e.g., β-agonists, methylxanthines, and anticholinergic drugs). The additive effect from the concomitant administration of different types of bronchodilators has been well documented. Failure to add additional medications needed to treat multiple triggers or pathophysiologic features of asthma may lead to less than optimal control of asthma.

On the other hand, the physician must guard against the unnecessary addition of medications for the treatment of asthma, as well as for other conditions. Correct decision making regarding addition of medications requires a careful, individualized benefit/risk assessment of the medications the patient is currently receiving. Although it is generally accepted that it is not appropriate to add one medication to treat symptoms produced by another medication, this situation may not always be obvious. For example, paradoxical bronchospasm produced by an inhaled β-agonist should be corrected by appropriate substitution rather than addition of another bronchodilator based on the incorrect assumption that the patient's symptoms represent undertreatment. The continued administration of any asthma medication without continuing reassessment of its efficacy and safety in each patient should be avoided.

An enlightened assessment that the patient needs several different types of drugs to effectively manage asthma is an acceptable and, in fact, encouraged approach. However, adding another drug of the same class as a reflex to an increase in asthmatic symptoms is not generally acceptable, not only because it may produce an unfavorable benefit/risk ratio but also because it may bypass utilization of another class of drugs, especially corticosteroids. This approach may be particularly dangerous in the elderly asthmatic patient, who is more likely to have underlying cardiovascular disease or to be receiving increasingly large numbers of medications. Hypokalemia, which has been demonstrated after the use of β-agonists and is potentially augmented by administration of corticosteroids or theophylline, may have a greater clinical effect in patients taking potassium-depleting diuretics.

β-Agonists or methylxanthines are frequently added to a treatment program already consisting of one of these two types of bronchodilators. Some patients demonstrate increased bronchodilation with the addition of a product of the other class, but other patients do not. In patients who fail to demonstrate improvement in symptoms with concomitant administration of a β-agonist and theophylline, the increased potential for adverse reactions does not justify the continued use of such a program. Although adverse cardiovascular effects have not been consistently

demonstrated in humans, lesions of myocardial necrosis, cardiac arrhythmias, and increased mortality have been demonstrated in animals when β–agonists and methylxanthines have been administered together.

It is generally recognized that macrolide antibiotics, as well as ciprofloxacin and cimetidine, may significantly alter theophylline metabolism when given concomitantly with theophylline. The increased potential for terfenadine and astemizole, when given concomitantly with macrolide antibiotics or ketoconazole, to prolong the QT interval and increase risk of ventricular arrhythmias, such as torsade de pointes, has recently been emphasized.

The number and variety of medications used to control asthma must therefore be individualized. Failure to add a potentially beneficial medication may be just as inappropriate as the addition of an unnecessary medication. When to use, or not to use, polypharmacy should be based on a careful analysis of the benefits and risks associated with such an approach in each patient.

F. IMMUNOTHERAPY IN THE ASTHMATIC PATIENT

Summary statements

- Allergen immunotherapy can be effective in patients with asthma and may lessen the effect of chronic allergen stimulation on hyperresponsive airways. In most cases allergen immunotherapy should be considered as a part of a well–planned program that includes pharmacotherapy and avoidance measures.
- Allergen immunotherapy should be considered a long–term therapeutic modality in patients with allergic asthma.
- Patient compliance is essential for the effective and safe application of allergen immunotherapy.
- Although precise mechanisms for efficacy of allergen immunotherapy are unknown, several specific immunomodulatory pathways have been implicated.
- Immediate and delayed local and systemic reactions may occur in the course of allergen immunotherapy.
- Patients should be informed about the relative risks of immediate and delayed reactions associated with allergen immunotherapy.
- Both patients and medical personnel should be instructed in detail about prevention and treatment of reactions to allergen immunotherapy.
- Although life–threatening reactions during the course of allergen immunotherapy are rare, fatalities can occur. Therefore supervising health care providers should be prepared to treat such reactions as promptly and effectively as possible.

Allergens not only precipitate exacerbations of asthma but also are important risk factors for the development of asthma. Persistent allergenic stimulation may induce or enhance chronic bronchial inflammation associated with chronic asthma. Double–blind studies in children and adults show that allergen immunotherapy reduces asthma symptoms associated with exposure to cat dander,[1] house dust mite,[2] *Alternaria* mold,[3] and grass pollen[4]; reduces specific bronchial reactivity to the allergen; and appears to reduce the amount of specific IgE antibody, as measured by skin sensitivity to the allergen. Late asthmatic reactions associated with the inflammatory bronchial response to an allergen and induction of bronchial hyperresponsiveness are also reported to be modified by allergen immunotherapy. Thus allergen immunotherapy may not only reduce sensitivity to allergen exposure but have even wider application in the treatment of allergic asthma.

Allergen immunotherapy is unlikely by itself to completely ameliorate asthma because (1) asthma is usually multifactorial and patients with allergic asthma can be significantly affected by nonallergic factors and (2) immunotherapy is allergen specific and is unlikely to reduce or eliminate sensitivity to all allergens to which a patient with multiple sensitivities is exposed. Therefore the primary goal of allergen immunotherapy is to reduce allergen sensitivity in conjunction with other therapeutic modalities (i.e., allergen and irritant avoidance and pharmacotherapy). A long–term goal of allergen immunotherapy, however, should be to reduce the need for asthma medication. On the other hand, pharmacotherapeutic agents used in the treatment of asthma do not interfere with allergen immunotherapy, and continuance of asthma medications is essential when immunotherapy is initiated and until sufficient relief of symptoms exists to warrant reduction of pharmacotherapy. Allergen immunotherapy can be efficacious in patients with IgE–mediated asthma but has no role in non–IgE–mediated asthma, chronic bronchitis, or emphysema.

Allergen avoidance should always be the first consideration in managing allergen–induced asthma. Immunotherapy should be considered when avoidance is not adequate or possible and it is strongly suspected that exposure to allergens, to which the patient has IgE antibodies, contributes significantly

to exacerbations of the patient's asthma. Correlation of a comprehensive allergic history with demonstration of specific IgE antibodies by in vitro or skin tests will usually identify relevant allergens. However, causal relationships between allergen exposure and asthma may not be obvious historically, and selection of inhalant allergens (e.g., house dust mite) for immunotherapy may need to be based on a combination of available evidence.

Careful selection of allergens and cautious progression to maximally tolerated doses are important elements in the success of immunotherapy. The optimal length of treatment with allergen immunotherapy is unknown. A treatment period of 3 to 5 years is common, although continuation for longer periods may be appropriate, and patients can and have safely received immunotherapy for many years without long-term adverse effects developing. The progress of patients receiving immunotherapy must be reassessed periodically, and in patients who have not improved significantly immunotherapy should be discontinued.

The mechanism underlying the effectiveness of immunotherapy is still not completely understood. Long-term immunotherapy may result in (1) an increase in specific IgG (blocking) antibodies,[5] (2) a reduction in specific IgE antibodies[6, 7] and corresponding skin test responses,[8] (3) T-cell tolerance,[9] and (4) an increase in specific T-cell suppressor populations.[10] In addition, allergen immunotherapy can blunt the late-phase response associated with allergen-induced bronchial inflammation[2] and may diminish bronchial hyperresponsiveness to other agents in addition to the specific allergen used for treatment. In patients with seasonal asthma, successful immunotherapy also blunts the expected pollen-induced seasonal rise in specific IgE as well.[11]

Local reactions from the injection of allergenic extracts include (1) the immediate development of a wheal and erythema at the site of the injection; (2) the development of more diffuse swelling persisting for several hours or, in severe cases, for 24 hours or more; and (3), rarely, delayed reactions beginning 1 hour or more after injection.[12] Systemic reactions are infrequent and rarely may be life threatening or even fatal.[13] Asthmatic symptoms occurring immediately before an allergy injection are a significant risk factor for a fatal systemic reaction. In addition, some patients may have an exacerbation of asthma associated with immunotherapy requiring reduction of the dose of allergenic extract.[14] Neither patient nor physician may always appreciate the role of immunotherapy in such exacerbations. Therefore the effect of immunotherapy on asthma must be continually reassessed, and systemic reactions can be minimized by postponing allergen administration when the patient is having an exacerbation of symptoms.

To minimize the potential for severe life-threatening reactions from immunotherapy, the following are recommended: (1) allergen administration should be under direct medical supervision; (2) personnel should be carefully trained in the technique for administration of allergenic extracts, with an understanding of the acceptability of administering a given dose on any given day, with a knowledge of potential adverse effects, and with a capability to provide emergency care including prompt cardiopulmonary resuscitation (selection of personnel who use good judgment in decision making cannot be overemphasized); (3) an adequate observation period should be provided after each injection, generally 20 to 30 minutes, but longer in individual cases, in a setting that allows for the early recognition and prompt treatment of systemic reactions; (4) adequate rescue modalities, including epinephrine, oxygen, and intravenous fluids, should be readily available. Second-line drugs such as hydrocortisone and diphenhydramine should also be on hand. Physicians and other health care providers should be prepared to treat anaphylaxis should it occur; and (5) the patient should be questioned about ongoing asthmatic symptoms, and, if needed, peak flow rates or other pulmonary function measures should be measured before the patient receives an injection and repeated before the patient leaves the medical facility.[12]

Although the risk of a fatal reaction to allergenic extracts is extremely small and often unpredictable, it is the physician's responsibility to inform the patient that compliance will maximize the prevention and proper treatment of these reactions. Patient compliance is essential for effective allergen immunotherapy. Patient compliance, in turn, depends on patient understanding of the goals of immunotherapy and maximizing patient convenience. This understanding requires education of the patient by the physician in regard to expectations from such a program.

It has been proposed that allergen immunotherapy in patients with underlying connective tissue disease or other diseases with immunologic features might place the patient at increased risk.[15] However, this is speculative and requires further study. Patients taking β-blockers must be selected for allergen immunotherapy on the basis of a careful appraisal of the benefit/risk of starting immunotherapy and an awareness of the potential for anaphylaxis that may be

resistant to conventional forms of treatment. In addition, consideration should be given to discontinuing allergen immunotherapy in patients who have repeated severe reactions that are not prevented by adjustment of the dosage regimen. Although continuation of maintenance immunotherapy in pregnant asthmatic patients is acceptable, immunotherapy generally should not be initiated in pregnant patients.[16]

In summary, allergen immunotherapy is effective in IgE–mediated diseases, including asthma, provided that allergens comprising the allergenic extract are carefully selected and the allergenic extract is administered in optimal doses with prudent regard for avoidance of severe systemic reactions.

REFERENCES

1. Taylor WW, Ohman JL, Lowell FC. Immunotherapy in cat-induced asthma: double–blind trial with evaluation of bronchial responses to cat allergen and histamine. J ALLERGY CLIN IMMUNOL 1978;61:283-7.
2. Warner J, Price JF, Soothill JF, Hey EN. Controlled trial of hyposensitization to *Dermatophagoides pteronyssinus* in children with asthma. Lancet 1978;2:912-5.
3. Metzger WJ, Donnelly A, Richerson HB. Modification of late asthmatic responses during immunotherapy for *Alternaria*–induced asthma. N Engl Regional Allergy Proc 1983;3:270.
4. Ortolani C, Pastorello E, Moss RB, et al. Pollen immunotherapy: a single year double blind placebo–controlled study in patients with grass pollen induced asthma and rhinitis. J ALLERGY CLIN IMMUNOL 1984;73:283.
5. Lichtenstein LM, Norman PS, Winkenwerder WL. Clinical and in vitro studies on the role of immunotherapy in ragweed hay fever. Am J Med 1968;44:514-24.
6. Lichtenstein LM, Ishizaka K, Norman PS, Sobotka AK, Hill BM. IgE antibody measurements in ragweed hay fever: relationship to clinical severity and the results of immunotherapy. J Clin Invest 1973;52:472-82.
7. Gleich GJ, Zimmerman BS, Henderson LL, Yunginger JW. Effects of immunotherapy on immunoglobulin E and immunoglobulin G antibodies to ragweed antigens: a six year prospective study. J ALLERGY CLIN IMMUNOL 1982;70:261-71.
8. Van Metre TE Jr, Marsh DG, Adkinson NF Jr, et al. Immunotherapy decreases skin sensitivity to cat extract. J ALLERGY CLIN IMMUNOL 1989;83:888-99.
9. Hsieh KH. Altered interleukin–2 (IL–2) production and responsiveness after hyposensitization to house dust. J ALLERGY CLIN IMMUNOL 1985;76:291-4.
10. Rocklin RE, Sheffer AL, Greineder DK, Melmon KL. Generation of antigen–specific suppressor cells during allergy desensitization. N Engl J Med 1980;302:1213-9.
11. Van Meter TE, Adkinson NF. Immunotherapy for aeroallergen disease. In: Middleton E, Reed C, Ellis E, et al, eds. Allergy principles and practice. St Louis: Mosby, 1988: 1327-43.
12. Norman PS, Van Matre TE Jr. The safety of allergenic immunotherapy. J ALLERGY CLIN IMMUNOL 1990;85: 522-5.
13. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). J ALLERGY CLIN IMMUNOL 1987;79:660-77.
14. Thompson RA, Bousquet J, Cohen S, et al. Current status of allergen immunotherapy. Lancet 1989;1:259.
15. Phanuphak P, Kohler PF. Onset of polyarteritis nodosa during allergic hyposensitization treatment. Am J Med 1980;68:479-85.
16. Metzger WJ, Turner E, Patterson R. The safety of immunotherapy during pregnancy. J ALLERGY CLIN IMMUNOL 1978;61:268-72.

G. PATIENT EDUCATION

Introduction

Perhaps William Osler had education and patient compliance in mind when he remarked how it was more important to know what sort of patient had a disease than what sort of disease the patient had. In the following sections, the issues of cooperative management, rehabilitation, and compliance will be addressed.

Patients must understand the nature of their asthma, how to monitor it, and what medications should be taken at a given time to achieve adequate control. In fact, adequate and appropriate asthma treatment and rehabilitation should provide enough control of the patient's asthma to achieve a productive meaningful life, not just a vegetative sedentary one. A child who is appropriately functioning in an asthma camp setting, for example, is learning to live a relatively normal life with his or her peers.

Patient noncompliance with medication regimens reflects a breakdown in patient–physician communication and knowledge about the potential seriousness of asthma, and other negative factors. Successful programs to improve patient compliance combine education with other techniques. The patient's involvement in planning and tailoring regimens may improve compliance. Lack of adherence to a medication program in an asthmatic patient is equally disruptive and inconvenient for the patient and family. Unfortunately, it may also be partly responsible for the increased mortality and morbidity from asthma in many countries.

Cooperative management through education

Summary statements

- Educating asthmatic patients, parents, and family about their disease and methods of treatment is essential in the effective control of asthma.
- Educational programs for asthmatic patients have generally been successful in producing increased patient understanding of asthma and decreased morbidity.

- Patients should be educated to effectively monitor their asthmatic status and know how to respond to changes in their status.
- Patients should be educated in the proper technique required for the effective use of inhaled medications.
- Physicians should recognize patient concerns and resolve these concerns through increased patient confidence in the management approach and their ability to implement this approach in the treatment of their asthma.
- Asthma education requires an understanding by the patient and physician of certain basic concepts related to pathophysiology and treatment but must, in addition, be individualized for each asthmatic patient.

Because of other demands and time constraints, health care providers too often fail to allocate appropriate time to ensure patient understanding of asthma. Recent interest in this problem has culminated in the National Asthma Education Program of the National Heart, Lung, and Blood Institute, which focuses on cooperative management through education.[1] Cooperative management through education is part of an approach to patient care that has previously been called asthma self–management.[2] It is, in reality, a cooperative venture, in which health care providers educate patients about asthma and then work with them to achieve sound asthma control. The patient must understand the importance of effective asthma control, recognizing that asthma can be lethal if there is failure on the part of the patient to recognize the severity of the condition. The patient must not only understand asthma and the reasons why such awareness is important but also be mentally and physically capable of using such knowledge through the perfection of necessary skills (e.g., techniques for administering inhaled medications, measurement of peak flow rate).

Cooperative management through education is the process by which medical information and directions about asthma are communicated to the patient by the health care provider and is an indispensable part of the therapeutic approach to the asthmatic patient. This approach, if done properly, should alleviate patient concern. The health care provider must determine not only what the patient *needs to know* but also what the patient *wants to know*. Therefore this approach cannot be entirely didactic: it must be done in a setting that encourages patient participation in the interactive learning process.

An effective program of cooperative management through education can significantly improve the care of asthmatic patients through increased compliance, formulation of an individualized treatment plan (in some cases a crisis plan), more effective monitoring of patient status through use of peak flow and other pulmonary function measurements as well as symptom diaries, and improved patient attitude associated with greater confidence and cooperation.[3, 4]

To achieve a better asthma program, the patient should be able to recognize the symptoms of asthma, including cough in the absence of wheezing, dyspnea, or tightness in the chest. The patient must know the names of medications prescribed, including indications for, method, and time of administration and potential side effects; know indications for obtaining medical assistance when symptoms occur; know how to monitor the condition, including the use of objective measures; be able to identify possible asthma triggers and methods of their avoidance and treatment; understand the role of emotions with regard to symptoms; recognize potential support from other patients with asthma; understand the relationship between asthma and other allergic conditions, especially allergic rhinitis; be aware of the importance of exercise while recognizing its potential effect on asthma; understand the role of immunotherapy; appreciate the most effective ways to communicate with health care providers; be aware of potential patterns of asthma based on age, environment, and known or suspected triggers; know the complications of asthma; and understand the pathophysiology of asthma as it relates to an understanding of asthma medications.[5]

These approaches have resulted in documented benefit as demonstrated by improvement in adjustment to illness; better school attendance and performance; reduction in emergency department visits and emergency visits to health care providers, hospitalizations, and symptoms; improvement in patient behavior in regard to the disease; and improvement in objective parameters such as peak flow rates.[4] Such improvement has been closely associated with prevention of attacks through recognition of and action on early signs, effective use of medications, better management of exacerbations, and the development of a crisis plan for emergency management.

Educational programs for patients with asthma have taken many different forms. Most of what is known about such programs has come from evaluation in children. Some have found that the use of a nurse educator to maintain patient contact has been very useful. Programs have also been designed for use in physician's offices, community

locations, schools, home settings, residential treatment centers, and asthma camps.

Practicing physicians must begin to consider the methods by which they will incorporate asthma education into the treatment program for each of their asthmatic patients. This may be accomplished by a knowledgeable asthma–educated physician allocating a greater amount of time for patients with asthma; by educating other health care providers within the office in the techniques of patient education and freeing them from other responsibilities so that they may effectively educate asthma patients; by using videos; or by encouraging and working with patients to stimulate their participation in asthma education programs in the community. The physician can receive guidance in these approaches through specialty organizations such as the American Academy of Allergy Asthma and Immunology, the American College of Allergy Asthma and Immunology, the American Lung Association, the Asthma and Allergy Foundation of America, Mothers of Asthmatics, and the National Jewish Hospital, all of which are extensively involved in asthma patient education. Examples of available pediatric programs include (1) outpatient programs such as Asthma Care Training for Kids (ACT for Kids), Air Power, Open Airways, Living with Asthma, and Family Asthma Programs; (2) emergency department programs (e.g., You Can Control Your Asthma, Health Belief Model, Case Western Reserve, and Self-Treatment by Adult Asthmatics); (3) home or office programs such as Superstuff, Pittsburgh Program, and Asthma Command (a computer–assisted program); and (4) school programs such as Open Airways at School and *Teaching Myself About Asthma.*[6] Two randomized, controlled self-management programs for adult asthma have been evaluated and found to be effective and cost beneficial.[7, 8]

REFERENCES

1. Parker S, Mellins RB, Sogn DD. Asthma education: a national strategy. Am Rev Respir Dis 1989;140:848-53.
2. Wilson–Pessano SR, Mellins RB. Workshop on asthma self–management: summary of workshop discussion. J ALLERGY CLIN IMMUNOL 1987;80(suppl):487-90.
3. Feldman CH, Clark NM, Evans D. The role of health education in medical management in asthma. Clin Rev Allergy 1987;5:195-205.
4. Mellins RB. Patient education is key to successful management of asthma. J Respir Dis 1989;10(suppl):S47-52.
5. Clark NC. Asthma self–management education: research and implications for clinical practice. Chest 1989;95:1110-3.
6. Rachelefsky GS. Review of asthma self–management programs. J ALLERGY CLIN IMMUNOL 1987;80(suppl):506-11.
7. Kotses H, Bernstein IL, Bernstein D. A self-management program for adult asthma. Part I: development and evaluation. J ALLERGY CLIN IMMUNOL 1995;95:529-40.
8. Bailey WC, Richards JM Jr, Brooks CM. A randomized trial to improve self-management practices of adults with asthma. Arch Intern Med 1990;150:1664-8.

Compliance in asthma

Summary statements

- Patient noncompliance can be manifested as underuse, overuse, or erratic use of prescribed medication.
- Improvement in patient compliance may be influenced by knowledge about therapy, the patient–physician relationship, perceived seriousness of the condition, perceived benefit of intervention, complexity of the program, frequency of taking the medication, and cost.
- The most successful programs to improve patient compliance combine techniques of education, reinforcement, and family interactions.
- Lack of patient compliance is one of the most important underrecognized problems in medicine today and can be due to psychologic, economic, or educational factors.

Compliance may be considered acceptance by the patient of the physician's prescribed therapeutic program. However, actual use can be classified in one of four ways:

1. Appropriate use: The patient takes the medication in a way that conforms satisfactorily to prescribed use.
2. Underuse: The patient persistently fails to take as much medication as prescribed.
3. Overuse: The patient frequently takes more medication than prescribed.
4. Erratic use: The patient both overuses and underuses prescribed medication at different times.

The goal of the therapeutic program in asthma should be the achievement of maximal improvement in pulmonary function with normalization of activities while producing minimal, if any, side effects. Ideally, these goals should be the same for patient and physician. This occurrence, however, requires patient education and patient involvement toward the desired goal of following the prescribed therapeutic program.

When it is considered that to comply with the medical program a number of behavior changes might be required, the potential problems with patient compliance may be better understood. The therapeutic program for asthma may be complex, necessitating a number of medications throughout

the day, some of which require inhalation of a substance in a defined way or oral ingestion of a pill at a certain time. Other behavior changes include avoidance of smoking and exposure to irritant fumes and odors, and environmental changes to decrease exposure to house dust mite and animal proteins. Understanding the rationale for possible changes in behavior might help the patient accept them and lead to better compliance.

The patient's lack of knowledge about the prescribed regimen may contribute to noncompliance,[1-3] but knowledge alone does not lead to compliance. Nevertheless, it is important to inform the patient as much as possible what the expectations are regarding medications and what the rationale is for the various recommendations. For example, the use of an inhaler as opposed to a tablet to deliver medicine is less convenient, but if the patient understands that there should be fewer side effects, the likelihood of compliance is greater.

Certain factors have been determined to affect patient compliance. The complexity of the program, particularly regarding medications, is known to influence compliance,[1,4] as is the frequency with which the medication must be taken.[4-6] Compliance declines as the number of pills prescribed per day increases.[7,8] In addition, pill counts, traditionally used as a compliance measure in clinical trials, commonly overestimate actual consumption of medications.[7] Compliance improves in the period immediately before and after a clinic visit.[9] If the cost of complying with the program is high, the patient may be unable to fully cooperate and certain parts of the program may be skipped because of lack of understanding of their importance. Treatment programs may have to be individualized recognizing religious, social, cultural, and economic factors. Therapeutic regimens planned by health care providers without taking into account a patient's social stresses may not be followed. Mutual determination of compliance strategies is a way to help patients develop a perceived sense of control.

Medication compliance diminishes with the passage of time.[10] This phenomenon suggests that the patient should be seen periodically and evaluated regarding achievement of goals of the program (pulmonary functions and level of activity). Studies attempting to determine drug compliance by monitoring blood levels and other methods have not been shown to have a lasting impact on compliance, although they may influence behavior during the course of the study. Self-monitoring with a peak flow meter is a means of reinforcing effective therapy over time. Patients can see the impact of alterations in their therapy and in some instances can see immediate changes with different interventions. At the very least, such self-monitoring allows the patient more control over the disease. Various comprehensive compliance programs have been developed that combine techniques of education, reinforcement, and family interaction. They include (1) Open Airways of Columbia University,[11] Living with Asthma developed at the National Asthma Center in Denver,[12] and Asthma Care Training (ACT).[13] Outpatient computer-oriented programs such as Asthma Command, self-administered programs such as Superstuff, and school-based programs have been reviewed elsewhere.[14] Noncompliance regardless of age, ethnic background, geographic location, educational level, religious affiliation, or marital status has been confirmed in many published studies,[4,15,16] including some that use state-of-the-art electronic monitoring devices.[7,17]

Attempts to monitor compliance are fraught with difficulty because patients may falsify their compliance perhaps to have monitors think well of them.[18]

Lack of patient or family adherence to a medication program clearly represents a significant problem in clinical medicine.[19,20] Patients and members of the family can take an active role in their treatment program if given the skills, encouragement or motivation, and support to do so. The extent of this possible involvement varies—and at times particularly in adolescents—but all patients should: (1) be given basic information about their disease and medications, (2) be taught how to recognize and treat their symptoms, and (3) know when and whom to call for help. "Compliance" not only involves the use of medications and control of the environment but also involves appropriate and timely use of medical facilities by knowing when, where, and how to get help as needed. The goal is "cooperative management" of asthma to improve the quality of health.[21-24]

REFERENCES

1. Becker M, Maiman L. Strategies for enhancing patient compliance. J Commun Health 1980;6:113-35.
2. Vertinsky P, Yang C, Macleod P, Haardwick D. A study of compliance factors in voluntary health behaviour. Int J Health Educ 1976;19:16-28.
3. Kirscht JB, Rosenstock IM. Patient adherence to anti-hypertensive medical regimens. J Commun Health 1977;3:115-25.
4. Haynes RB, Taylor DL, Sackett DL, eds. Compliance with therapeutic regimens. Baltimore: Johns Hopkins University Press, 1976.
5. Spector SL. Is your asthmatic patient really complying? Ann Allergy 1985;55:552-6.
6. Ayd FJ Jr. Single daily dose of anti-depressant. JAMA 1974;230:263-4.
7. Cramer JA, Mattson RH, Prevey ML, et al. How often is

medication taken as prescribed? A novel assessment technique. JAMA 1989;261:3273-7.
8. Eisen SA, Miller DK, Woodward RS, et al. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med 1990;150:1881-4.
9. Cramer JA, Scheyer RD, Mattson RH. Compliance declines between office visits. Arch Intern Med 1990;150:1509-10.
10. Sackett D, Hynes R, Gibson E, et al. Patient compliance with anti-hypertensive regimens. Patient Counseling Health Educ 1978;1:18-21.
11. Clark NM, Feldman CH, Evans D, et al. The impact of health education on frequency and cost of health care use of low income children with asthma. J ALLERGY CLIN IMMUNOL 1986;78:104-14.
12. Creer TL, Backiel M, Ullman S, Leung P. Living with asthma. NIH publication 84-2364. Bethesda, Maryland: National Heart, Lung, and Blood Institute, 1985.
13. Lewis CE, Rachelefsky GS, Lewis MA, de la Sota A, Kaplan M. A randomized trial of ACT (asthma care training) for kids. Pediatrics 1984;74:478-86.
14. Rachelefsky GS. Review of asthma self-management programs. J ALLERGY CLIN IMMUNOL 1987;80(suppl):506-13.
15. Eraker SA, Kirscht JP, Becker MH. Understanding and improving patient compliance. Ann Intern Med 1984;100:258-68.
16. Tinkleman DA, Vanderpool GE, Carroll MS, et al. Compliance differences following administration of theophylline at six and twelve hour intervals. Ann Allergy 1980;44:282-6.
17. Spector SL, Kinsman RA, Mawhinney H, et al. Compliance of patients with asthma with an experimental aerosolized medication: implications for controlled clinical trials. J ALLERGY CLIN IMMUNOL 1986;77:65-70.
18. Mawhinney H, Spector SL, Kinsman RA, et al. Compliance in clinical trials of two nonbronchodilator, anti-asthma medications. Ann Allergy 1991;66:294-9.
19. Spector SL, Lewis CE, Feldman CH, et al. In: Bernstein IL, Hargreave FE, Nicklas RA, Reed CE, eds. Report of the American Academy of Allergy and Immunology task force: guidelines for clinical investigation of nonbronchodilator, antiasthmatic drugs. J ALLERGY CLIN IMMUNOL 1986;78(suppl):529-33.
20. Sbarbaro JA, Steiner JF. Noncompliance with medications: vintage wine in new (pill) bottles. Ann Allergy 1991;66:273-5.
21. McCann DP, Blossom J. The physician with patient education from theory to practice. West J Med 1990;153:44-9.
22. Clark NM. Asthma self management education: researched implications for clinical practice. Chest 1989;95:1110-3.
23. Blessing-Moore J. Self-management of pediatric asthma. Clin Rev Allergy 1987;5:191-3.
24. Kotses H, Bernstein IL, Bernstein D. A self-management program for adult asthma. Part I: development and evaluation. J ALLERGY CLIN IMMUNOL 1995;95:529-40.

Rehabilitation of the patient with asthma

Summary statements

- Specific goals of rehabilitation include maximizing school or work attendance, encouraging participation and productivity, encouraging participation in age-appropriate physical activities with peers, promoting self-esteem and self-confidence, and decreasing anxiety about the illness.
- Information needed to evaluate the need for and the effectiveness of a rehabilitation program should be obtained in the course of caring for a patient on a regular basis.
- Problems in any area of rehabilitation should prompt the initiation of specific measures to correct this deficiency.
- Community resources including structured fitness programs are available and should be used when appropriate.
- Rehabilitation goals should be coordinated and monitored by the physician so that therapy can be adjusted appropriately.

Definition and general principles. Rehabilitation involves all aspects of the patient's care, with the goals of expanding as much as possible the patient's potential (mental, social, and economic) while minimizing restrictions from both disease and its treatment. Achieving these goals requires careful coordination of medical care, asthma education, care in the community at large (especially in the school or workplace), physical fitness programs, and, in some cases, psychologic care. Care of the asthmatic patient involves a team of health care and educational professionals, with the patient as a full partner. As a coordinator of care, the physician must identify the professionals needed for the team and maintain regular contact with them.

Information needed to evaluate the need for and the effectiveness of a rehabilitation program should be obtained in the course of caring for a patient on a regular basis. Thus, in addition to assuring adequacy of medical care and asthma education, the physician should be aware of the patient's performance in the school or workplace, the level of physical activity, and the presence of psychologic problems.

Goals of rehabilitation. The goals of rehabilitation are as follows: to maximize school or work attendance, participation, and productivity; to allow participation of the patient in age-appropriate physical activities with peers; and to promote self-esteem and self-confidence and decrease anxiety about the illness.

Mechanisms of rehabilitation

Screening for identification of deficiencies. Patients (and family members) should be questioned about school or work absences and performance. The physician should be concerned about *absences* if more than 7 to 10 days of school are missed per

year or absence from work is more than the maximum allowed per year.[1] The physician should be concerned about *performance* of the patient (and the family) and whether asthma or asthma medications are interfering with performance.

Physical fitness/physical activity. Exercise-induced asthma may limit a patient's capacity to exercise and result in decreased fitness. Because many patients assume that having asthma means not being able to be active, they may not identify as problems their exercise limitation and decreased level of fitness. The physician must initiate questioning concerning the patient's level of activity and capacity to keep up with peers. In addition, the physician and the patient must agree on what the goals of asthma therapy should be with regard to exercise. Examples of goals for children are being able to participate in organized physical education programs at school and to play actively with friends outside of school. Children with asthma can be (and should be) as fit as their peers.[2] Standardized tests for determination of fitness are performed in regular physical education programs at school on a yearly basis and are an excellent mechanism to monitor this goal.

An example of goals for adults is being able to participate in physical activities (sports) of their choice, including a regular aerobic conditioning program.[3] Interference of asthma and asthma medications with sexual activity is a concern of many patients; it is important to explore the possibility that this interference exists.

Being unable to achieve these physical activity goals should initiate concern and should stimulate modification of medical programs.

Psychologic functioning. A method of screening for the presence of psychologic problems is for the physician to ask the following questions:

1. Is there evidence of persistent medical noncompliance or poor self-care?
2. Is the patient aware of anger, frustration, or antagonism within the family?
3. Have there been important losses to the patient, such as death of spouse, parent, child; divorce; loss of employment; or geographic relocation?
4. Is the patient concerned about depression or have references to death or expressions of hopelessness been made?
5. Has there been a notable personality change, unusual behavior, emotional lability, decline in school or work function, or onset of drug or alcohol use or abuse?
6. Is there evidence of sexual or physical abuse?

Positive answers to any of these questions should initiate concern.

A number of longer, but standardized, instruments are available that can be used to detect the presence of psychologic problems in both children and adults (e.g., Achenbach Child Behavior Checklist,[4] Coopersmith Self-Esteem Inventory, Minnesota Multiphasic Personality Inventory,[5] and several indices to detect depression.[6]

Treatment of problems in individual patients

PROBLEMS IN THE SCHOOL OR WORKPLACE. For patients with excessive absences, communication between physician, patient or parent, and work supervisor or schoolteacher and nurse may be used to obtain information about the reason(s) for the increases in absences so that appropriate intervention can be initiated.

Reported interference of asthma or asthma medications with performance may require modification of the therapeutic regimen. The work supervisor or schoolteacher may be needed to collect data independent of the patient's observations about the levels of performance before and after the changes in medications.

PROBLEMS WITH PHYSICAL FITNESS AND PHYSICAL ACTIVITY. The health care provider should educate the patient about exercise-induced asthma and the use of medication prophylactically. Prescribe medications to prevent exercise-induced asthma and monitor their effectiveness with a diary (and perhaps a peak flow meter).

Patients with limitations in physical activity that cannot be overcome may need to participate in a specialized fitness program. Therapeutic modalities in such fitness programs may include breathing exercises, relaxation techniques, and one of several forms of aerobic exercise. All programs should include activities suited to the patient's personality and resources to assure that it will be sustainable and lifelong.

PROBLEMS IN PSYCHOLOGIC FUNCTIONING. Suspicion of psychologic problems interfering with control of asthma should result in referral to a professional knowledgeable about issues relevant to patients with asthma. Plans for treatment require communication between the therapist and the physician to define problems, goals, and criteria for follow-up.

Suggestions on how rehabilitation of patients can be approached on a community-wide basis

PHYSICIAN INFLUENCE. Physicians can have a significant impact on the approach of the community to patients with asthma. Examples of areas where this impact can be realized are decreasing fears of having someone with asthma in school or the workplace and

decreasing the tendency for people in the community to reject individuals with asthma because of their disease. Providing this impact requires a commitment by the community that extends beyond the specific care of individual patients. It is also obvious that this impact can be achieved only by spending time to influence the attitudes of the community and the practices of individuals in it.

FACILITATE NORMAL ATTENDANCE AND PERFORMANCE IN THE SCHOOL OR WORKPLACE. Teachers and supervisors at the school or workplace may need education about asthma. In-service programs about asthma and its treatment may be useful.

The school system may need help in changing rules to allow patients with asthma to use medications during school (e.g., use of a metered-dose inhaler before physical education or recess).

FACILITATE NORMAL PHYSICAL FITNESS AND PHYSICAL ACTIVITY. The health care provider should become familiar with the character of the physical education and athletic programs in the school as well as resources outside of the school or workplace that are available to patients with asthma for ongoing assistance with physical conditioning (e.g., programs at the YMCA or programs run by the local American Lung Association or Asthma and Allergy Foundation of America).

FACILITATE NORMAL PSYCHOLOGIC FUNCTIONING. The health care provider should establish liaison with providers of psychologic care (psychiatrists, psychologists, social workers) in their community and become familiar with both the expertise and interest of practitioners in dealing with the psychologic issues presented by patients with asthma and their families.

Monitoring rehabilitation goals. Progress with rehabilitation goals should be monitored on visits to the physician so that therapy can be readjusted. This readjustment may require contact with the appropriate individual in the school or workplace, the individual helping with physical conditioning, or the mental health provider involved in the treatment of the patient. Physician interest in the process of rehabilitation can stimulate motivation of the patient.

REFERENCES

1. Parcel GS, Gilman SC, Nader PR, Buncee H. A comparison of absentee rates of elementary school children with asthma and non-asthmatic school mates. Pediatrics 1979; 64:878-81.
2. Ludwick SK, Jones JW, Jones TK, Fukuhara JT, Strunk RC. Normalization of cardiopulmonary endurance in severely asthmatic children after bicycle ergometry therapy. J Pediatr 1986;109:446- 51.
3. Wolf SI, Lampl KL. Pulmonary rehabilitation: the use of aerobic dance as a therapeutic exercise for asthmatic patients. Ann Allergy 1988;61:357-60.
4. Achenbach TM, Edelbrock C. A manual for child behavior checklist and revised child behavior profile. Burlington, Vermont: Queen City Printer, 1983.
5. MMPI Reporting Service. Minnesota Multiphasic Personality Inventory [Revised ed]. New York: Psychological Corp, 1989.
6. Pozanski E, Grossman J, Buchsbaum Y, Banegas M, Freeman L, Gibbons R. Preliminary studies of the reliability and validity of the Children's Depression Rating Scale. J Am Acad Child Psychiatry 1984;23:191-7.

Asthma camps

Summary statements

- The major goal of a camp for children with asthma is to provide a positive learning experience in an enjoyable setting. The camp provides an environment that encourages social interests, reduces anxiety, and allows for a sense of independence.
- Operational guidelines for an asthma camp should include administrative structure, medical structure, appropriate structure of activities, and camp format.

One of the goals in the care of children with asthma is to build the confidence necessary to allow them to fully participate in normal childhood activities. A summer camping experience is one such activity and has long been recognized as being beneficial for children. However, many children with moderately severe to severe asthma have never attended camp. Many parents are concerned about the availability of medical coverage. Many camps will not accept children with asthma. In addition, children with asthma often feel uneasy about their ability to interact with children without asthma. Summer camps specifically for children with asthma have been in existence for more than 20 years. They provide a safe, enjoyable, and educational camping experience for children with asthma who might otherwise be denied a camping experience.[1-3]

In the United States, more than 90 summer camp programs for children with asthma are currently in existence.[4] Approximately 80% of these camps are sponsored by local chapters of the American Lung Association. Others are sponsored by local chapters of the Asthma and Allergy Foundation of America or by local groups of allergists. Recent parameters have been established for maximizing the effectiveness of such camp programs.[5]

Goals and objectives.[6, 7] The major goal of camp is to provide a positive learning experience while the child has fun. Asthma camps often prepare the child for attending a "regular camp."

The major objective is educating the child about asthma while at camp. These special camps for children with asthma provide a relaxed and secure opportunity for children to learn more about their disease.[8,9]

Another key objective includes providing the child with specific self-care skills that he or she can use beyond the camp experience. Through an active program of physical activity and association with other children with asthma, the child will gain greater self-esteem and a more positive outlook toward his or her illness. Camps encourage social interaction, reduce anxiety, and allow for a sense of independence on the part of children.[10,11]

Asthma camps meeting these objectives offer an unparalleled resource in the management of children with asthma. A child can benefit medically, psychologically, and socially in a positive environment that is difficult to duplicate elsewhere.

Administrative structure[6]

Sponsoring organization. Camps require local sponsors: local chapters of the allergy societies, the American Lung Association, local chapters of the Asthma and Allergy Foundation of America, hospitals and clinics, physician offices, and parents working with physicians. Before beginning a new camp, the sponsoring organization must establish a need for a camp for children with asthma. There should also be delineation of the type of camping experience to be provided.

Planning committee. The efforts of a number of individuals must be combined to plan policy and direction of the camp. Such planning is required to ensure an enjoyable, educational, and safe camping experience. The planning committee is responsible for establishing written objectives, setting a camp policy, and reviewing the ongoing operations of the camp. This group includes the medical director, the head nurse, and the person responsible for respiratory therapy. The addition of clinical pharmacists, mental health workers, and health educators is strongly recommended. These individuals should have particular expertise in dealing with asthma and chronic illness in children. A program director from the sponsoring organization should be chosen to coordinate the activities of the Planning Committee. Additional individuals who should be involved in the Planning Committee include a director of education and representatives of the camping facility being used. Written job descriptions should be prepared for all individuals involved in the conduct of the camp. The committee should seek objective means of measuring and evaluating the success of the camping program. Procedures for the care of asthma and other medical problems should also be in writing and be reviewed by the medical director each year.[12]

Administrative policies for emergencies. The administration of the camp should have a written policy to deal with any potential crisis at camp. This should include an organized plan to be put into action at the time of any particular emergency. Such factors as counseling children, notifying and counseling parents, and medical/legal aspects should all be addressed.

Insurance. The sponsoring or support organization should make adequate arrangements for liability coverage in an amount appropriate to the size and scope of its camp. All medical and allied personnel should be required to carry malpractice insurance. Accident insurance should be provided for all the children. The sponsoring organization should obtain legal counsel as to the adequacy of the insurance coverage.

Contracts. Detailed contracts should be obtained from the camping facility. This should be the responsibility of the administrative director of the sponsoring organization. It is recommended that the camp be accredited by the American Camping Association and that camp counselors undergo proper training as required by the American Camping Association.

Medical structure[5]

Medical director. The medical director should be a licensed physician with specialty training and board certification in allergy/immunology or pulmonology. The medical director assumes responsibility for the health and welfare of the children, coordinates the activities of all allied health personnel, and reviews all policies and procedures concerning medical care. The medical director takes responsibility for recruiting qualified physicians to provide medical coverage during the time the camp operates. The director is also responsible for assuring that all appropriate medications and emergency equipment are available at camp, for developing a liaison with local emergency departments, and for arranging for the transport of critically ill children. The director or designated medical personnel should review the medical records of all campers before camp begins to determine whether it is medically and psychologically appropriate for the child to attend the camp. The medical director also should ensure that accurate records of campers' health status and performance are maintained and that each referring physician receives a report of the child's progress at camp. The family should also have the opportunity to discuss with the medical director and staff

any concerns they have about their child's health during camp and at discharge. Campers' families should be given feedback about their children's camp experience and opportunities for continuing educational programs in the community.

Medical staff. At least one physician, preferably two, should be on-site and available 24 hours a day. Nursing support should be available, consistent with the needs of the individual camp. Additional staff might include respiratory therapists and clinical pharmacists. All medical personnel should be certified in basic life support and preferably advanced life support. They should be fully oriented before the camping experience and familiar with all camp policies and guidelines.

Infirmary. Although the dispensing of medications may take place in a variety of locations, it is important to have a central infirmary where children may receive medical care. This area should be appropriately equipped to measure airway obstruction objectively and have medications for dealing with asthma, as well as minor medical problems.

Emergency care. Arrangements should be made for the transport of any critical ill child to a center dealing in pediatric emergencies. This should include air transport where indicated. Prior arrangements with the hospital should be made. Arrangements should be made with an emergency department or other medical facility in the vicinity of the camp to handle nonasthma problems that cannot be handled at the on-site infirmary.

Medical questionnaire and application form. A complete medical questionnaire should be developed and provided to all potential campers. It should include information from the family and the child's physician. A physician's assessment of the potential benefit to the particular child and any information that may have bearing on the social and emotional manifestations of the disease in the child is also important.

Program of activities[15]

Camping activities. An objective of the camp is to provide a planned program of normal summer camp activities for the children. They should be designed with the enjoyment of the children in mind. The children should always be encouraged to participate in the activities to the maximum of their abilities. Children can often be integrated into the usual program of activities developed by the camp, but certain restrictions may need to be taken. Counselors should also be made aware of children who are having a particularly difficult time and who may need limitations placed on their activities.

Educational program. Education is an integral part of the asthma camp experience. A program already developed may be integrated into the camping experience. These may be American Lung Association programs, programs developed by the Asthma and Allergy Foundation of America, or others. Although most camps develop their own educational programs based on their own facilities, personnel, and previous experience, certain objectives should be uniform. Children should be able to identify and react to early warning signals of asthma and be able to identify and avoid their own triggers. Instructions in proper relaxation and breathing may be helpful. They should develop an understanding of their medications, both in terms of their pharmacologic action and their potential side effects, and be instructed in the use of inhalers and the appropriate use of the peak flow meter. General review of self-care skills, including the importance of regular medical therapy, should be stressed. Educational programs should be age-appropriate. Often two separate programs need to be used, one for younger children and one for older children. Ideally, an individual with special skills in asthma education should direct the education program. It can be advantageous to have counselors who are successfully managing their own asthma serve as role models.

Camper selection. Camper selection can be one of the most difficult tasks for the medical staff. The camp planning committee must establish policies concerning (1) waiting lists for children who cannot be accommodated at camp, (2) children returning to camp after more than one or two sessions, and (3) possible restrictions of acceptance based on severity. Severe asthma should not be a reason for denying a child the opportunity to participate in the camp experience. However, the medical director and other medical staff should take into consideration the impact of a severely ill child with unstable asthma on the general operation of the camp, as well as the applicant's best interests. Asthma is not predictable, and life-threatening situations may arise in children who have severe disease. Issues of financial need should be dealt with by the sponsoring organization of the camp. Adequate financial support should be made available to families in need to allow participation of all qualified children.

Camp format. There are many different formats for organizing a camp for children with asthma. Many asthma camps have their own campsite dedicated exclusively to children with asthma. During the period the camp is in progress, only children with asthma are at the campsite. They are able to relate to

other children who are experiencing similar problems, and it often allows them to see they are not the only children with asthma. It also provides the medical staff with the opportunity to closely supervise the campers for episodes of asthma. The educational activities, mealtimes, and recreational activities can also be easily supervised. A variation of this format uses a large campsite in which the children with asthma are housed separately from other children at camp. An advantage of this arrangement is to provide an experience for children with asthma in common with their peers without asthma.

Many physicians believe that segregating children with asthma from other children at the campsite or not allowing them to participate side-by-side with children without asthma makes the child with asthma feel different. Therefore many asthma camps use the technique of "mainstreaming." In these camps children with asthma are in facilities with children without asthma. Adequate supervision is provided so that these children receive their medication at appropriate times and are carefully observed. This mainstreaming has worked very effectively in many camps.

Children with asthma who have developed adequate recognition of early warning signs, a clear understanding of asthma triggers, and the confidence and skill in providing self-care with limited supervision should be encouraged to participate in "regular" camps.

Conclusions. Asthma camps are a wonderful opportunity for children with asthma. Follow-up studies have demonstrated that the camping experience has a very positive impact on self-care skills, self-image, and general control of asthma. Parents are often reassured that their children can be away from home and do well, and this reassurance gives them an added sense of security. The opportunity also exists for health professionals to gain knowledge that will improve their skills in the future care of children with asthma. It is essential for the allergists-immunologists and the pulmonologists in the community to be involved in and support asthma camp programs. It encourages the children and their families to know that the physicians have recognized the value of these programs. Physicians, nurses, pharmacists, respiratory therapists, and other staff members who participate in the camp generally have a very positive experience from working with the children. They are able to transmit this information to others in the community and to provide more appropriate and up-to-date medical care. Camp organizers should make an effort to encourage a variety of individuals to participate in the camp each year. The more widespread the participation of the medical staff, the greater acceptance and recognition the camp will have in the community.

REFERENCES

1. Becker A, McGhan S, Dolovich J, et al. Essential ingredients for an ideal education program for children with asthma and their families. Chest 1994;106:231S-241S.
2. Campbell M, Cormier J, Daglish S, Miles P, Kesten S. Consideration of public programs and techniques for public/community health education. Chest 1994;106: 274S-8S
3. Tinstman TC, Wass AR. A camp for children with asthma. Nebr Med J 1981;66:261-3.
4. Sosin A. Asthma camps: an up-to-date listing. Pediatr Asthma Allergy Immunol 1991;5:39-50.
5. Parameters for the operation of camps for children with asthma 1993: ALA, New York, N.Y.
6. Summer camps for children with asthma. 1995; ALA of Hennepin County, Minneapolis, Minnesota.
7. Asthma camps: an up-to-date list. Pediatr Asthma Allergy Immunol 1992;6:115.
8. Blessing-Moore J, Fritz G, Lewiston NJ. Self management programs for childhood asthma. Chest 1985;87:107S-10S.
9. Wilson-Pessano SR, McNabb WL. The role of patient education in the management of childhood asthma. Prev Med 1985;14:670-87.
10. Parrish RH, Camp TLC: helping children help themselves. Am Pharm 1980;NS20:37-40.
11. Hazzard A, Angert L. Knowledge, attitudes and behavior in children with asthma. J Asthma 1986;23:61-7.
12. Robinson LD Jr. Evaluation of an asthma summer camp program. Chest 1985;87:105S-7S.
13. Holbreich M, Weisberg SC. Asthma camps: who to send, what to look for? J Respir Dis 1990;11:366-76.

VII. Special conditions

A. CONCOMITANT CONDITIONS

Summary statements

- Weight control should be advised in patients with asthma because exogenous obesity may complicate the treatment of asthma.
- Although the coexistence of obstructive sleep apnea and asthma is rare, nocturnal asthma may be exacerbated in patients with both conditions.
- A decision regarding antituberculous chemotherapy in an asthmatic patient who requires corticosteroids should be carefully individualized, if there is a documented past history of tuberculosis.
- Hyperthyroidism may aggravate asthma and complicate the management of asthmatic patients.
- Asthma in patients with Addison's disease is usually severe but improves with glucocorticoids.
- The best method of avoiding the diabetogenic properties of corticosteroids in asthmatic patients with diabetes is use of inhaled corticosteroids if the patient's asthma can be controlled with this form of therapy.
- The treatment of asthma in patients with coexisting hypertension and/or heart disease should be based on an understanding of the potential for asthma medications to exacerbate cardiovascular status and the potential for antihypersensitive medication and cardiac drugs to exacerbate asthma.
- Asthma medications are often helpful in managing so-called "fixed" obstructive lung diseases in adults and children.
- Cessation of smoking by the patient and family members should be a major goal in the overall management of asthma.

Management of coexisting diseases

Obesity. Coexistence of morbid obesity with asthma can make the latter condition worse. Pulmonary function could also be compromised in obese asthmatic patients because of a decrease rather than the usual increase in total lung capacity associated with chronic asthma.[1] For these reasons weight control must be persistently advised in such patients.

Sleep apnea. The coexistence of obstructive sleep apnea and asthma is rare but should be considered in patients with heavy snoring, obstructing nasal polyps, or those who develop erythrocytosis. In children enlarged tonsils, adenoids, or both may cause this problem. Such patients may display only mild hypoxemia while awake, but tissue anoxia could become life-threatening at night because of obstructive apnea. Moreover, nocturnal asthma attacks are often exacerbated in these patients. When this condition is suspected, a thorough sleep analysis should be conducted. If the diagnosis is confirmed, either surgical procedures for relief of anatomic obstruction or continuous intranasal positive airway pressure during sleep may be recommended.[2] Good response has been observed with such treatment. Occasionally a tracheostomy is required. If it is determined that obstructive sleep apnea is worsened by chronic nasal obstruction, appropriate evaluation, including allergic causes and appropriate treatment, may be an adjunctive aid in the management of the problem.

Tuberculosis. A decision regarding antituberculous chemotherapy in an asthmatic patient who requires corticosteroids must be carefully individualized if there is a documented past history of tuberculosis. At the initiation of or early in the treatment with systemic corticosteroids, a chest x-ray film should be obtained in such patients. Anyone at high risk because of previous contact with active tuberculosis or who is known to have a positive tuberculin skin test requires special consideration.[3] Prophylactic antituberculosis therapy should be considered for recent tuberculin converters less than 35 years of age or patients with suspicious lesions on radiographs.[4] However, antituberculosis prophylaxis with isoniazid is not indicated in older tuberculin-positive patients because of increased risks of isoniazid-induced hepatoxicity.[4] The modern drug treatment of active tuberculosis in the non–HIV-infected patient is so effective that the treatment of concomitant asthma with corticosteroids is rarely a problem. Although a problem in HIV-infected patients, primary infection with drug-resistant or atypical mycobacterial organisms has not emerged as a significant problem in chronic asthmatic patients. However, reports of tuberculosis resistance to multiple drugs

warrants vigilence by all physicians treating patients with lung disease.

Diabetes mellitus. The diabetogenic properties of corticosteroids require close supervision in prediabetic and diabetic asthmatic individuals who require systemic corticosteroids.[5] Proper control of diabetes can often be achieved by diet or oral antidiabetic drugs. Occasionally insulin is required. The best way to avoid the dilemma of corticosteroid treatment in asthmatic patients with diabetes is to use inhaled corticosteroids, provided that the patient's disease can be controlled in this way.

Hyperthyroidism. Concurrent hyperthyroidism may aggravate asthma and complicate the management of the asthmatic patient.[6] The mechanism is unknown. The corticosteroid dosage may have to be increased if active hyperthyroidism coexists. At the same time, adrenergic drugs should either not be used or used with caution in asthmatic patients with hyperthyroidism. The treatment of a thyroid crisis with nonselective β-blockers in asthmatic patients with symptoms is contraindicated. Asthma symptoms may also improve dramatically when the patient is treated with appropriate antithyroid medication.[7]

Other endocrine disorders. Asthma in patients with Addison's disease is unusually severe.[8] As soon as adrenal insufficiency is corrected by proper quantities of hydrocortisone, asthma suddenly and dramatically improves. Despite such isolated occurrences, little evidence exists that asthma is associated with pituitary or adrenal insufficiency.

The severity of asthma varies with the menstrual cycle in some women for unknown reasons. Severe premenstrual asthma can sometimes be completely prevented by injection of progesterone at the appropriate time.[9]

Hypertension and heart disease. Hypertension and heart disease are common coexisting diseases in patients with asthma. Moreover, patients with impaired left ventricular function and acute congestive heart failure have increased airway reactivity.[10, 11] Patients with asthma and concurrent hypertension or heart disease may be adversely affected by chronic corticosteroid therapy because of the hypertensive and fluid retentive properties of corticosteroid agents. Therefore, if corticosteroid-induced fluid retention complicates congestive heart failure, diuretic or other therapy may be indicated.

Several important pharmacologic principles should be emphasized in treating asthmatic patients who have either hypertension or heart disease. Nonselective β-adrenergic blocking drugs, such as propranolol, should be used with great caution in asthmatic patients with hypertension, angina pectoris, and other types of cardiovascular diseases because they can induce bronchoconstriction. However, under special conditions, β_1-cardioselective drugs (metoprolol and atenolol) may be administered beginning with low doses.[12] Some β-blockers also have partial β_2-agonist effects (e.g., pindolol) and are therefore less likely to precipitate bronchospasm than a nonselective β-agonist. They are well tolerated in about two thirds of the patients with asthma.[12] Agents with combined β-antagonist activities may be desirable antihypertensive therapy for patients with a recent transmural myocardial infarct.

Angiotensin-converting enzyme inhibitor agents are particularly useful in patients with left ventricular dysfunction and congestive heart failure. Occasionally they produce a dry cough, which can be accompanied by a bronchospastic component and must be discontinued. Calcium channel blockers appear to be a good choice for antihypertensive therapy in asthmatic patients. They are effective for treatment of coexisting coronary artery disease and do not aggravate bronchospasm.

Some patients with cardiovascular disease appear to have an increased susceptibility to tachycardia and arrhythmia after intravenous infusion of aminophylline. Therefore in patients with cardiovascular disease, continuous cardiac monitoring is advised in the initial phases of acute intravenous treatment with this drug.

Peptic ulcer, gastritis, and esophagitis. These conditions commonly coexist in corticosteroid-dependent asthmatic patients. Antacids are usually sufficient to neutralize the ulcerogenic effects associated with corticosteroids. Metoclopramide after meals is advisable for esophagitis or gastritis associated with a hiatus hernia. Parenteral corticosteroids should be used if acute bleeding occurs. Inhaled corticosteroids should replace systemic corticosteroids wherever possible in patients with peptic ulcer. Theophylline may also aggravate upper gastrointestinal symptoms in patients with peptic ulcer, esophagitis, or gastritis.[5]

Fixed obstructive disorders in adults. Asthma is frequently confused with emphysema and chronic bronchitis in adult patients. These diseases can coexist with asthma. Therefore appropriate diagnostic techniques are necessary to differentiate fixed obstructive disorders from asthma.

Fixed obstructive disorders in children. Several chronic obstructive conditions are often confused

with asthma in childhood. The most important of these is cystic fibrosis (CF), which is an inherited multisystem disorder characterized by generalized dysfunction of the exocrine glands or epithelial surfaces due to the synthesis of a mutant chloride transport protein.[13] The clinical manifestations of CF vary with the extent and severity of involvement of the different organ systems. However, chronic pulmonary disease is one of the most characteristic features of this disorder and is responsible for most of the morbidity of the disease. The suspected diagnosis of CF is confirmed by a quantitative analysis of sweat electrolytes after pilocarpine iontophoresis and evaluation of the clinical criteria for the diagnosis of CF. Patients with CF have an increased incidence of allergy, allergic bronchopulmonary aspergillosis, and demonstrate variable bronchial hyperresponsiveness, all of which require appropriate therapy.

Bronchopulmonary dysplasia (BPD) is another fixed obstructive respiratory disorder characterized by airway and lung parenchymal inflammation related to neonatal acute lung injury. It has highly variable clinical manifestations and prognosis.[14] Although the precise qualifying criteria for diagnosing this disease remain controversial, it may be appropriate to limit the diagnosis to a respiratory disorder that begins with acute lung injury during the first 2 weeks of life in an infant older than 28 days with clinical, radiologic, and significant blood gas abnormalities. Bronchial hyperreactivity has been recognized as an important clinical problem in long-term survivors of BPD.[15] A variety of studies have demonstrated the benefits of bronchodilators in these patients.

Other childhood respiratory disorders associated with obstructive sequelae to airway injury include tracheoesophageal fistula, recurrent aspiration from gastroesophageal reflux, foreign body aspiration, hydrocarbon aspiration, or near drowning.[16] A variety of viral infections are common causes of reversible hyperreactive airway disease in children.

Bronchiolitis obliterans. Bronchiolitis obliterans may occur after inhalation of toxic fumes, especially anhydrous ammonia, certain viral or *Mycoplasma* infections, and allogeneic marrow, heart-lung, or lung transplantation. In the case of inhaled anhydrous ammonia, fibrosing bronchiolitis obliterans may occur as early as 2 months after exposure.[17] Bronchiolitis obliterans affects 10% of patients with graft-versus-host disease occurring after bone marrow transplantation.[18] The syndrome may develop from 3 to 18 months after bone marrow transplantation. The severity and clinical course vary, but airway obstruction tends to be progressive and most patients die within 3 years.

Effect of active smoking on the asthmatic patient. The adverse effects of active and passive smoking are well documented. Smoking increases the risk of hypertension, heart disease, diabetes, and fixed obstructive pulmonary diseases. Cessation of smoking by the patient and family members, by whatever means, must therefore be a cardinal goal in the overall management of chronic asthma.

REFERENCES

1. Melzer E, Souhrada JF. Decrease of respiratory muscle strength and static lung volume in obese asthmatics. Am Rev Respir Dis 1980;121:17-22.
2. Shu Chan C, Woolcock J, Sullivan CE. Nocturnal asthma: role of snoring and obstructive sleep apnea. Am Rev Respir Dis 1988;137:1502-4.
3. Schatz M, Patterson R, Kloner R, Falk J. The prevalence of tuberculosis and positive tuberculin skin tests in a steroid-treated asthmatic population. Ann Intern Med 1976;84: 261-5.
4. Comstock GW, Edwards PQ. Competing risks of tuberculosis and hepatitis for adult tuberculin reactions [Editorial]. Am Rev Respir Dis 1975;111:570-3.
5. Bernstein IL. Asthma in adults. In: Middleton E, Reed CE, Ellis EF, eds. Allergy principles and practice. 2nd ed. St Louis: The CV Mosby Co, 1983:901-34.
6. Settipane GA, Schoenfeld E, Hamolsky MW. Asthma and hyperthyroidism. J ALLERGY CLIN IMMUNOL 1972;49:348-55.
7. Settipane GA, Hamolsky MW. Status asthmaticus associated with hyperthyroidism. NER Allergy Proc 1987;8:323-6.
8. Green M, Lim KH. Bronchial asthma with Addison's disease. Lancet 1971;1:1159-62.
9. Benyon HLC, Garbett ND, Barnes PJ. Severe premenstrual exacerbation of asthma: effect of intramuscular progesterone. Lancet 1988;2:370-1.
10. Cabanes LR, Weber SN, Matran R, et al. Bronchial hyperresponsiveness to methacholine in patients with impaired left ventricular function. N Engl J Med 1989;320: 1317-22.
11. Cardiac asthma [Editorial]. Lancet 1990;1:693-4.
12. Gradman AH, Kohl-Lachs SL. Managing hypertension in patients with obstructive airway disease. J Respir Dis 1990;11:68-80.
13. Smith JM. Epidemiology and natural history of asthma, allergic rhinitis and atopic dermatitis (eczema). In: Middleton E, Reed CE, Ellis EF, Atkinson NF, Yunginger JW, eds. Allergy principles and practice. 3rd ed. St Louis: The CV Mosby Co, 1988:897.
14. Northway WH Jr, Rosin RC, Porter DY. Pulmonary disease following respiratory therapy of hyaline-membrane disease: bronchopulmonary dysplasia. N Engl J Med 1967; 276:357-62.
15. Nickeson BG, Taussig LM. Family history of asthma in infants with bronchopulmonary dysplasia. Pediatrics 1980; 65:1140-4.
16. Siegel SC, Katz RM, Rachelefsky GS. Asthma in infancy and childhood. In: Middleton E, Reed CE, Ellis EF, eds. Allergy principles and practice. 2nd ed. St Louis: The CV Mosby Co, 1983:863-900.

17. Sobonya R. Fatal anhydrous ammonia inhalation. Hum Pathol 1977;8:293-9.
18. Clark JG, Crawford SW, Madtes DK, et al. Obstructive lung disease after allogeneic marrow transplantation. Ann Intern Med 1989;111:368-76.

B. ASTHMA AND ANAPHYLAXIS

Summary statements

- Anaphylaxis may be accompanied by sudden severe bronchospasm.
- Patients taking β-blockers who develop life-threatening anaphylaxis may respond poorly to usual treatment for anaphylaxis.
- Inhaled β_2-selective agonist bronchodilators and intravenous aminophylline may be required to reverse bronchospasm in patients not immediately responsive to subcutaneous epinephrine.
- Oxygen, 5 to 10 L/min, should be used when bronchospasm is accompanied by significant dyspnea or cyanosis.
- Prolonged therapy, including corticosteroids, may be necessary to reverse protracted anaphylaxis or anaphylaxis that occurs later after exposure to the triggering agent.

Characteristics of anaphylaxis

Generalized anaphylaxis is an acute life-threatening systemic reaction that may be characterized by cutaneous manifestations (urticaria, flushing, pruritus, erythema, and angioedema), respiratory distress, cardiovascular collapse, central nervous system symptoms (dizziness, syncope, seizures, and confusion), and gastrointestinal manifestations (vomiting, crampy abdominal pain, and diarrhea).[1] Respiratory components of anaphylaxis may include laryngeal edema, bronchospasm, pulmonary edema, and intraalveolar hemorrhage.[2, 3]

Causes of anaphylaxis

Most triggers of anaphylaxis (foods, drugs, insect venom, allergenic extracts, etc.) cause release of mediators from basophils and mast cells as part of an IgE-mediated immediate hypersensitivity reaction. Other immune and nonimmune mechanisms may produce anaphylactic reactions (e.g., to radiographic contrast material) that are clinically indistinguishable from IgE-mediated anaphylaxis.

Special considerations

Patients who have developed bronchospasm associated with anaphylaxis may have cough, wheezing, tightness in the chest, and/or dyspnea, which can be protracted and associated with severe hypoxemia and hypercapnia.[4] Patients can develop severe bronchospasm, with or without accompanying features of anaphylaxis, related to administration of allergenic extracts. Bronchospasm may also be the initial feature of anaphylaxis. It is a more frequent component of anaphylaxis in patients known to have asthma.

Anaphylaxis may be of particular concern in patients who are taking β-adrenergic blocking agents. β-Adrenergic blocking agents not only produce bronchospasm unrelated to anaphylaxis, but patients taking these drugs who develop severe anaphylaxis from various causes may also be unresponsive to usual modalities of treatment.[5] Therefore when possible, β-adrenergic blocking agents and allergen immunotherapy should not be used concomitantly.[6]

Treatment

Prevention of anaphylaxis by avoidance of well-defined triggers is, of course, of paramount importance. When anaphylaxis occurs, attention should be directed toward maintaining upper airway patency, blood pressure, and pulmonary function. The initial therapy for anaphylaxis is epinephrine, 1:1000 (0.3 to 0.5 ml) subcutaneously. Inhaled epinephrine (Medihaler-Epi or racemic epinephrine) can be used but should not replace the subcutaneous administration of epinephrine. Close monitoring of the patient is essential. Physicians administering agents known to have a high risk of causing anaphylaxis should have resuscitative equipment readily available. The effect of initial therapy on bronchospasm, if present, should be monitored closely by eliciting symptoms, auscultating the lungs at frequent intervals, and measuring pulmonary function with spirometry if possible.

For prolonged reactions, epinephrine can be repeated every 20 minutes. In addition, inhaled bronchodilators and/or intravenous aminophylline may be necessary at doses appropriate for the patient's age and with consideration of other medications and concomitant clinical conditions.

Additional therapeutic modalities that may be of benefit include diphenhydramine, 1 to 2 mg/kg, up to 50 mg, intravenously or intramuscularly. Intravenous diphenhydramine should be given slowly over a 3- to 5-minute period to prevent exacerbation of hypotension. H_2 blockers are not effective in the treatment of bronchospasm, but they may be effective in the treatment of upper airway obstruction. Ranitidine, 50 mg, or cimetindine, 300 mg,

can be given slowly intravenously over 3 to 5 minutes. In addition glucagon may be useful in this situation.[7] Maintenance of adequate oxygenation is essential. Oxygen, 5 to 10 L/min, should be used if cyanosis or significant dyspnea is associated with wheezing. In patients with significant irreversible obstructive airway disease, no more than 2 L/min is indicated to avoid O_2-induced decreases in respiratory drive, and other measures must be considered (see Section VI A 2, "Severe Intractable Asthma"). Intravenous corticosteroids can be used on a repetitive basis to reduce the likelihood of the late component of biphasic reactions.[8] The use of inhaled bronchodilators and inhaled corticosteroids can be continued for a prolonged period of time for patients who develop severe bronchospasm.

REFERENCES

1. Bochner BS, Lichtenstein LM. Anaphylaxis. N Engl J Med 1991;324:1785-90.
2. Lichtenstein LM. Anaphylaxis. In: Wyngaarden JB, Smith LH Jr, eds. Cecil textbook of medicine, 17th ed. Vol 2. Philadelphia: WB Saunders, 1985:1870.
3. Sullivan TK III. Systemic anaphylaxis. In: Lichtenstein LM, Fauci AS, eds. Current therapy in allergy, immunology, and rheumatology—4th Edition. Toronto: BC Decker, 1988:91.
4. Smith PL, Kagey-Sodotka A, Bleecker ER, et al. Physiologic manifestations of human anaphylaxis. J Clin Invest 1980;66: 1072-80.
5. Toogood JH. Risk of anaphylaxis in patients receiving beta-blocker drugs. J ALLERGY CLIN IMMUNOL 1988;81:1-5.
6. Position statement. Beta-adrenergic blockers, immunotherapy, and skin-testing. J ALLERGY CLIN IMMUNOL 1989;84: 129-30.
7. Lee ML. Glucagon in anaphylaxis [Letter]. J ALLERGY CLIN IMMUNOL 1982;69:331-2.
8. Stark BJ, Sullivan TJ. Biphasic and protracted anaphylaxis. J ALLERGY CLIN IMMUNOL 1986;78:76-80.

C. MANAGEMENT OF ASTHMA DURING PREGNANCY

Summary statements

- There is more risk to the mother and fetus during pregnancy from poorly controlled asthma than from the usual medications used to treat asthma.
- Asthmatic patients should not smoke, especially during pregnancy.
- Identification and avoidance of potential triggers of asthma are essential during pregnancy.
- Assessment of asthma should include regular measurements of pulmonary function during pregnancy.
- Pregnancy is not a contraindication to continued allergen immunotherapy in patients who are at maintenance.
- Additional considerations apply to the management of asthma during labor and delivery.
- In general, the same medications used during pregnancy are appropriate during labor and delivery.
- Oxytocin is the preferred medication for labor induction, and intracervical prostaglandin E_2 gel can be used for cervical ripening before labor induction.
- For regional anesthesia during labor and delivery, the concomitant use of epidural analgesia should be considered; for general anesthesia, ketamine may be the agent of choice, possibly with preanesthetic use of a β_2-agonist.
- Currently oxytocin is considered the medication of choice for postpartum hemorrhage. Ergonovine and methylergonovine have been associated with bronchospasm.

General considerations

Maternal asthma has been associated with increased perinatal mortality and morbidity, but information suggests that optimal control of asthma during pregnancy reduces this risk.[1, 2] Emerging data suggest that the currently accepted goals of asthma therapy (symptomatic control, prevention of acute episodes, and optimizing pulmonary function) are beneficial for the fetus and the mother.

Asthma severity may increase, decrease, or remain unchanged during pregnancy. Although it is difficult to predict the course of gestational asthma in an individual patient, some studies suggest that women with more severe asthma are more likely to worsen during pregnancy than to improve. In addition, the course of asthma during a prior pregnancy may be somewhat predictive because approximately 60% of women tend to react similarly regarding the course of asthma on successive pregnancies.[3]

The uncertain course of asthma during pregnancy and the potential adverse effects of uncontrolled asthma on the fetus and the mother dictate that a woman with asthma should be closely followed during pregnancy. Ideally, asthma management during pregnancy should entail (1) regular visits to an asthma specialist, who is monitoring

subjective and objective (including pulmonary function) asthma parameters; (2) easy accessibility to care for uncontrolled exacerbations; and (3) frequent communication between the asthma specialist and the obstetrician about the patient's asthma therapy and obstetric status.

Avoidance therapy

Avoidance of known triggers of asthma is particularly important during pregnancy. Such avoidance will potentially increase asthma control, thereby decreasing the need for medication or other therapy. Allergen skin testing may be unnecessary if the history is sufficient to identify allergenic triggers. Skin testing may be performed cautiously if confirmation of the history is necessary. An alternate approach would be in vitro testing (i.e., RAST or ELISA).

Asthmatic patients should discontinue smoking because smoking may aggravate asthma and adversely affect the fetus.[4-6]

Pharmacologic therapy

Medications are chosen for use during pregnancy because the available information about their gestational use and efficacy in asthma suggests that the risk of their use is less than the risk of uncontrolled asthma.[7]

The risks of uncontrolled asthma for the mother and the fetus, the alternative asthma medications available, and the rationale for choosing among those alternatives based on their efficacy, side effects, and the data available regarding their use during pregnancy should be discussed with the patient. Based mainly on animal data, cromolyn and terbutaline have a better risk factor rating than does beclomethasone,[8, 9] thereby prompting the recommendations shown in the listed material that follows.

Chronic asthma

A suggested stepwise pharmacologic management of chronic asthma during pregnancy (when there is no demonstrable evidence of a concurrent infection or self-limited triggering factor), in the generally recommended order of trial, according to increasing severity of asthma, is as follows:

1. Inhaled β-agonist (terbutaline preferred*), two inhalations every 4 hours as needed up to 8 inhalations per day; regular daily use suggests the need for additional medication(s). Frequent use in excess of 8 inhalations per day may require further therapy.
2. Regular inhaled cromolyn, two inhalations four times a day
3. Regular inhaled beclomethasone, two to four inhalations four times a day
4. Regular oral theophylline
5. Oral prednisone

Patients requiring regular medication should initially receive inhaled cromolyn. If a 1-month trial of cromolyn is not effective, beclomethasone should be substituted or added, and if this is not adequate, regular theophylline should be added. Oral prednisone should be used in short courses or long-term at the lowest effective dose if asthma is not controlled despite the previously mentioned therapy. Prednisone may be used in some patients with asthma that is difficult to manage, depending on factors such as the severity of the episode, the triggering event, and the course of prior acute asthma episodes experienced by the patient.

Patients who are adequately controlled on theophylline before pregnancy, and who have not been tried on cromolyn or beclomethasone, may warrant trials of those medications during pregnancy depending on parameters such as: (1) the presence of nausea or gastroesophageal reflux, which may be exacerbated by theophylline; (2) other theophylline side effects; (3) compliance considerations; and (4) subjective and objective indices of severity.

Antibiotics should be given only when appropriate. Certain antibiotics, such as tetracycline, are contraindicated.

A high index of suspicion must be maintained for sinusitis exacerbating asthma during pregnancy because: (1) sinusitis has been reported to be six times more common during pregnancy than in nonpregnant patients[10]; and (2) the classic signs of sinusitis may be absent in approximately half of women with documented sinusitis during pregnancy. Procedures used to diagnose sinusitis need to be carefully considered regarding the benefit to the mother versus the risks to the mother and fetus.

Acute asthma

Recommendations for the pharmacologic management of acute severe asthma during pregnancy in a medical setting are as follows:

* Based on animal studies, terbutaline has a safer teratogenic profile; no human data indicate that one β-agonist is safer than another.

1. Nebulized β_2 agonist (terbutaline preferred)* which may be repeated every 20 to 30 minutes
2. Intravenous methylprednisolone (SoluMedrol) (given initially concomitantly with nebulized β_2-agonist, especially if there is a poor response to initial β_2 agonist treatment)
3. Consider intravenous aminophylline; loading dose (if indicated) 5.6 mg/kg; maintenance dose (initially) 0.5 mg/kg/hr depends on serum theophylline levels
4. Consider inhaled anticholinergic medication
5. Subcutaneous terbutaline, 0.25 mg, if the patient is not responding to the above therapy

In evaluating the pregnant woman with acute asthma, it must be remembered that normally during pregnancy a compensated respiratory alkalosis develops with a higher P_{O_2} (102 to 106) and a lower P_{CO_2} (28 to 30) than in the nonpregnant state.[11] Thus a P_{CO_2} greater than 35 or a P_{O_2} less than 70 (at sea level) associated with acute asthma represents more severe respiratory compromise during pregnancy than would similar arterial blood gases in the nongravid state. In addition to pharmacologic therapy, initial therapy of acute asthma in pregnancy should include supplemental oxygen and intravenous fluids. For acute asthma a course of oral prednisone should generally be used unless: (1) bronchodilator treatment readily clears the episode; or (2) there is resolution by clinical and objective parameters, and the triggering event and episode are not considered to be ongoing. Careful monitoring of the fetus and mother is essential. (see Section VI B).

Immunotherapy

Allergen immunotherapy does not increase the risk of perinatal complications, although anaphylactic reactions to immunotherapy may be dangerous for both the mother and fetus.[12] No contradiction exists to continuing immunotherapy in women who are on a maintenance program. The maintenance dose should be reduced or maintained at the same level throughout pregnancy and, as an extra precaution, dose increases, if necessary, should be conservative. In general, immunotherapy should not be started during pregnancy. However, there may be specific situations in which the initiation of immunotherapy may be justified (e.g., life-threatening *Hymenoptera* sensitivity). In patients whose pregnancy is established after immunotherapy is initiated but before the maintenance dose is reached, a decision to continue, increase, discontinue, or remain at the same dosage must be individualized.

Labor and delivery

In general, the same medications used during pregnancy are appropriate during labor and delivery as long as the patient's asthma has been adequately controlled before labor. If oral corticosteroids had been required during or shortly before pregnancy, a short course of systemic corticosteroids should be given during labor and the immediate postpartum period because of the stress of labor and delivery.[13] If systemic corticosteroids are necessary, a commonly used regimen is 100 mg hydrocortisone given every 8 hours until 24 hours post partum.

Considerations during labor. The intensity of fetal monitoring largely depends on the severity of the asthmatic symptoms experienced by the mother. For low-risk mothers with minimal or no asthmatic symptoms, a short initial period of electronic fetal heart rate monitoring may be sufficient. Intermittent fetal heart rate monitoring may be necessary for patients with moderate asthma. During labor and with severe uncontrolled asthma, more intensive fetal monitoring is required. Assessment of the mother's condition is accomplished with frequent auscultation, peak flow rate measurement, and/or oximetry.

For labor induction, oxytocin is the preferred medication. Analogs of prostaglandin $F_{2\alpha}$, such as 15 methylprostaglandin $F_{2\alpha}$, could cause bronchoconstriction and should be avoided.[14] Despite reports that it can cause bronchospasm, prostaglandin E_2 has been safely used in the patient with asthma for therapeutic abortion or labor induction with a dead fetus.[15] Intracervical prostaglandin E_2 gel used for cervical ripening before labor induction has not been associated with bronchoconstriction, even though inhaled prostaglandin E_2 may be irritating to the tracheobronchial tree.[16, 17]

Considerations with anesthetics and analgesics. The therapeutic effect of morphine and other opioids in patients with asthma, when used in the customary doses, is small.[18] In large doses, however, morphine and meperidine (Demerol) may be associated with bronchospasm. Fentanyl has not been associated with exacerbation of asthma, but it has a relatively short duration of action, approximately 20 minutes.

Epidural analgesia has definite advantages over general anesthesia. It makes intubation of the trachea unnecessary. Lumbar epidural analgesia

* Based on animal studies, terbutaline has a safer teratogenic profile. However, this dosage form is not currently approved for this route of administration. No human data indicate that one β-agonist is safer than another.

also reduces oxygen consumption and minute ventilation during the first and second stages of labor, which may prove beneficial to a patient with asthma.[19] Even high thoracic epidural anesthesia does not alter airway resistance.[20]

It should be remembered that a significant percentage of patients with asthma have idiosyncratic reactions to aspirin and/or other nonsteroidal anti-inflammatory medications.

If general anesthetic is required, vigorous preanesthetic use of an inhaled β-agonist is the preferred method of producing bronchodilation. Atropine or ipratropium bromide might also be used to prevent bronchoconstriction induced by intubation.[21] Of anesthetic agents currently available for anesthetic induction, ketamine may be the preferred agent, because it decreases airway resistance[22] and can prevent bronchospasm.[23] Propofol has recently been shown to reduce the incidence of bronchospasm on induction.[24]

Postpartum hemorrhage. Postpartum hemorrhage is associated with a high mortality rate. Therefore oxytocin is considered the medication of choice for postpartum hemorrhage. Ergonovine and methylergonovine should be avoided because they may cause bronchospasm.[25] If their use is absolutely necessary, patients should be pretreated with high doses of corticosteroids. Analogs of prostaglandin $F_{2\alpha}$ may worsen asthma and should be avoided,[14] but a 20 mg prostaglandin E_2 rectal suppository can help ameliorate the uterine hemorrhage and is less likely to produce bronchospasm.

Preterm labor. During exacerbation of asthma, uterine contractions are common, although they usually do not progress to preterm labor. Usually if the exacerbation is successfully treated, uterine contractions will stop without additional treatment. If tocolytic therapy for premature labor is required, care should be taken to avoid the use of more than one type of β-agonist. If the patient is already taking a systemic β-agonist for asthma, magnesium sulfate, which has tocolytic and bronchodilator properties, should be considered. Supplemental oxygen may be necessary because bronchodilators may worsen hypoxemia.

REFERENCES

1. Fitzsimmons R, Greenberger PA, Patteson R. Outcome of pregnancy in women requiring corticosteroids for severe asthma. J ALLERGY CLIN IMMUNOL 1986;78:349-53.
2. Stenius-Aarnicala B, Piirila P, Teramo K. Asthma in pregnancy: a prospective study of 198 pregnancies. Thorax 1988;43:12-8.
3. Schatz M, Hearden K, Forsythe A, et al. The course of asthma during pregnancy, postpartum, and with successive pregnancies: a prospective analysis. J ALLERGY CLIN IMMUNOL 1988;81:509-17.
4. Shiono PH, Klebanof MA, Rhoads GG. Smoking and drinking during pregnancy: their effects on preterm birth. JAMA 1986;255:82-4.
5. Cnattinquis S, Haglund B, Merik O. Cigarette smoking as risk factor for late fetal and early neonatal deaths. Br Med J 1988;297:258-61.
6. Brooke OG, Anderson HR, Bland JM, et al. Effects on birth weight of smoking, alcohol, caffeine, socioeconomic factors, and psychosocial stress. Br Med J 1989;298:795-801.
7. Mawhinney H, Spector SL. Optimum management of asthma in pregnancy. Drugs 1986;32:178-87.
8. Greenberger PA, Patterson R. Beclomethasone dipropriate for severe asthma during pregnancy. Ann Intern Med 1983;98:478-80.
9. Schatz M. Asthma during pregnancy: interrelationships and management. Annals of Allergy 1992;68:123-33.
10. Sorri M, Bortikanen-Sorri AL, Karja J. Rhinitis during pregnancy. Rhinology 1980;18:83.
11. Schatz M, Hoffman CP, Zeiger RS, et al. The course and management of asthma and allergic diseases during pregnancy. In: Middleton E Jr, Reed CE, Ellis EF, Atkinson NF Jr, Yunginger JW, eds. Allergy: principles and practice. 3rd ed. St Louis: The CV Mosby Co, 1988:1097.
12. Metzgr WJ, Turner E, Patterson R. The safety of immunotherapy during pregnancy. J ALLERGY CLIN IMMUNOL 1978; 61:260-72.
13. Spector SL. Asthma and chronic obstructive lung disease: a pharmacological approach. Dis Mon 1991;37:1-58.
14. Fishburne JI Jr, Breener WF, Braaksma JT, Hendricks CH. Bronchospasm complicating intravenous prostaglandin F2-alpha for therapeutic abortion. Obstet Gynecol 1972;39: 892-6.
15. Towers CV, Rojas JA, Lewis DF, Asrat T, Nageotte MP, Briggs GG. Usage of prostaglandin E_2 (PGE_2) in patients with asthma. Am J Obstet Gynecol 1991;164:295-8.
16. Lao TT, Huengsburg M. Labour and delivery in mothers with asthma. Eur J Obstet Gynecol Reprod Biol 1990;35: 183-90.
17. Rayburn WF. Prostaglandin E_2 gel for cervical ripening and induction of labor: a critical analysis. Am J Obstet Gynecol 1989;160:529-34.
18. Eschenbacher WL, Bethel RA, Boushey HA, Sheppard D. Morphine sulfate inhibits bronchoconstriction in subjects with mild asthma whose responses are inhibited by atropine. Am Rev Respir Dis 1984;130:363-7.
19. Chestnut DH, Pollack KL, Laszewski LJ, Bates JN, Choi WW. Continuous epidural infusion of bupivacaine-fentanyl during the second stage of labor. Anesthiology 1989;71: A481.
20. Hagerdal M, Morgan CW, Sumner AE, Gutsche BB. Minute ventilation and oxygen consumption during labor with epidural analgesia. Anesthesiology 1983;59:425-7.
21. Gal TJ, Suratt PM. Atropine and glycopyrrolate effects on lung mechanics in normal man. Anesth Analg 1981;60:85-90.
22. Corssen G, Gutierrez J, Reves JG, Huber PC Jr. Ketamine in the anesthetic management of asthmatic patients. Anesth Analg 1972;51:588-96.
23. Hirschman CA, Downes H, Farbood A, Bergman NA.

Ketamine block of bronchospasm in experimental canine asthma. Br J Anaesth 1979 Aug;51:713-8.
24. Pizou R, Brown RH, Baranov D, Hennes H, Weiss YS, Hirschman CA. The incidence and relative risk of wheezing during induction of anesthesia in patients with asthma. Anesthesiology 1994;81:A1471.
25. Crawford JS. Bronchospasm following ergonovine. Anesthesiology 1980;35:397-8.

D. NOCTURNAL ASTHMA

Summary statements

- A high percentage of deaths occur during nocturnal and early morning periods.
- Nocturnal asthma has been associated with factors such as decreased pulmonary function, hypoxemia, decreased mucociliary clearance, and circadian variations of histamine, epinephrine, and cortisol concentrations.
- A general goal of asthma therapy should be the complete control of nocturnal symptoms.
- Longer acting, sustained-release theophylline preparations, long-acting preparations of oral β-agonists, or long-acting inhaled β-agonists may be an effective way to control nocturnal asthma in many patients.
- Better overall control of the patient's asthma may be necessary before nocturnal symptoms will be adequately controlled (i.e., avoidance, immunotherapy, and daytime medications, especially anti-inflammatory drugs such as corticosteroids and cromolyn).

For centuries, asthmatic patients and their physicians have noted worsening of asthma during nighttime hours, most notably from midnight to 6:00 AM.[1-5] Several different expiratory air flow patterns have been demonstrated, of which an early morning dip is the most common in asthmatic patients. A double-dip pattern with morning and evening drops is more characteristic of bronchitic patients.[6] Surveys of asthma mortality have revealed that a high percentage of deaths related to asthma occur during nocturnal and early morning hours. In the 1971 London survey, 68% of asthmatic deaths occurred between midnight and 8:00 AM.[7] Seven of nine hospitalized asthmatic patients, who suffered sustained respiratory crises with respiratory arrest, did so during the hours between midnight and 6:00 AM.[8] Hypoxemia has been shown to worsen during sleep in patients with severe airway obstructive disease.[9, 10]

In a survey of 7729 asthmatic patients in England, 74% reported awakening at least once a week because of an asthma attack, and 64% reported awakening at least three times a week; 55% of these patients also documented nocturnal airway obstruction by objective peak flow measurements.[11] Nocturnal awakening from asthma is both common and probably underreported unless patients are specifically asked about nocturnal symptoms.

Etiology and pathogenesis

Nocturnal and early morning asthma represents *exaggerated* airway obstruction resulting from a normal diurnal rhythm of airway patency.[12] The cause of *exaggerated* nocturnal airway obstruction, however, remains unclear.[13] Nocturnal exposure to dust mites can increase bronchial hyperresponsiveness and diurnal variation of peak expiratory flow rates in mite-sensitive asthmatic patients.[14] Nocturnal asthma is also a feature of nonallergic asthma.[15] Cooling of the airways with nighttime sleep is a possible cause because nocturnal bronchospasm can be reduced by inhalation of warm humidified air.[16] Recumbency has no effect on the usual diurnal variation of airway peak flow values, and in fact the usual exaggerated nocturnal deterioration in airflow is unchanged whether patients are asleep or awake.[17] The role of gastroesophageal reflux in producing nocturnal asthma is not clear. Inhalation of acid secretions as a cause of nocturnal asthma is controversial. However, stimulation of irritant receptors in the lower esophagus with resultant reflex bronchoconstriction mediated through the vagus nerve is a possible mechanism.[18] Mucociliary clearance is significantly reduced during sleep in patients *without* asthma and could contribute to, although not totally explain, pathologic changes seen in nocturnal asthma.[19] Whatever other factors are involved, normal diurnal variation in airway patency probably occurs in most asthmatic patients, but in some it may be sufficiently pronounced to make nocturnal asthmatic symptoms a prominent part of their clinical presentation.

The therapeutic response of patients with nocturnal asthma to inhaled bronchodilators supports the concept that this condition is characterized by a significant bronchospastic component. Many studies[20-23] have suggested that bronchial hyperresponsiveness and extensive airway inflammation are also prominent in these patients. Bronchial hyperresponsiveness may persist for days even after a single allergen exposure.[20, 23, 24] With repeated allergen exposure, bronchial inflammatory changes may be even more prolonged, and nonspecific bronchial hyperresponsiveness may worsen as demonstrated by methacholine or histamine challenge.[25]

Based on the close association between increased bronchial hyperresponsiveness to inhaled histamine challenge and the extent of fall in morning peak flow, it has been suggested that asthma is related to an alteration in the homeostatic mechanisms of airway patency.[26] It has been demonstrated that: (1) a close *correlation* exists between reduced nocturnal peak flow values *and* urinary catecholamine levels[27]; (2) plasma epinephrine and adenosine monophosphate values are highest at 4:00 PM and lowest at 4:00 AM[28]; (3) plasma histamine levels are highest at 4:00 AM and lowest at 4:00 PM; and (4) plasma cortisol values are highest at 7:00 AM and lowest at midnight. These findings suggest that increased respiratory symptoms in the early morning hours in patients with nocturnal asthma are related to increased airway hyperresponsiveness resulting in part from circadian variation in hormone and mediator concentration. In addition, hypoventilation may complicate nocturnal asthma.

Diagnosis

A history of nocturnal or early morning awakening from wheezing, dyspnea, coughing, or chest tightness should alert the physician to the possibility of nocturnal asthma. In fact, these nocturnal symptoms may be the earliest indication of asthma. Nocturnal variation can be confirmed by having the patient measure and record early morning and late afternoon or evening peak flow measurements at home.

Treatment

The goals of therapy should include: (1) an overall reduction of the patient's respiratory symptoms on a 24-hour basis; (2) an attempt to provide the patient with an undisturbed night's rest; and (3) reduction in the risk for morbidity and mortality. Therapeutic measures should be directed at underlying pathologic changes, including bronchial inflammation.

Medications

Longer acting controlled-release theophylline preparations should be administered such that serum theophylline peaks at the most vulnerable time, between midnight and 6:00 AM.[29-31] This is best done by the evening administration of a once-daily sustained-action theophylline preparation. Sustained-release β-agonist tablets (e.g., albuterol or a long-acting inhaled β-agonist [salmeterol]) can also be used.[32] Salmeterol, an inhaled β_2-agonist with a long duration of action, provides good bronchodilator control throughout the night.[33] Inhaled cromolyn and inhaled corticosteroids play a major role in controlling bronchial inflammation and hyperresponsiveness, thereby providing better overall control of the patient's asthma. Different combinations of all the therapeutic approaches noted above may be necessary for good therapeutic control and management of nocturnal symptoms.

Allergen avoidance and immunotherapy

To reduce airway inflammation in atopic patients, the identification and avoidance of allergens are important. Although it is not clear that nocturnal allergen exposure (e.g., to house dust mite) is an important cause of nocturnal asthma, evidence suggests that it is a common cause of heightened bronchial sensitivity.[14] Therefore in properly selected atopic patients, dust control measures and/or immunotherapy can be helpful in long-term management of nocturnal asthma.

REFERENCES

1. Floyer J. A treatise of the asthma. London: Wilkin and Innis, 1986.
2. Turner-Warwick M. On observing patterns of airflow obstruction in chronic asthma. Br J Dis Chest 1977;71:73-86.
3. Clark TJH, Hetzel MR. Diurnal variations of asthma. Br J Dis Chest 1977;71:87-92.
4. Smolensky MH, Barnes PJ, Reinberg A, McGovern JP. Chronobiology and asthma. I. Day-night differences in bronchial potency and dyspnea and circadian rhythm dependencies. J Asthma 1986;23:321-43.
5. De Vries K, Goe JT, Booy-Noord H, Oric NGM. Changes during 24 hours in the lung function and histamine hyperreactivity of the bronchial tree in asthmatic and bronchitic patients. Int Arch Allergy 1962;20:93-101.
6. Connolly CK. Diurnal rhythms in airway obstruction. Br J Dis Chest 1979;73:357-66.
7. Cochrane GM, Clar TJH. A survey of asthma mortality in patients between ages 35 and 64 in the Greater London hospitals in 1971. Thorax 1975;30:300-5.
8. Hetzel MR, Clark TJH, Branthwaite MA. Asthma: analysis of sudden deaths and ventilatory arrests in hospital. Br Med J 1977;1:808-11.
9. Track CH, Cree EM. Oximeter studies in patients with chronic obstructive emphysema awake and during sleep. N Engl J Med 1962;266:639-42.
10. Fletcher EC, Gray BA, Levin DC. Non-apneic mechanisms of arterial oxygen disaturation during rapid eye movement sleep. J Appl Physiol 1983;54:632-9.
11. Turner-Warwick M. Epidemiology of nocturnal asthma. Am J Med 1988;85 (suppl 1B):6-8.
12. Hetzel MR, Clark TGH. Comparison of normal and asthmatic circadian rhythms in peak expiratory flow. Thorax 1980;35:732-8.
13. Barnes PJ. Circadian variation in airway function. Am J Med 1985;79:5-9.
14. Platts-Mills TAE, Tovey ER, Mitchell ER, Moszoro H,

Nock P, Wilkins SR. Reduction of bronchial reactivity during prolonged allergen avoidance. Lancet 1982;765-7.
15. Kerr HD. Diurnal variation of respiratory function independent of air quality. Arch Environ Health 1973;26:144-52.
16. Chen WY, Chai H. Airway cooling and nocturnal asthma. Chest 1982;81:675-80.
17. Hetzel MR, Clark TJH. Does sleep cause nocturnal asthma? Thorax 1979;34:749-54.
18. Dees S. The role of gastroesophageal reflux in nocturnal asthma in children. NC Med J 1974;35:230-3.
19. Bateman JRM, Pavin D, Clardke SW. The retention of lung secretions during the night in normal subjects. Clin Sci Mol Med 1978;55:523-7.
20. Newman-Taylor AJ, Davies RJ, Hendrick DJ, Pepys J. Recurrent nocturnal asthmatic reactions to bronchial provocation tests. Clin Allergy 1979;9:213-9.
21. Ryan G, Latimer KM, Dolovitch J, Hargreave FE. Bronchial responsiveness to histamine: relationship to diurnal variation of peak flow rate, improvement after bronchodilator, and airway caliber. Thorax 1982;37:423-79.
22. Cockcroft DW, Ruffin RE, Dolovich J, Hargreave FE. Allergen-induced increase in non-allergic reactivity. Clin Allergy 1977;7:503-13.
23. Chan-Yeung M, MacLean L, Paggiaro PL. Follow-up study of 232 patients with occupational asthma by Western red cedar *(Thuja plicata)*. J ALLERGY CLIN IMMUNOL 1987;79:792-6.
24. Davies RJ, Green M, Schofield NM. Recurrent nocturnal asthma after exposure to grain dust. Am Rev Respir Dis 1976;114:1011-9.
25. Reed CE, Li JTC. Nocturnal asthma: approach to the patient. Am J Med 1988;85:14-6.
26. Barnes P, Fitzgerald G, Brown M, Dollery C. Nocturnal asthma and changes in circulating epinephrine, histamine and cortisol. N Engl J Med 1980;303:263-7.
27. Soutar CA, Carruthers M, Pickering CA. Nocturnal asthma and urinary adrenaline and nonadrenaline excretion. Thorax 1977;32:677-83.
28. Barnes PJ. Inflammatory mechanisms and nocturnal asthma. Am J Med 1988;85:64-70.
29. Li JTC, Reed CE. Nocturnal asthma and timing of treatment. Am J Med 1985;79:10-5.
30. Busse WW, Bush RK. Comparison of morning and evening dose with a 24 hour sustained release theopylline, uniphyl for nocturnal asthma. Am J Med 1985;79:62-6.
31. Grossman J, et al. Multicenter comparison of one daily uniphyl tablet administered in the morning or evening with baseline twice daily theophylline therapy in patients with nocturnal asthma. Am J Med 1988;85:11-3.
32. Fairfax AJ, McNabb WR. Slow release oral salbutamol and aminophylline in nocturnal asthma: relation of overnight changes in lung function and plasma drug levels. Thorax 1980;35:526-30.
33. Fitzpatrick MF, Mackay T, Driver H, Douglas NJ. Salmeterol in nocturnal asthma: a double-blind, placebo-controlled trial of a long-acting inhaled beta-2 agonist. Br Med J 1990;301:1365-8.

E. EXERCISE-INDUCED ASTHMA

Summary statements

- Exercise-induced asthma (EIA) occurs in up to 90% of patients with asthma.
- EIA is probably triggered by heat and water loss from the respiratory tract, which causes mediator release resulting from bronchial hyperosmolality.
- Inhalation of a β_2-agonist within 15 to 30 minutes before exercise is the treatment of choice for EIA.
- Inhaled cromolyn sodium, taken alone or in conjunction with an inhaled β_2-agonist, 15 to 30 minutes before exercise can also effectively prevent or modify EIA.
- Pretreatment with theophylline, anticholinergic agents, antihistaminic agents, and other medications may benefit some patients with EIA.
- General stabilization of the patient's asthma may be required before effective control of EIA can be achieved.
- Nonpharmacologic methods can be effectively used in some patients to prevent EIA (e.g., exercise under conditions where warm humid air is inhaled).

EIA occurs in 70% to 90% of asthmatic patients.[1] From 2.8% to 14% of world-class athletes manifest EIA.[2] EIA can have a profound effect on patients of all ages. It can affect the spontaneous play of the toddler and young child, the physical education and sports performance of individuals of any age, and the participation of world-class athletes in the Olympic games.[3] Fortunately, the recognition of EIA has led to improved treatment of this entity in the past 15 years.[4] Of the 67 athletes with asthma or EIA on the 1984 U.S. Olympic team (11% of the team), coordinated medical care and the use of International Olympic Committee (IOC)-approved medications enabled 41 to win medals.[3]

Pathogenesis

Proposed causes for EIA include respiratory heat loss, water loss from the airway leading to hyperosmolarity of the fluid interface of the respiratory epithelium,[5,6] or a combination of these two mechanisms.[7,8] The fact that medications that inhibit mediator release from mast cells block EIA provides indirect evidence that heat and water loss trigger bronchospasm through mediator release from these cells.[8] Further evidence for the role of mediators in EIA comes from studies showing increased levels of histamine and neutrophilic chemotactic factor during EIA.[9-11]

Diagnosis

Characteristically, symptoms of bronchospasm, which may consist of cough or dyspnea alone,

TABLE. Selected pharmacologic management of EIA

Normal resting pulmonary function*
Administer before exercise
β_2-agonists
Oral inhalation—administer 15-30 min before exercise
Albuterol†
Metaproterenol
Terbutaline†
Pirbuterol
Biotolterol
Syrup or tablets—administer 1-2 hr before exercise
Albuterol
Metaproterenol
Terbutaline
Cromolyn sodium†—administer 15-30 min before exercise
MDI
Solution by nebulizer
Theophylline†—administer 1-4 hr before exercise
Ipratropium bromide†—administer 20-30 min before exercise

*If lung function is not normal, stabilization of asthma is required (see text).
†IOC approved (1991). Inhaled corticosteroids are also IOC approved.

associated with a fall in FEV_1 of 15% or more, begin minutes after the onset of vigorous activity, peak about 5 to 10 minutes after exercise is stopped, and resolve 20 to 30 minutes after exercise is stopped. Symptoms may also develop during exercise, especially during variable intensity exercise[12] or have been reported to occur as a late response to exercise challenge,[13] although the existence of a late phase response after exercise challenge is controversial. Because the reliability of the history varies, a definitive diagnosis of EIA in any individual patient may require standardized exercise challenge testing.[5]

Treatment

Nonpharmacologic. Several nonpharmacologic methods have been proposed for the management of EIA.[14] Vigorous warmup to the point of bronchospasm can render the athlete relatively refractory to EIA for the ensuing 2 to 3 hours.[15] Physical training can lessen the degree of EIA.[16] Sports performed in environments with warm, humid air produce less bronchoconstriction for a given amount of exercise than sports performed in environments with dry or dry, cold air.[17] Facemasks serve to warm the air and can decrease bronchoconstriction.[18] Exercise at times when bronchial hyperresponsiveness may be increased, such as with viral respiratory infections or sinusitis, may increase symptoms of EIA.[19] Asthma of any kind, including EIA, can be potentiated by β-blockers.[20]

Pharmacologic

GENERAL. The major drugs used in the management of EIA are β-adrenergic agonists and cromolyn sodium (Table). Other compounds, such as methylxanthines, anticholinergics, antihistamines, and calcium antagonists, have been evaluated and show varying degrees of potential for therapeutic use in EIA.[4] Considerations in choosing drugs should include the drug's pharmacology (speed of onset, site, and duration of action), the patient's age and ability to manage the delivery system, the patient's pattern of exercise (plays all day or specific times of exercise), in selected cases IOC and national athletic federation restrictions, and the patient's resting pulmonary status.[4]

Patients with normal resting pulmonary function should be treated 15 to 30 minutes before exercise with either an inhaled β-agonist and/or cromolyn sodium. Theophylline and ipratropium bromide, as well as terfenadine and other antihistamines, have also been shown to be effective in blocking EIA in some patients but should not be considered as first-line agents for the treatment of this condition.

β-ADRENERGIC AGONISTS. The β-adrenergic agonist drugs are the most effective agents for modifying EIA.[21, 22] These medications, especially when given by oral inhalation, have been shown to be potent blockers of EIA.[23] Although all of these agents cause significant bronchodilation and subsequent blockade of EIA, agents with maximum β_2-selectivity are preferable because of the decreased potential for adverse reactions. Formulations include syrups, tablets, metered dose inhalers (MDIs), nebulizer solutions, and dry powder inhalers. Syrups have a slower onset of action, and the response may be variable, but they may be useful in children too young to use inhalers. Longer acting dosage forms may be useful before prolonged exercise or when it is inconvenient to use medication just before exercise.

These drugs can significantly lower serum potassium,[24] which may be potentiated by exercise. One should keep this effect in mind in a patient with unexplained weakness. Although oral formulations of these agents have more systemic side effects than inhaled formulations, inhaled β-agonists have been associated with the development of hypokalemia. Because of ease of use, decreased potential

for adverse effects, and effectiveness, the preferred route of administration is by oral inhalation using a MDI.

CROMOLYN. Inhaled cromolyn sodium is an effective treatment in atopic and nonatopic asthmatic patients with EIA,[25] but may not be effective in all patients.[26] It also blocks the increase in airway resistance induced by cold air in normal individuals. Use of cromolyn sodium in combination with a β_2-agonist is additive in blocking EIA and is synergistic in protecting against both cold-induced and hyperventilation-induced bronchospasm.[27] Formulations include a powder delivered by spinhaler, a MDI, and a nebulizer solution. The isotonic form of nebulized cromolyn sodium, although not usually available, provides better protection against EIA than does the standard hypotonic solution.[28] Cromolyn's effectiveness is dose related,[29] and the optimal dosage varies among patients. The MDI provides the best flexibility in treatment, although the nebulized form gives the highest plasma concentration.[30] Cromolyn may be useful in patients with EIA whose EIA is inadequately controlled with β-agonists alone or who develop adverse reactions after the use of inhaled β-agonists before exercise.

THEOPHYLLINE. Both rapid-acting and sustained-release preparations of theophylline have been shown to be effective in the prevention of EIA in some patients.[31, 32] The protective effect has been shown to be present at serum levels as low as 6 mg/L in patients exercising in cold air[33] and appears to depend on the strength of the stimulus and the serum concentration, which may vary considerably from patient to patient.[23] The major disadvantages from the use of theophylline are the need to take the rapid-acting formulation 30 to 60 minutes before exercise and the frequent adverse reactions (primarily nausea and headache) associated with rapid attainment of a therapeutic level, particularly in patients not regularly taking theophylline. These have limited the use of theophylline as prophylaxis for EIA. The major use of theophylline should be to stabilize asthmatic patients with abnormal pulmonary function at rest, thereby allowing other medications to be more effective in preventing EIA. Concern also exists that theophylline may be ergogenic, providing a competitive advantage in those athletes using the drug. One study, however, in world-class athletes without EIA,[34] which analyzed a number of variables, could find no competitive advantage for patients taking theophylline compared with patients who received placebo.

ANTICHOLINERGICS. Both atropine and ipratropium bromide have been shown to be effective in preventing EIA in some patients[35, 36] but are not as effectively as cromolyn or β_2-agonists.[37] In most instances, protection provided by anticholinergic agents is variable, incomplete, and acts predominantly on central airways.[38] Anticholinergic agents are not universally effective in patients with atopic disease and moderate-to-severe EIA[39] but are more likely to be effective in patients with marked receptor reactivity in cold air and/or reactivity to air pollutant.[40]

ANTIHISTAMINES. Terfenadine has been shown to attenuate hyperventilation-induced bronchospasm[41] and to block treadmill-induced EIA in a dose-dependent fashion.[42] Other antihistamines that have been shown to have an inhibitory effect on EIA include azatidine (by oral inhalation),[43] ketotifen[44, 45] (although data on ketotifen are conflicting, especially in adults),[46] and azelastine.[47]

CALCIUM CHANNEL BLOCKERS. Nifedipine,[48, 49] flordipine,[49] PY108-068,[50] felodipine,[51] gallopamil,[52] diltiazem,[52] and verapamil[53] provide only modest protection against EIA, at best, with short duration of action.

OTHER MEDICATIONS. Other compounds that have an effect on EIA include the α-adrenergic agent prazosin,[54] the cromolyn-like drug nedocromil sodium,[55, 56] and inhaled furosemide.[57] The nonsteroidal anti-inflammatory agent indomethacin is ineffective in blocking EIA but prevents refractoriness to repeated exercise at short intervals in asthmatic patients,[58] which may have additional therapeutic implications because many athletes use nonsteroidal anti-inflammatory drugs. Steroids have not been effective when used immediately before exercise in preventing EIA.

In asthmatic patients with abnormal resting pulmonary function, treatment of EIA often requires optimizing control of asthma before pretreatment with the medications noted above will be effective. This can be accomplished with regular use of cromolyn, theophylline (sustained-release), β-agonists, and/or inhaled corticosteroids. Once this is done, the patient can be treated before exercise in the same manner as those with normal resting pulmonary function.

REFERENCES

1. Kawabori I, Pierson WE, Conquest LL, et al. Incidence of exercise induced asthma in children. J ALLERGY CLIN IMMUNOL 1976;58:447-55.
2. Godfrey S. Symposium on special problems and management of allergic athletes. International symposium on spe-

cial problems and management of allergic athletes: part 2. J ALLERGY CLIN IMMUNOL 1984;73:630-3.
3. Voy RO. The U.S. Olympic Committee experience with exercise-induced bronchospasm, 1984. Med Sci Sports Exerc 1986;18:328-30.
4. Pierson WE. The effect of drugs on exercise-induced asthma. In: Oseid A, Edwards E, eds. The asthmatic child: in play and sport, Bath, England: Pitman Press, 1983:187-96.
5. McFadden ER Jr, Ingram RH Jr. Exercise-induced asthma: observations on the initiating stimulus. N Engl J Med 1979;301:763-8.
6. Anderson SD, Schoeffel RE, Follet R, et al. Sensitivity to heat and water loss at rest and during exercise in asthmatic patients. Eur J Respir Dis 1982;63:459-71.
7. Bascom R, Bleecker ER. Bronchoconstriction induced by distilled water: sensitivity in asthmatics and relationship to exercise-induced bronchospasm. Am Rev Respir Dis 1986; 134:248-53.
8. Haltom JR, Strunk RC. Pathogenesis of exercise-induced asthma: implications for treatment. Ann Rev Med 1986;37: 143-8.
9. Barnes PJ, Brown MJ. Venous plasma histamine in exercise- and hyperventilation-induced asthma in man. Clin Sci 1981;61:159-62.
10. Anderson SD, Bye PTP, Schoeffel RE, Seale JP, Taylor KM, Ferris L. Arterial plasma histamine levels at rest, and during and after exercise in patients with asthma: effects of terbutaline aerosol. Thorax 1981;36:259-67.
11. Lee TH, Nagakura T, Papageorgiou N, Cromwell O, Iikura Y, Kay AB. Mediators in exercise-induced asthma. J ALLERGY CLIN IMMUNOL 1984;73:634-9.
12. Beck KC, Offord KP, Scanlon PD. Bronchoconstriction occurring during exercise in asthmatic subjects. Am Rev Respir Crit Care Med 1994;149:352-7.
13. Rubinstein I, Levison H. Immediate and delayed bronchoconstriction after exercise in patients with asthma. N Engl J Med 1987;317:482-5.
14. Katz RM. Prevention with and without the use of medications for exercise-induced asthma. Med Sci Sports Exerc 1986;18:331-3.
15. Morton AR, Kitch KD, Davis T. The effect of "warm-up" on exercise-induced asthma. Ann Allergy 1979;42:257-60.
16. Bundgaard A, Ingemann-Hansen T, KalkJaer-Kristensen J, et al. Short-term physical training in bronchial asthma. Br J Dis Chest 1983;77:147-52.
17. Pierson WE. Exercise-induced bronchospasm in children and adolescents. Ped Clin North Am 1988;35:1031-40.
18. Schachter EN, Lach E, Lee M. The protective effect of a cold weather mask on exercise-induced asthma. Ann Allergy 1981;46:12-6.
19. Slavin RG. Sinusitis. International symposium on special problems and management of allergic athletes: part 2. J ALLERGY CLIN IMMUNOL 1984;73:712-6.
20. Schwartz S, Davies S, Juers JA. Life-threatening cold and exercise-induced asthma potentiated by administration of propranolol. Chest 1980;78:100-1.
21. Bierman CW. Exercise-induced asthma. New Engl Reg Allergy Proc 1988;9:193-7.
22. Rohr AS, Siegel SC, Katz RM, Rachelefsky GS, Spector SL, Lanier R. A comparison of inhaled albuterol and cromolyn in the prophylaxis of exercise-induced bronchospasm. Ann Allergy 1987;59:107-9.
23. Sly RM. Management of exercise-induced asthma. Drug Therapy 1982;12:95-99, 102-7.
24. Allon M, Dunlay R, Copkney C. Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. Ann Intern Med 1989;110:426-9.
25. Konig P. The use of cromolyn in the management of hyperreactive airways and exercise. J ALLERGY CLIN IMMUNOL 1984;73:686-9.
26. Debelic M, Gunter H, Konig J. Double-blind crossover study comparing sodium cromoglycate, reproterol, reproterol plus sodium cromoglycate, and placebo in exercise-induced asthma. Ann Allergy 1988;61:25-9.
27. Latimer KM, O'Byrne PM, Morris MM, et al. Bronchoconstriction stimulated by airway cooling: better protection with combined inhalation of terbutaline sulfate and cromolyn sodium than with either alone. Am Rev Respir Dis 1983;128:440-3.
28. Weiner P, Saaid M, Reshef A. Isotonic nebulized disodium cromoglycate provides better protection against methacholine- and exercise-induced bronchoconstriction. Am Rev Respir Dis 1988;137:1309-11.
29. Patel KR, Wall RT. Dose-duration effect of sodium cromoglycate aerosol in exercise-induced asthma. Eur J Respir Dis 1986;69:256-60.
30. Patel KR, Tullett WM, Neale MG, Wall RT, Tan KM. Plasma concentrations of sodium cromoglycate given by nebulization and metered dose inhalers in patients with exercise-induced asthma: relationship to protective effect. Br J Clin Pharmacol 1986;21:231-3.
31. Bierman CW, Shapiro GG, Pierson WE, et al. Acute and chronic theophylline therapy in exercise-induced bronchospasm. Pediatrics 1977;60:845-9.
32. Weinberger M. Theophylline for treatment of asthma. J Pediatr 1978;92:1-7.
33. Magnussen H, Reuss G, Jorres Rudolf. Methylxanthines inhibit exercise-induced bronchoconstriction at low serum theophylline concentration and in a dose-dependent fashion. J ALLERGY CLIN IMMUNOL 1988;81:531-7.
34. Morton AR, Scott CA, Fitch KD. The effects of theophylline on the physical performance and work capacity of well-trained athletes. J ALLERGY CLIN IMMUNOL 1989;83: 55-60.
35. Rachelefsky GS, Tashkin DP, Katz RM. Comparison of aerosolized atropine, isoproterenol, atropine plus isoproterenol, disodium cromoglycate and placebo in the prevention of exercise-induced asthma. Chest 1978;73(suppl): 1017-9.
36. Kamburoff PL. Effects of different drugs on exercise-induced asthma (EIA). Eur J Respir Dis 1980;106(suppl):65-9.
37. Thomson NC, Patel KR, Kerr JW. Sodium cromoglycate and opratroprium bromide in exercise-induced asthma. Thorax 1978;33:694-9.
38. Godfrey S, Konig P. Inhibition of exercise-induced asthma by different pharmacological pathways. Thorax 1976;31: 137-43.
39. Harries MG, Parkes PEG, Lessof MH, et al. Role of bronchial irritant receptors in asthma. Lancet 1981;i:5-7.
40. Pierson WE, Covert DS, Koenig JQ. Air pollutants, bronchial hyperactivity and exercise. J ALLERGY CLIN IMMUNOL 1984;73:717-21.
41. Badier M, Beaumont D, Orehek J. Attenuation of hyperventilation-induced bronchospasm by terfenadine: a new antihistamine. J ALLERGY CLIN IMMUNOL 1988;81:437-40.
42. Pierson WE, Bierman CW, Shapiro GG, et al. Terfenadine dose-response blockage of exercise-induced bronchospasm [Abstract]. J ALLERGY CLIN IMMUNOL 1987;79:96.

43. Harries MG, Burge PS, O'Brien I, et al. Blood histamine levels after exercise testing. Clin Allergy 1979;9:437-41.
44. Osterballe O, Nielsen EAL. The protective effect of a new agent, ketotifen syrup, in the treatment of childhood asthma. Allergy 1979;34:125-9.
45. Petheram IS, Moxham J, Bierman CW, et al. Ketotifen in atopic asthma and exercise-induced asthma. Thorax 1981; 36:308-12.
46. Tan WC, Lim TK. Double-blind comparison of the protective effect of sodium cromoglycate and ketotifen on exercise-induced asthma in adults. Ann Allergy 1987;42:315-7.
47. Magnussen H, Reuss G, Jorres R, Aurich R. The effect of azelastine on exercise-induced asthma. Chest 1988;93:937-40.
48. Patel KR. The effect of calcium antagonist, nifedipine, in exercise-induced asthma. Clin Allergy 1981;11:429-32.
49. Gordon EH, Wong SC, Klaustermeyer. Comparison of nifedipine with a new calcium channel blocker, flordipine, in exercise-induced asthma. J Asthma 1987;24:261-4.
50. Ben-Dov I, Sue DY, Hansen JE, Wasserman. Bronchodilatation and attenuation of exercise-induced bronchospasm by PY 108-068, a new calcium antagonist. Am Rev Respir Dis 1986;133:116-9.
51. Patel KR, Peers K. Felodipine, a new calcium antagonist, modified exercise-induced asthma. Am Rev Respir Dis 1988;138:54-6.
52. Massey KL, Harman E, Hendeles L. Duration of protection of calcium channel blockers against exercise-induced bronchospasm: comparison of oral diltiazem and inhaled gallopamil. Eur J Clin Pharmacol 1988;34:555-9.
53. Boner AL, Antolini A, DeStefano G, Sette L. Comparison of the effects of inhaled calcium antagonists verapamil sodium cromoglycate and ipratroprium bromide on exercise-induced bronchoconstriction in children with asthma. Eur J Pediatr 1987;146:408-11.
54. Souza LM, Silverman M. Prostaglandins in exercise-induced asthma. Clin Allergy 1981;11:506-7.
55. Juniper EF, Kline PA, Morris MM, Hargreave FE. Airway constriction by isocapnic hyperventilation of cold, dry air: comparison of magnitude and duration of protection by nedocromil sodium and sodium cromoglycate. Clin Allergy 1987;17:523-8.
56. Chudry N, Correa F, Silverman M. Nedocromil sodium and exercise induced asthma. Arch Dis Childhood 1987;62:412-3.
57. Bianco S, Robuschi M, Vaghi A, Pasargiklian M. Prevention of exercise-induced bronchoconstriction by inhaled fursemide. Lancet 1988;30:252-6.
58. O'Byrne PM, Jones GL. The effect of indomethacin on exercise-induced bronchoconstriction and refractoriness after exercise. Am Rev Respir Dis 1986;134:69-72.

F. NASAL AND SINUS DISEASE AND ASTHMA

Summary statements

- Frequently, there is an association between asthma and sinusitis, and improvement in asthma may occur when sinusitis is properly treated.
- Sinusitis should be considered in patients with refractory asthma.
- Evaluation of sinus disease may require sinus radiographs, computed tomographic (CT) scans, and/or endoscopic procedures.
- Many local and/or systemic factors may increase the risk of sinusitis developing. Certain diseases, such as cystic fibrosis, and local factors, such as nasal polyps, may increase the risk of developing sinusitis.
- Nasal polyps may occur in association with sinus disease, and both conditions may affect asthma.

Infection of the paranasal sinuses is a common medical condition that accounts for substantial loss of work days and causes great financial expense for individuals and the national health care system. In personal terms, sinusitis causes discomfort, fatigue, and general lassitude in many adults and children. Although sinusitis has been generally underdiagnosed and unappreciated in the past, interest in this disease and its link with asthma have increased.

Pathogenesis

The sinuses are protected against infection largely by a self-cleansing mucociliary mechanism.[1] To be fully operative, this mechanism requires functional cilia, patent sinus ostia, and the secretion of mucus with the appropriate physical and chemical characteristics.[2] Other protective factors include lysozymes and secretory IgA.[3]

Bacterial infection of the sinuses occurs when the self-cleansing mechanism becomes impaired. Mucus accumulates, stagnates, and becomes infected by relatively harmless opportunistic pyogenic bacteria normally found in the nose. Bacteria responsible for acute sinusitis are largely aerobic.[4] *Haemophilus influenza* and *Streptococcus pneumoniae* are the most common pathogens. *Streptococcus viridans* and *Moraxella catarrhalis* are present less often. Anaerobic bacteria are also responsible for chronic sinusitis.[5] Common pathogens include α-streptococci and species of *Bacteroides, Veillonella,* and *Corynebacterium.* Fungal infection of the paranasal sinuses may also occur, with *Aspergillus fumigatus* the most common offender.[6]

Sinusitis occurs most commonly as a complication of a viral infection of the upper respiratory tract. During such an infection, acute rhinitis is associated with a decrease in paranasal sinus ciliary action, edematous obstruction of the sinus ostia, and increased production of mucus as a result of inflammation. The stage is thereby set for the development of secondary bacterial infection, namely, the conversion of mucus to mucopus. Mucopus further impairs ciliary functioning and increases the swelling around the ostia, thus creating a vicious cycle.

Other common local conditions that can predispose a person to sinusitis include allergic rhinitis, overuse of topical decongestants (rhinitis medicamentosa), hypertrophied adenoids, deviated nasal septum, and the presence of nasal polyps, tumors, or foreign bodies. The common denominator shared by these conditions is mechanical obstruction of the sinus ostia. Slower ciliary movement and increased mucus production are known effects of cigarette smoking and may predispose the smoker to develop sinusitis. When a person is swimming or diving, water may invade the sinus cavities and initiate an inflammatory process because it is either chemically irritating or contaminated with bacteria.

In addition to local factors, underlying medical conditions may foster the development of sinusitis. These include immune deficiency, cystic fibrosis, and the immotile cilia syndrome.

Diagnosis of sinusitis

General lack of pain or systemic symptoms makes chronic sinusitis difficult to diagnose based on the history alone.[7, 8] Patients with chronic sinusitis generally do not complain of headache, facial pain, fullness in the face, pain in the teeth, or discomfort when they bend over. Rather, nasal obstruction, which is sometimes unilateral, purulent postnasal drainage, hyposmia, sore throat, and unpleasant breath are the most common presenting signs. Chronic cough, particularly at night, commonly accompanies sinusitis. Physical examination of the patient with chronic sinusitis may reveal an edematous nasal mucosa occasionally bathed in mucopus.

The most important clinical clue to the diagnosis of *acute* sinusitis is the continuation of symptoms after a typical cold has subsided. If previously clear nasal discharge becomes yellow or green, this indicates that a bacterial infection may be present. Fever may persist, and chills may develop. Pain or pressure over the sinus areas of the face and/or the area of the upper teeth may be associated with sinusitis and is often worse with bending or straining.

On physical examination the patient may have thick, purulent, green or deep yellow secretions in the nose on the side of the diseased sinus. Because the maxillary sinus is most frequently involved, purulent secretions will be seen most often in the middle meatus, which is the drainage site of the maxillary sinus, after appropriate shrinkage of the inferior turbinates. Transillumination of the paranasal sinuses may be useful in following patients with proven sinusitis or in a pregnant patient with asthma. However, this procedure lacks sensitivity.[9]

Sinus radiographs are a useful first approach in establishing a clinical diagnosis of sinusitis. The correlation between antral puncture results and roentgenographic appearance indicates that sinusitis is highly associated with either mucosal thickening of 6 mm or more in adults or 4 mm or more in children, an air-fluid level, or opacification.[9] However, nasopharyngeal cultures do not provide significant diagnostic information and bacterial sinusitis may be present in the absence of x-ray film abnormalities.[8, 10] CT scanning may reveal disease, particularly in the ethmoid sinuses, that is not detectable by ordinary sinus radiographs.[11]

Management of sinusitis

Analgesics, decongestants (either oral or topical), antibiotics, and nasal corticosteroids can be appropriately used in the medical management of sinusitis. The antibiotic of choice in acute or chronic sinusitis is ampicillin or amoxicillin if the organisms do not produce β-lactamases. If the responsible organisms are sensitive to these antibiotics, adequate mucosal and sinus fluid concentrations can be attained.[12, 13] For patients who are penicillin sensitive, an adequate alternative is trimethoprim-sulfamethoxazole. Certain bacteria may be resistant to penicillin and cephalosporins by producing β-lactamase enzymes that destroy the β-lactam nucleus of these antibiotics. Clavulanic acid, an inhibitor of the β-lactamases, has been introduced in combination with amoxicillin; these drugs may prove to be useful in some patients, particularly in children with *M. catarrhalis* infection. Quinalones and cephalosporins may also be useful.

The duration of treatment is as important as the choice of antibiotics. The usual treatment course of acute sinusitis is a minimum of 10 days. The treatment of chronic recurrent sinusitis usually requires 3 to 4 weeks or longer. If no significant clinical or roentgenographic improvement is seen after 1 month of antibiotic therapy, referral to an otolaryngologist should be considered for conditions such as osteomeatal disease.

Sinusitis and asthma

Studies in adults and children have demonstrated a common association between asthma and sinusitis, as well as an improvement in asthma in some patients when sinusitis is properly managed.[14] Sinusitis should be suspected in cases of

recalcitrant asthma.[15] The basis for this association is not known.[16-18]

Allergic rhinitis and asthma

Patients with nasal allergy without clinical manifestations of asthma may exhibit bronchial hyperresponsiveness as demonstrated by bronchial provocation with methacholine, histamine, cold air, or pollen.[19-23] In addition, some patients with seasonal allergic rhinitis may have seasonal variation in bronchial hyperresponsiveness.[24-26] It has been shown that treatment of nasal inflammation with intranasal corticosteroids improves asthma symptoms and decreases bronchial hyperresponsiveness.[27] Therefore treatment of upper airway inflammation and nasal symptoms may be helpful in the effective control of asthma.

REFERENCES

1. Wagenmann M. Anatomic and physiologic considerations in sinusitis. J ALLERGY CLIN IMMUNOL 1992;90:419-23.
2. Reiner A, von Mecklenburg C, Toremalm NG. The mucociliary action of the upper respiratory tract. III Acta Otolaryngol 1978;355(suppl):1.
3. Kaliner MA. Human nasal host defense and sinusitis. J ALLERGY CLIN IMMUNOL 1992;90:424-9.
4. Wald ER, Milmoe GJ, Bowen A, et al. Acute maxillary sinusitis in children. N Engl J Med 1981;304:749.
5. Brook I. Bacteriologic features of chronic sinusitis in children. JAMA 1981;246:967.
6. Morgan MA, Wilson WR, Neel HB III, Robert GD. Fungal sinusitis in healthy and immunocompromised individuals. Am J Clin Pathol 1984;82:597.
7. Slavin RG. Nasal polyps and sinusitis. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, eds. Allergy: Principles and practice. 3rd ed. St Louis: The CV Mosby Co, 1988.
8. Druce HM. Diagnosis of sinusitis in adults: history, physical examination, nasal cytology, echo and rhinoscope. J ALLERGY CLIN IMMUNOL 1992;90:436-41.
9. Fireman P. Diagnosis of sinusitis in children: Emphasis on the history and physical examination. J ALLERGY CLIN IMMUNOL 1992;90:433-6.
10. Zinreick SJ. Imaging of chronic sinusitis in adults: x-ray, computed tomography, and magnetic resonance imaging. J ALLERGY CLIN IMMUNOL 1992;90:445-51.
11. Cable HR, Jeans WD, Cullen RJ, et al. Computerized tomography of the Caldwell-Luc cavity. J Laryngol Otol 1981;95:775.
12. Urdal K, Berdal P. The microbial flora in 81 cases of maxillary sinusitis. Acta Otolaryngol 1949;37:20-5.
13. Winther B, Gwaltney JN Jr. Therapeutic approach to sinusitis: antiinfectious therapy as the baseline of management. Otolaryngol Head Neck Surg 1990;103:876-9.
14. Slavin RG, Connor RE, Friedman WH, et al. Sinusitis and bronchial asthma. J ALLERGY CLIN IMMUNOL 1980;66:250.
15. Slavin RG. Asthma and sinusitis. J ALLERGY CLIN IMMUNOL 1992;90:534-7.
16. Friday GA, Fireman P. Sinusitis and asthma: clinical and pathogenetic relationships. Clin Chest Med 1988;9:557-65.
17. McFadden ER. Nasal-sinus pulmonary reflexes and bronchial asthma. J ALLERGY CLIN IMMUNOL 1986;78:1-3.
18. Adinoff AD, Irvin CG. Upper respiratory tract disease and asthma. Semin Respir Med 1987;8:308-14.
19. Townley RG, Yun Ryo V, Miller Kolotkin B, Kang R. Bronchial sensitivity to methacholine in current and former asthmatic and allergic rhinitis patients and control subjects. J ALLERGY CLIN IMMUNOL 1975;56:429-42.
20. Stevens WJ, Vermeire PA. Bronchial responsiveness to histamine and allergen in patients with asthma, rhinitis, cough. Eur J Respir Dis 1980;61:203-12.
21. Fish JE, Ankin MG, Kelly JF, Peterman VT. Comparison of responses to pollen extract in subjects with allergic asthma and non-asthmatic subjects with allergic rhinitis. J ALLERGY CLIN IMMUNOL 1980;65:154-61.
22. Ahmed T, Fernandez RJ, Wanner A. Airway response to antigen challenge in allergic rhinitis and allergic asthma. J ALLERGY CLIN IMMUNOL 1981;67:135-45.
23. Chandler Deal E Jr, McFadden ER Jr, Ingram RH Jr, Breslin FJ, Jaeger JJ. Airway responsiveness to cold air and hyperpnea in normal subjects and in those with hay fever and asthma. Am Rev Respir Dis 1980;121:621-8.
24. Gerblich AA, Schwartz HJ, Chester EH. Seasonal variation of airway function in allergic rhinitis. J ALLERGY CLIN IMMUNOL 1986;77:676-81.
25. Madonini MD, Briatico-Vangosa G, Pappacoda A, Cardiani A, Saporiti F. Seasonal increase of bronchial reactivity in allergic rhinitis. J ALLERGY CLIN IMMUNOL 1987;79:358-63.
26. Braman SS, Barrows AA, DeCotiis BA, Settipane GA, Corraso WM. Airway hyperresponsiveness in allergic rhinitis, a risk factor for asthma. Chest 1987;91:671-4.
27. Watson WTA, Becker AB, Simons FER. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. J ALLERGY CLIN IMMUNOL 1993;91:97-101.

G. GASTROESOPHAGEAL REFLUX AND ASTHMA

Summary statements

- Gastroesophageal reflux (GER) occurs commonly in patients with asthma.
- GER should be suspected in patients with nocturnal asthma or in patients who are not responding adequately to optimal medical management.
- A number of objective diagnostic modalities are available for establishing a relationship between GER and asthma.
- Medical or surgical treatment of GER in asthmatic patients may improve their respiratory symptoms.
- Surgical correction of GER should only be considered when medical therapy is unsuccessful and a causal relationship between GER and asthma has been objectively established.

An association between bronchial hyperresponsiveness and GER has been postulated for several

years. Multiple studies have demonstrated that GER is a common medical problem. Depending on the criteria used to diagnose reflux, between 45% and 65% of adults with asthma and 25% to 80% of children with asthma have significant GER.[1,2] Despite these observations, the nature of the relationship between GER and asthma remains controversial. Questions including, "Is GER the cause of or a contributing factor in asthma?" and "Does asthma and/or its medical therapy cause or contribute to GER?" remain to be answered.

This section will explore the pathophysiology of GER, the evidence of a causative relationship between GER and asthma, and the diagnostic evaluation and treatment of patients with GER.

Pathophysiology of GER

Some of the factors reported to induce GER include: (1) certain bronchodilator medications (theophylline and oral adrenergic agents), (2) increased negative intrapleural pressures (caused by airway obstruction and hyperinflation), (3) transient increased intra-abdominal pressure (coughing), (4) cigarette smoking, (5) inadequate primary or secondary esophageal peristalsis, and (6) delayed gastric emptying.

Competence of the lower esophageal sphincter (LES) is a primary defense factor in preventing GER. LES relaxation with loss of competence has been shown to be induced by some medications used to treat asthma, including theophylline and oral and intravenous but not inhaled β-adrenergic agonists.[2,3] Cigarette smoking, probably mediated by nicotine and/or adrenergic stimulation, can also reduce lower esophageal sphincter pressure (LESP).[4] Whether environmental tobacco smoke has a similar effect is not known. Decreased LESP, however, is not the only causative factor in symptomatic GER, because many individuals with GER have normal resting LESP.[5] Both defective esophageal clearing of gastric acid and inadequate esophageal peristalsis have been demonstrated in selected patients with GER.[4] The common effect of these abnormalities is delayed acid clearing and the resultant potential for esophageal mucosal injury, which may progress to esophagitis and its complications. During sleep, delay in acid clearance may be further magnified by the normally occurring diminished buffering capacity that occurs as a result of decreased salivary flow and frequency of swallowing.[5] Because theophylline increases gastric acid secretion, therapy with this agent may further increase the acidity and potential damage of refluxed gastric contents.[2] Some patients with chronic reflux also demonstrate delayed gastric emptying. This may heighten the potential for postprandial reflux, and the resultant larger gastric volume may strain the antireflux mechanism. Lastly, transient increases in intraabdominal pressure above the level of the resting LESP, such as induced by asthma and coughing, can result in reflux.

For many years it was hypothesized that even minimal aspiration of gastric contents caused reflux-induced bronchospasm. Although aspiration has been found to cause other pulmonary diseases, little evidence supports its direct causal role in asthma.[6] Rather, there is now evidence to support a vagally induced reflex mechanism.

Several investigators have described selected patients in whom overt pulmonary symptoms, including cough and wheezing, develop (especially at night) in association with decreased esophageal pH as measured by a pH probe and worsening pulmonary function tests. On further evaluation, esophageal abnormalities (esophagitis and/or abnormal motility) and delayed clearing of gastric acid were noted in these patients. In addition, clinical and pulmonary function evidence of asthma induced by acid installation into the esophagus of asthmatic patients with esophagitis could be prevented by treatment with atropine.[7,8] Bilateral interruption of vagus nerve conduction in dogs with carbocaine also prevented an increase in respiratory airway resistance that occurs after acid installation into the esophagus.[9] A study has demonstrated that intraesophageal acid perfusion can potentiate methacholine-induced airway hyperresponsiveness in adult asthmatic patients without necessarily causing asthma.[2] It has also been observed that medical or surgical treatment of GER aimed at blocking vagal responses in asthmatic patients may improve respiratory symptoms.[1] Hence there has been speculation that stimulation of exposed vagal esophageal nerve endings, presumably resulting from esophagitis, can result in vagally induced reflex bronchospasm.

Diagnosis of GER

GER should be suspected in the asthmatic patient with (1) heartburn, (2) significant nocturnal symptoms (especially cough), and/or (3) asthma resistant to optimal medical management.[2]

Multiple modalities are available to diagnose reflux. Appropriate consultation with a gastroenterologist should be obtained during this evaluation. Endoscopy as a useful evaluation procedure

has been previously discussed (see section on "Other Diagnostic Techniques").

Invasive studies are often required to attempt to document a temporal and causal relationship between GER and asthma. Monitoring by pH probe with concomitant observation of signs and symptoms of asthma and objective deterioration of pulmonary function tests are helpful only if positive. Causality is more conclusively demonstrated when simulation of reflux with esophageal acid infusion produces symptoms of substernal discomfort (Bernstein test) or deterioration in pulmonary function tests and/or clinical signs of asthma (modified Bernstein test).

Treatment of GER in the asthmatic patient

It is important to outline a practical approach to the management of GER. Asthmatic patients with GER should be without food or fluids at least 1½ hours before retiring and should sleep with the head of the bed elevated. Further suggestions in adults include avoiding tobacco, alcohol, and possible aggravating foods (e.g., citrus fruits, chocolate, and caffeine) and weight loss.

Medical treatment of GER in asthmatic patients consists of one or a combination of the following medications: (1) antacids including sucralfate; (2) H_2 receptor antagonists such as cimetidine, ranitidine, or famotidine; (3) sphincter-augmenting agents such as metoclopramide (Reglan) or cisapride (Propulsid) (in adults); and (4) omeprazole, which inhibits gastric acid secretion, for short-term (4 to 8 weeks) use. Medical therapy should be administered for at least 6 to 8 weeks.

Bethanecol should be avoided because it may produce bronchospasm. Because theophylline and oral β_2-agonists have been shown to decrease LESP, it is possible that certain patients may benefit from discontinuation of this therapy. Corticosteroids are not contraindicated in asthmatic patients with GER.

If medical treatment is not effective in controlling GER in the asthmatic patient, surgical therapy may be necessary.[10-12]

REFERENCES

1. Gonzalez ER, Castell DO. Respiratory complications of gastroesophageal reflux. Am Fam Physician 1988;37:169-72.
2. Orenstein S, Orenstein D. Gastroesophageal reflux and respiratory diseases in children. J Pediatr 1988;112:847-58.
3. Schindlbeck N, Heinnch C, Huber R, et al. Effects of albuterol (salbutamol) in esophageal motility and gastroesophageal reflux in healthy volunteers. JAMA 1980;260:3156-8.
4. Richter J, Castell D. Gastroesophageal reflux. Ann Intern Med 1982;97:93-102.
5. Sondheimer J. Gastroesophageal reflux: Update on pathogenesis and diagnosis. Pediatr Clin North Am 1988;35:103-15.
6. Harper P, Bergner A, Kay M. Antireflux treatment for asthma. Arch Intern Med 1987;147:56-60.
7. Davis RS, Larsen GL, Grunstein MM. Respiratory response to intraesophageal acid infusion in asthmatic children during sleep. J ALLERGY CLIN IMMUNOL 1983;72:393-8.
8. Anderson L, Schmidt A, Bundgaard A. Pulmonary function and acid application in the esophagus. Chest 1986;90:358-63.
9. Mansfield L, Hameister H, Spaulding H, et al. The role of the vagus nerve in airway narrowing caused by intraesophageal hydrochloric acid provocation and esophageal distension. Ann Allergy 1981;47:431-4.
10. Barish C, Wallace C, Castell D. Respiratory complications of gastroesophageal reflux. Arch Intern Med 1985;145:1882-8.
11. Goldman J, Bennett JR. Gastro-oesophageal reflux and respiratory disorders in adults. Lancet 1988;2:493-5.
12. Harnsberger JK, Corey J, Johnson D, et al. Long term follow-up of surgery for gastroesophageal reflux in infants and children. J Pediatr 1983;102:505-8.

H. ASPIRIN/NONSTEROIDAL ANTI-INFLAMMATORY DRUG/ PRESERVATIVE SENSITIVITY

Summary statements

It should be recognized that:

- Aspirin (ASA) and nonsteroidal anti-inflammatory drug (NSAID) idiosyncrasy occurs in up to 10% to 15% of all asthmatic patients and in 30% to 40% of asthmatic patients with nasal polyps and pansinusitis. These reactions are non–IgE mediated and designated as idiosyncrasies.
- Ultimately, many patients with ASA or NSAID idiosyncrasy develop corticosteroid-dependent asthma.
- ASA desensitization may be useful therapeutic adjunct in some patients, especially those who have concurrent diseases that require ASA or NSAIDs.
- Sulfite additives in drugs and foods may induce severe adverse reactions in susceptible asthmatic patients.
- Tartrazine in foods or drugs may induce asthma in a small number of patients with ASA idiosyncrasy.
- Similar to ASA reactions, almost all of the reactions to tartrazine are not IgE-mediated.
- Asthmatic reactions may occur in a few monosodium glutamate–susceptible patients

after double-blind, controlled challenge with this food flavoring agent.

- Several other dye and preservative additives in foods and drugs have also been implicated as inducers of asthma.

Aspirin, nonsteroidal anti-inflammatory drugs, and preservatives as precipitants of asthma

Aspirin (ASA) idiosyncrasy, as characterized by bronchospasm that may at times be life-threatening, is present in 10% to 15% of all asthmatic patients and in 30% to 40% of a subpopulation of asthmatic patients with nasal polyps and pansinusitis.[1] Cross-reactions between ASA and nonsteroidal anti-inflammatory drugs (NSAIDs) occur routinely but almost never occur even with very high dosages of acetaminophen, salsalate, and sodium salicylate.

Mechanisms responsible for ASA idiosyncrasy are incompletely understood. Although ASA and NSAIDs share the pharmacologic effects of cyclooxygenase inhibition, it is unlikely that this inhibition alone accounts for the pathogenic effects. More likely is the possibility that ASA/NSAIDs stimulate mast cells or other inflammatory cells to release leukotrienes during the reaction and that the associated inflammatory mucosal disease is the product of eosinophilic infiltration and local release of mediators.

Treatment of patients with ASA/NSAID idiosyncratic asthma depends on the degree of inflammation in the respiratory tract. Some patients can be managed with standard bronchodilators and topical corticosteroids. Others continue to form nasal polyps and develop sinusitis and intractable asthma. Systemic corticosteroids are then required to manage the underlying inflammatory disease. At this point the physician needs to decide whether disease control with corticosteroids outweigh this benefit. Alternately, patients can either undergo sinus surgery or ASA densensitization.[2] ASA desensitization may decrease inflammation in the respiratory tract and may also be used if the patient requires daily NSAIDs for the treatment of concurrent conditions such as arthritis and prevention of thromboembolic disease.[3] ASA desensitization is a potentially hazardous procedure and should only be performed by physicians knowledgeable in the challenge procedure and treatment of life-threatening reactions.

Sulfites

Sulfites such as metabisulfite, bisulfite, sulfite, and sulfur dioxide are antioxidants and preservatives used in foods and medications. Sulfur dioxide and sulfuric acid are liberated into the atmosphere with combustion of sulfur-containing fossil fuels and therefore contribute to air pollution in many locations. Sulfites are used in processed foods, restaurant foods, beer, wine, and other beverages, and in some injectable and inhaled medications, including bronchodilator solutions for nebulization and epinephrine for parenteral use.[4]

Sulfites are capable of producing life-threatening bronchospasm in susceptible individuals, and classic IgE-mediated anaphylaxis has been reported in a few cases.[5] These reactions may occur within minutes after ingestion of a sulfite-containing food or beverage. A sudden choking sensation by the patient may incorrectly be attributed to aspiration of food or thought to be caused by food hypersensitivity. Reactions occurring after the use of nebulized bronchodilator solutions may present as anaphylaxis, paradoxical bronchospasm, or a lack of expected bronchodilator response.[6, 7] Although this reaction may be IgE mediated in some cases, in most instances it is most likely due to the inhalation of sulfur dioxide.[8] High concentrations of inhaled sulfur dioxide can cause bronchoconstriction in all individuals, but relatively small concentrations (i.e., <1 part per million [ppm]) during exercise are known to induce bronchospasm in most asthmatic patients. Sulfite reactions may also be more likely to occur in patients who have a deficiency of the enzyme, sulfite oxidase.[8]

Although a diagnosis of sulfite sensitivity can be suspected on the basis of the history, a definitive diagnosis can be made only after the patient is challenged with sulfites, a procedure that must be done under controlled conditions by experienced investigators.[8] Approximately 4% of all asthmatic patients and 8% of corticosteroid-dependent asthmatic patients have asthmatic reactions to oral challenges with 100 mg of acidified sulfite solution (equivalent to >2 ppm of inhaled sulfur dioxide), and a small number of asthmatic patients via unknown mechanisms react to 5 to 50 mg doses of sulfites administered by capsules. Challenge with oral sulfite solutions will identify sulfur dioxide–reactive asthmatic patients more readily, whereas oral challenge with sulfite capsules will detect patients with susceptibility to the sulfite ion itself.

Large amounts of sulfites (>1 ppm sulfur dioxide) may be encountered in dried fruit (white raisins, apricots, apples, etc.,) labeled as sulfur dioxide treated), wines, shrimp, processed potatoes, and certain inhaled bronchodilator solutions (e.g., isoetharine [Bronkosol], isoproterenol [Isuprel]).

Asthmatic patients with a history of reaction to foods or beverages containing sulfites can usually avoid further ingestion of these foods. In addition, bronchodilator solutions that do not contain sulfites (e.g., metaproterenol, terbutaline, and albuterol) should be used in place of sulfite-containing drugs of this class. Because metered dose inhalers do not contain sulfites, bronchodilators delivered by this route can also be used. Patients with a history of documented severe reactions to sulfites should carry parenteral epinephrine. Some injectable forms of epinephrine contain a small amount of sulfites (10 mg/ml). The Food and Drug Administration permits use of these preparations for emergency use because it has been reported that sulfite-sensitive individuals do not react to doses 10 times the amount of sulfite found in these formulations when sulfites are administered subcutaneously.[8]

Azo dyes, monosodium glutamate, and other chemicals as precipitants of asthma

Azo dyes are the most commonly certified food, drug, and cosmetic (FD&C) dyes used as drug colorants in pharmaceutical formulations. Among these tartrazine (FD&C yellow dye No. 5) is one of the most commonly used colorants in drugs.[9] It is classified as an azo dye, but it is unique in that it also has a pyrazolone structure. Documented instances of nonimmunologic bronchial asthma may occur after ingestion of this dye.[10] Objective confirmation of asthma induced by tartrazine is rare but can occasionally be demonstrated.[11]

There are also scattered reports about reactions caused by other FD&C dyes. Although some investigators have suggested that there may be cross-reactivity between yellow dye No. 6 and yellow dye No. 5, this has not been confirmed. Isolated outbreaks of occupational asthma induced by other reactive azo dyes, anthraquinone, and carmine have occurred under conditions of occupational exposure.

The flavoring agent, monosodium glutamate, may induce symptoms of headache, chest pain, burning, warmth, pressure, chest tightness, sweating, nausea, and numbness and tingling of the face, neck, and upper chest in some susceptible individuals.[11] It was reported that a few of these patients also had asthma after challenge with monosodium glutamate in a single-blind, placebo-controlled fashion. The mechanism of this association is unexplained.

REFERENCES

1. Settipane GA. Aspirin and allergic diseases: a review. Am J Med 1983;74(6A):102-9.
2. Stevenson DD, Simon RA, Mathison DA. Aspirin-sensitive asthma: tolerance to aspirin after positive oral aspirin challenges. J ALLERGY CLIN IMMUNOL 1980;66:82-8.
3. Stevenson DD. Aspirin desensitization. Allergy Proc 1986; 7:101-8.
4. Simon RA. Sulfite sensitivity. Ann Allergy 1986;56:281-91.
5. Prenner M, Stevens JJ. Anaphylaxis after ingestion of sodium bisulfite. Ann Allergy 1976;37:180-2.
6. Twarog FJ, Leung DYM. Anaphylaxis to a component of isoetharine (sodium bisulfite). JAMA 1982;248(16):2030-1.
7. Baker GJ, Collett P, Allen DH. Bronchospasm induced by metabisulphite-containing foods and drugs. Med J Aust 1981;28:614-7.
8. Gunnison AF, Jaconsen DW. Sulfite sensitivity: a critical review. Crit Rev Toxicol 1987;17:185-214.
9. Tse CS, Bernstein IL. Adverse reactions to tartrazine. Hosp Forum 1982;17:1625-37.
10. Bernstein IL, Gallagher JS, Johnson H, et al. Immunologic and nonimmunologic factors in adverse reactions to tartrazine: proceedings of the 4th FDA Symposium. Washington, DC: US Government Printing Office, 1980:258-60.
11. Weiner M, Bernstein IL, eds. Adverse reactions to drug formulation agents: a handbook of excipients. New York: Marcel Dekker, 1989:273-4.

I. THE EFFECTS OF AIR POLLUTION IN ASTHMATIC PATIENTS

Summary statements

- Although asthmatic patients living in urban environments are generally exposed to a large number of pollutants, only a few of these pollutants have been implicated in causing adverse effects.
- Inhalation of sulfur dioxide, nitrogen dioxide, or ozone is capable of inducing bronchospasm in patients with asthma.
- One of the common sources of air pollution in residential areas, especially in Western states, is household woodburning devices.
- Albuterol is the most selective and potent blocker of sulfur dioxide–induced airflow obstruction in asthmatic patients; and cromolyn sodium has also been shown to block SO_2-induced bronchoconstriction.

Urban environments are generally contaminated by a large number of pollutants. The few that have been implicated in producing adverse health effects in the National Ambient Air Quality Standards (NAAQS) include sulfur dioxide, carbon monoxide, nitrogen dioxide, hydrocarbons, oxidants (e.g., ozone), particulate matter, and lead.[1] Among these pollutants it is mostly acid inhalants that present a significant risk for inducing respiratory problems. Inhalation of acid aerosols and the resultant irritation and inflammation of respiratory tract epithelium are believed to produce a spectrum of reversible obstructive airway responses.[2] The health effects of air pollutants

have been studied with epidemiologic, animal toxicology, and controlled human exposure studies. Although epidemiologic studies indicate that significant groups of people have been adversely affected by air pollutants, very few population-based studies have directly measured pollutant exposure and response.[2] Burning of leaves may be a significant pollutant in certain areas of the country.

Air pollution chemistry

Dockery and Speizer[2] have delineated three sets of conditions that result in acid inhalation of aerosols. These include (1) direct industrial emission of acids such as sulfuric acid (e.g., industrial processes and fossil fuel combustion), (2) catalytic conversion of sulfur oxides and particulates into acid inhalants, and (3) photochemical reactions of nitrogen oxides with reactive hydrocarbons to produce hydroxyl radicals (OH) and ozone. In addition, sulfur dioxide reacts very quickly with hydroxyl radicals to produce sulfuric acid.

Epidemiologic studies

Several air pollution disasters have been reported to result in significant morbidity and mortality in the exposed population. In 1930 in the Meuse Valley, Belgium, 60 deaths were reported on the fourth and fifth day of a dense fog. The exposure was noted to be only a few hours. Several hundred additional individuals came to local health facilities with acute respiratory distress frequently complicated by cardiac insufficiency. In the autopsy studies that followed, superficial inflammatory changes in the bronchial mucosa were more consistent with sulfuric acid exposure than other possible pollutants. Subsequent evaluations of emissions in this narrow industrial valley showed that sulfur dioxide was transformed into sulfuric acid in the presence of oxidation catalysts, such as ferric acid and zinc oxide.[3, 4]

In 1948 a similar pollution disaster occurred in Donora, Pa. This small industrial town located in the Monongahela River Valley has a large steel and wire plant as well as a zinc smelting plant from which sulfuric acid emissions were a byproduct. An irritating fog occurred in late October 1948, and resulted in acute respiratory symptoms (cough and dyspnea) in 43% of the population, of which approximately 10% were severely affected.[5] Nineteen deaths were ultimately attributed to this pollution event. It is believed that oxides of sulfur and oxidation byproducts were the major causes for the morbidity and deaths.[6]

In early December 1952, a slow moving weather front came to a halt over the city of London. Smoke, particulates, and sulfur oxide pollution built up in a dense fog. A large number of individuals developed varying degrees of bronchial irritation resulting in cough, dypsnea, and bronchospasm. An estimated 4000 deaths occurred from acute respiratory and cardiovascular illness. Sulfuric acid was considered to be a participant in the causation, although direct measurements were not available.[7] Many valued pets at the Smithfield Club's show in London developed acute respiratory symptoms. The pens of the less affected animals were said to contain decomposing urine and fecal material generating ammonia, which neutralized the acid fog droplets.[8]

Subsequent studies in Ontario, Canada, by Bates and Sizto[9, 10] uncovered highly significant associations between excess admissions to the hospital for respiratory disease and ambient levels of sulfur dioxide, ozone, and temperature. Their observations suggested that sulfates tended to be more acidic in the summer than in the winter.

Animal toxicology studies

Several studies in animals have confirmed observations in population studies. Acute exposures to low concentrations of sulfuric acid in animals have been shown to increase clearance rates in the bronchial mucosa.[11] Retardation of clearance occurs at higher concentrations, and the studies suggest that the hydrogen ion concentration may be the critical factor in determining the response.[12] Acute exposures to sulfuric acid in rabbits did not increase the number of alveolar macrophages recovered by lavage but increased the number of neutrophils recovered.[13] Repeated low-level exposures of rabbits to sulfuric acid induce protracted depression of mucociliary clearance that may persist for more than a year.[14] Increased numbers of epithelial secretory cells are found in the bronchial mucosa of animals after only 1 month of exposure.[15]

Clinical studies

In controlled exposure studies in humans, no changes in pulmonary function have been observed in normal individuals after short-term exposures to sulfuric acid.[16] However, a variety of susceptible subgroups have been identified who acutely react to the effect of sulfuric acid. In particular, asthmatic patients are extremely sensitive to the inhaled effects of sulfur oxides, sulfur dioxide, and sulfuric acid. Adolescents with exercise-induced bronchospasm have shown reductions in FEV_1, V_{max} 50, and total resistance after exposure to 100

$\mu g/m^3$ of sulfuric acid during exercise.[17, 18] Adult asthmatic patients exposed to 450 and 1000 $\mu g/m^3$ sulfuric acid had reduced specific airway conductance (SGaw) and FEV_1.[19] Exposure to different inhaled forms of sulfate showed that the degree of bronchoconstriction increased with increasing acidity (i.e., $H_2SO_4 > (NH_4)_2SO_4 > NaHSO_4 >$ NaCl). Nasal function has also been adversely affected by sulfur dioxide inhalation.[19]

Asthmogenic effects of NAAQS pollutants

A variety of air pollutants, particularly the acid aerosols, are known to have the capacity to induce bronchospasm by disrupting the delicate balance of neurogenic control involved in the maintenance of bronchial tone. To a large extent, this may be mediated through irritant receptors in the bronchial wall as well as by a direct inflammatory action on the bronchial mucosa.[20, 21] The reaction tends to be acute and does not require a latent period. Inhalation of sulfur dioxide, nitrogen dioxide, or ozone is capable of inducing bronchospasm in patients with established asthma.[22-26]

The relationship between levels of regulated pollutants, including total suspended particulates, nitrogen oxide, ozone, and sulfur dioxide, and cross-sectional measurements of spirometry obtained in children, adolescents, and young adults was assessed during the Second National Health and Nutrition Examination Survey (NHANES II).[27] Forced vital capacity, FEV_1, and peak expiratory flow rate were significantly negatively correlated with annual concentrations of total suspended particulates, nitrogen dioxide, and ozone.

One of the common sources of fine particulate air pollution in residential areas, especially in Western states, is household wood-burning devices. Wood smoke contains many toxic constituents, including nitrogen dioxide, formaldehyde, carbon monoxide, and polycyclic aromatic hydrocarbons such as benzopyrene. Young children may be at greatest risk from wood smoke exposure. Children from homes using wood stoves had a greater incidence of respiratory disease and significantly lower pulmonary function than counterparts in homes without wood stoves.[28]

Neither carbon monoxide nor lead are pulmonary irritants and thus do not present special problems for the asthmatic patient.

Therapeutic approach to pollution-induced asthma

β_2-agonists

Albuterol can be extremely effective in the prevention of sulfur dioxide–induced bronchoconstriction.[29] At a dosage of 180 μg of albuterol (two puffs), bronchoconstriction induced by sulfur dioxide exposure is completely prevented, and a moderate degree of bronchodilation is noted.

Cromolyn sodium

Cromolyn has been shown to cause a dose-related inhibition of sulfur dioxide–induced bronchoconstriction in allergic patients. Twenty milligrams taken 20 minutes before exposure provided no protection, but 40 mg partially blocked and 60 mg nearly completely inhibited sulfur dioxide–induced bronchoconstriction.[30] Nedocromil has also been shown to cause a dose-response blockade of sulfur dioxide–induced bronchoconstriction. Neither compound appears to have significant adverse side effects or adverse interaction with various air pollutants.

Antihistamines

Chlorpheniramine has a significant effect on upper airway response to sulfur dioxide in allergic individuals.[31] A dose of 4 mg given 1 hour before exposure did not alter nasal responsiveness, but 12 mg administered 1 hour before exposure significantly blocked nasal symptoms from sulfur dioxide exposure. Neither dose prevented pulmonary hyperresponsiveness to sulfur dioxide. The presence of a large number of H_1 receptors in the nasal or upper airway may explain why antihistamines would be effective in blocking upper airway responsiveness when they do not produce a similar effect in the lung. Terfenadine (120 mg) given 1 hour before exposure as a single dose failed to prevent sulfur dioxide–induced bronchoconstriction.[32]

Theophylline

Asthmatic patients exposed to sulfur dioxide (1 part per million [ppm] for 10 minutes) during moderate exercise 3 to 4 hours after they received theophylline were not protected against sulfur dioxide–induced bronchoconstriction.[33] There did not appear to be any relationship found between the theophylline level and the magnitude of bronchoconstriction.

Anticholinergic agents

Ipratropium bromide at a dose of 60 mg showed little protective effect against sulfur dioxide–induced bronchoconstriction after exposure to 0.5 to 1 ppm of sulfur dioxide for 20 minutes at rest and after 10 minutes of light to moderate exercise.[34]

Summary

The β_2-agonist, albuterol, has been shown to be the most selective and potent blocker of sulfur dioxide–induced airflow obstruction in allergic patients. Cromolyn sodium, at a dose of 60 mg also produces substantial blockade of sulfur dioxide–induced bronchoconstriction. Antihistamines (H_1 blockers) produce some blockage of sulfur dioxide–induced nasal changes but do not block sulfur dioxide–induced bronchoconstriction. Theophylline at therapeutic levels has no protective effect against sulfur dioxide–induced bronchoconstriction. Anticholinergic medication (ipratropium bromide) produces substantial bronchodilation but does not prevent the bronchoconstriction effects of sulfur dioxide. There is reason to believe that many of the responses seen after inhalation of sulfur dioxide apply to a similar extent to other NAAQS pollutants, although specific studies relating to this do not presently exist.

REFERENCES

1. Calabrese EJ. Methodologic approaches to deriving environmental and occupational health standards. New York: John Wiley & Sons, 1978.
2. Dockery DW, Speizer FE. Epidemiological evidence for aggravation and promotion of COPD by acid air pollution. In: Henseley MJ, Saunders NA, eds. Clinical epidemiology of chronic obstructive pulmonary disease. Vol 43. Lung Biology in Health and Disease Series. New York: Marcel Dekker, 1989:201-21.
3. Firket M. Sur les causes des accients survenus dans la vallee de la meuse, lors des brouillards de decembre 1930. Bull Acad R Med Belg 1931;11:683-741.
4. Firket M. Fog along the Meuse Valley. Trans Faraday Soc 1936;32:1192-7.
5. Shrenk HH, Heimann H, Clayton GD, et al. Air pollution in Donora, PA: epidemiology of the unusual smog episode of October, 1948. Washington, DC: Public Health Service, 1949; Public Health Bulletin No. 306.
6. Hemeon WCL. The estimation of health hazards from air pollution. Arch Ind Health 1955;41:29-35.
7. Waller RE. Acid droplets in town air. Int J Air Water Pollution 1963;7:773.
8. Meetham AR. Atmospheric pollution. Oxford: Pergamon Press, 1964:231.
9. Bates DV, Sizto R. Relationship between air pollution levels and hospital admissions in Southern Ontario. Can J Publ Health 1983;74:117-22.
10. Bates DV, Sizto R. Air pollution and hospital admissions in Southern Ontario: the acid summer haze effect. Environ Res 1987;43:317-31.
11. Schlesinger RB, Chen LC, Driscoll KE. Exposure-response relationship of bronchial mucociliary clearance in rabbits following acute inhalations of sulfuric acid mist. Toxicol Lett 1984;22:249-54.
12. Holma B, Lindegren M, Anderson JM. pH effects on ciliomotility and morphology of respiratory mucosa. Arch Environ Health 1977;32:216-26.
13. Naumann BD, Schlesinger RB. Assessment of early alveolar and macrophage function following acute oral inhalation exposures to sulfuric acid mists. Toxicologist 1985;5: 180-90.
14. Gearhart JM, Schlesinger RB. Response of the tracheobronchial mucociliary clearance system to repeated irritant exposure effect of sulfuric acid mist on function and structure. Exp Lung Res 1988;14:587-605.
15. Schlesinger RB, Naumann BD, Chen LC. Physiological and histological alterations in the bronchial mucociliary clearance system of rabbits following intermittent oral and nasal inhalation of sulfuric acid mist. J Toxicol Environ Health 1983;12:441-65.
16. Utell MJ. Effects of inhaled acid on lung mechanics: an analysis of human exposure studies. Environ Health Perspect 1985;63:39-44.
17. Koenig JQ, Pierson WE. Pulmonary effects of inhaled sulfur dioxide in atopic adolescent subjects: a review. In: Franck R, O'Neil JJ, Utell MJ, Hackney JD, Van Ryzin J, Brubaker PE, eds. Inhalation toxicology of air pollution: clinical research considerations. Philadelphia: American Society for Testing and Materials, 1985:85-91.
18. Koenig JQ, Pierson WE, Horike M, Frank R. Effects of So_2 plus NaCl inhaled combined with moderate exercise in effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. N Engl J Med 1989;321:1426-32.
19. Utell MJ, Morrow PE, Speers DM, et al. Airway responses to sulfate and sulfuric acid inhaleds in asthmatics: an exposure-response relationship. Am Rev Respir Dis 1983; 128:444-50.
20. Frank NR, Amdur MO, Worcester J, et al. Effect of acute controlled exposure to So_2 on respiratory mechanics on healthy male adults. J Appl Physiol 1962;17:252-8.
21. Hogg JD, Macklem PT, Thurlbeck WW. Site and nature of airway obstruction in obstructive lung disease. N Engl J Med 1968;278:1355-60.
22. Euston RE, Murphy SD. Experimental ozone pre-exposure and histamines. Arch Environ Health 1967;15:160-6.
23. Molfino IIA, Wright SC, Katz I, et al. Effect of low concentrations of ozone in inhaled allergen responses in asthmatic subjects. Lancet 1991;2:199-202.
24. Kreit JW, Gross KB, Moore TB, et al. Ozone-induced changes in pulmonary function and bronchial responsiveness in asthmatics. J Appl Physiol 1989;66:217-22.
25. Orehek J, Mussari JP, Gayrard P, et al. Effect of low level nitrogen dioxide exposure on bronchial sensitivity of asthmatic patients. J Clin Invest 1976;57:301-6.
26. Utell MJ, Morrow PE, Hyde RW. Latent development of airway hyperreactivity in human subjects after sulfuric acid inhaled exposure. J Aerosol Sci 1983;14:202-5.
27. Schwartz J. Lung function and chronic exposure to air pollution: a cross-sectional analysis of NHANES II. Environ Res 1989;50:309-21.
28. Pierson WE, Koenig JQ, Bardana EJ. Potential adverse health effects of wood smoke: a position statement. West J Med 1989;151:339-42.
29. Koenig JQ, Marshall SG, Horike M, et al. The effects of albuterol on sulfur dioxide–induced bronchoconstriction in allergic adolescents. J ALLERGY CLIN IMMUNOL 1987;79:54-8.
30. Koenig JQ, Marshall SG, van Belle G, et al. Therapeutic range cromolyn dose-response inhibition and complete obliteration of So_2-induced bronchoconstriction in atopic adolescents. J ALLERGY CLIN IMMUNOL 1988;81:897-901.

31. Koenig JQ, McManus MS, Bierman CW, et al. Chlorpheniramine–sulfur dioxide interactions on lung and nasal function in allergic adolescents. Pediatr Asthma Allergy Immunol 1988;2:199-205.

J. PSYCHOLOGICAL FACTORS

Summary statements

- Asthma affects psychologic and social aspects of life for virtually all patients with this disease.
- The patient may or may not be aware of the presence of psychological problems, which may constitute significant impediments to the optimal management of asthma.
- The management of psychological or social problems that accompany asthma depends on the extent to which they interfere with medical management, or produce severe dysfunction in the patient's life.
- Age and maturity are important considerations in both the medical and psychological treatment of asthma.
- Family members of patients with severe asthma or asthma that is out of control require support from the clinician because of the demands of caring for an individual with asthma. Referral to support groups and/or counseling can be helpful in these situations.

Every clinician who treats asthmatic patients eventually realizes that psychological and/or social factors can play a significant role in some of these patients. Exacerbations of asthma may increase anxiety and/or depression.[1] The role of these factors may be obvious, e.g., when the patient deliberately avoids taking prescribed medication for some reason; or their role may be more subtle, e.g., the patient who lives in profound fear of asthma attacks or uses the presence of asthma for secondary gains. The patient may or may not be aware of such factors. The clinician, however, may recognize that they constitute significant impediments to the optimal medical management of asthma. Unless these emotional and social factors are acknowledged and dealt with, control of asthma may be less than optimal. This section (1) proposes a framework within which to consider the emotional aspects of some patients with asthma, from childhood to adult life, (2) suggests some "red flags" that can alert the clinician to the presence of such factors, and (3) proposes some clinical intervention strategies for dealing with these factors from childhood to adult life.

Prevention is the most important and basic intervention and involves education of the asthmatic patient (or parents) in the avoidance of factors that can precipitate asthma. This may include environmental control, e.g., removal of allergens from the home, school, or work area, the use of medications, from episodic use of medications having few side effects to daily corticosteroids or even cytotoxic agents, or even residential care in a hospital. Psychotherapy and family therapy for the emotional component underlying or accompanying asthma may be required.

The clinician should view the management of the psychological or social issues that accompany asthma in much the same way as the overall medical treatment; that is, as occurring on a number of levels. In determining the intensity of the psychosocial intervention, it is helpful for the clinician to be aware of danger signs or "red flags." These are behaviors or attributes that may interfere with medical management and often reveal severe dysfunction in the patient's life. As these danger signs are sought, it is important to remember that prevention is important in the psychosocial realm as well. Some frequently observed and significant red flags are presented in the Table.

Developmental-based approach

Developmental age is an important consideration in both the medical and psychosocial treatment of asthma. Just as the age and size of the patient are considerations in the amount of medication used, psychosocial intervention for the asthmatic patient must also occur within a developmental framework. In the younger patient or the less developmentally mature, more responsibility must be assumed by a parent (caretaker). The older or more mature patient is expected to assume greater responsibility for his or her own treatment.

Healthy emotional development for children requires that most of their energy be used to meet the demands of developmental tasks.[2] If chronic illness, such as asthma, is allowed to interfere with normal development, this may leave the patient without the necessary skills to meet life demands of later years. The lack of such skills may lead to increased "red flag" signals in older asthmatic patients. Thus interference with childhood developmental milestones may have lifelong consequences.[3, 4]

Approach to young and school-age children

The following suggestions are offered to assist physicians in normalizing the family life of younger

TABLE

Clinical "red flags"	Possible psychosocial contributing factors
Acute episodes in the absence of allergic or infectious precipitants	Stress in home, school, or job; increased vulnerability to stress via depression or anxiety; loss of support via illness; death, divorce, etc.
Symptoms improve when patient is separated from family or spouse	Family conflict, marital conflict, family member colluding against physician, lack of general boundaries
Inability to function on job, at school, or socially	Actual learning skill deficit, overuse or underuse of medication, parent or spouse fostering dependency, lack of expectation due to overprotection
Disregard of symptoms	Lack of asthma education, low-anxiety lifestyle, unrealistic sense of independence, denial of need for help
Inability to recognize improvement	High-anxiety lifestyle, extreme awareness of slightest symptom, depression with feelings of hopelessness or wishing to die
Increased frequency of emergency room visits	Associated environmental change or demands, inreased noncompliance with medications or environmental control, impending emotional decompensation
Case evokes strong feelings in clinician, i.e., anger, rejection, or protectiveness	Overinvestment in outcome, overidentification with patient, competition with parent or spouse, breakdown in clinical team collaboration or disagreement on treatment plan

and school-age children and thereby minimizing the psychological behavioral effects of the disease.

1. Parents of children with asthma require a great deal of support from the clinician because of the demands of caring for the child; it is primarily with them that the therapeutic alliance is formed. Many parents view asthma as psychologically caused and feel responsible, and it is most important that this myth be dispelled. Any chronic illness can produce psychological problems in adults or children. Sick children are demanding of time and emotion and offer little positive feedback for parents. It is not abnormal for a parent of a child who has severe asthma to feel frightened, angry, frustrated, or even hopeless and fatalistic. A trusting relationship with a physician is essential to effective treatment for the child, but referral for mental health support may also be necessary in more severe or complicated cases. This may take the form of parental support groups such as those sponsored by the Allergy and Asthma Foundation of America (AAFA) or individual or family therapy, if this degree of intervention seems warranted. Even when the physician considers that the child's asthma is mild, the parents may have difficulty coping. Therefore a list of national and local resources should be made available to parents.
2. For the child, particularly those requiring frequent hospitalizations, the caregivers must be especially attuned to the need for stimulation, opportunities for parental bonding, and consistency of care. The value of a fixed daily routine for medication and treatment times cannot be overestimated, and fear of confrontations should not deter the establishment of a routine.
3. Attention must be consciously focused on normal development and asthma prevented from becoming a central focus for the family. Normal developmental activities should be encouraged, and asthma treatments should be given without undue expressions of emotion. The overprotective parent represents one of the greatest dangers to the healthy development of the chronically ill child.[5]
4. It is not unusual for at least some confrontation to develop around the administration of medications or other treatment. The asthmatic child exhibits the same developmental stages as all other children. Medications are often used as a "testing" issue. It is important that altercations about medications and other treatment not become the only significant attention that the child receives. Provision for giving some positive attention must be made. The parent may read to the child or play a game on satisfactory completion of a treatment; this puts therapy in a positive light and can greatly reduce negative behavior and confrontation. The use of a positive incentive system, whether it be a star chart in the young child or some tangible token reward in the older child, may prove helpful.

5. The school-age asthmatic child must be encouraged to enjoy a full-life experience. Some children with asthma may be easily distracted, and this may be especially noticeable in the classroom. Distractibility may be due to asthma symptoms or medication side effects. In these children preferential classroom seating may be a means of helping the child profit from the educational experience. Children who have avoided activities because of fear of asthma or parental overprotection may be exercise intolerant only because of poor conditioning. Clinically designed exercise programs may help greatly to recondition such asthmatic children when combined with an adequate medical regimen. Activity involvement is critical in developing normal self-esteem.

Approach to the adolescent and adult[6]

Older individuals can assume a commensurately greater role in responsibility for their own care; however, the belief that asthma symptoms can be controlled is essential to provide the energy necessary to meet the demands of adolescence and adulthood. In the management of adolescents with asthma there should be the expectation that the patient actively participates with the clinician in his or her own care. Regarding active participation, the issues to be considered in the adolescent asthmatic patient merge with those of the adult; for this reason we consider these two age groups together. The issues to be considered in these two age groups are similar to those in the younger child, but the order of importance is somewhat different. Although in the infant/child the primary alliance is with the parent and the child is subsidiary, in the adolescent/adult the primary alliance is directly with the patient.

1. The clinician must make an ally of the patient in his or her own care if therapy is to be successful. Establishment of a therapeutic alliance will entail explaining procedures and their rationale, as well as the benefits of medications. Especially in the case of corticosteroids that may affect the body profoundly and have been viewed as a stigma in recent years, this informed alliance may provide the difference between patient compliance and noncompliance. A dynamic interchange between the physician and patient is of utmost importance. The establishment of timeframes for accomplishment of therapeutic goals, objective scoring systems (e.g., nights of undisturbed sleep, days of work and school attendance, or peak flow measurement), and periodic reevaluations of therapy are methods that will serve the clinician well. The patient and physician must discuss and then agree on specific tasks or therapeutic goals. This process bespeaks an active partnership, helps generate mutual trust, and can usually be established with both adolescent and adult patients.
2. All types of therapy will be most effective if it is provided in a consistent manner. This consistency can be best achieved when a daily routine for treatment is established. This recommendation, made above for management of small children, is one that is never outgrown. The patient must have contact with and support from the clinician as a facet of this consistency, because the physician will reinforce positive behaviors by praise and approval of tasks done well and provide redirection on those tasks not properly performed.
3. To as great an extent as possible the patient with chronic asthma should be encouraged to live a full life. Just as asthma should not be the focus of a child, it should not be the focus of the adolescent or adult's life. In this respect the clinician must strike a balance between helping the patient to avoid factors known to aggravate asthma and leading a fulfilling, relatively unrestricted existence. Achieving this kind of balance can be one of the most challenging aspects of treating patients with asthma, but also one of the most rewarding, because the quality of life of the patient is directly affected.
4. Because patients usually live as members of family or social units, the attitude of the family toward the patient's illness and its management may determine success or failure. Most physicians have experienced situations in which treatment has been sabotaged by a family member who urges noncompliance with medications or otherwise undermines the physician-patient relationship. The clinician who recognizes the potential of the family to be either a help or a hindrance and who tries to enlist their support as a positive force will inevitably succeed more often in managing the patient's asthma. The physician may engage the family by asking them into the office to hear the assessment and treatment plan or may phone a concerned spouse or other family member. It is always helpful to learn how the family views the patient's disease. Whether the asthma is seen as frightening or as an economic or emotional burden, the family will feel better about the

physician who is perceived as aware of their feelings and sympathetic toward them. The family is much more likely to support the patient's therapy if the physician is perceived in this light.

For children, adolescents, or adults, the more severe cases of asthma may require residential treatment or long-term hospitalization as well as psychiatric intervention to identify and treat the exacerbating psychological factors in this disease. In any case, mental health support should be recommended if asthma symptoms or behavioral problems persist despite medical treatment.[6]

Conclusion

Asthma affects psychological and social aspects of life for all patients. The degree to which this can interfere with quality of life must be recognized and dealt with early in the treatment process. Asthma treatment requires a team approach, which sometimes includes a mental health professional.

REFERENCES

1. Janson C, Bjornsson E, Hetta J, Boman G. Anxiety and depression in relation to respiratory symptoms and asthma. Am J Respir Crit Care Med 1994;149:930.
2. Erikson E, ed. Childhood and society. New York: WW Norton, 1963.
3. Matus I. Assessing the nature and clinical significance of psychological contributions to childhood asthma. Am J Orthopsychiatry 1981;51:327-41.
4. Paley A, Luparello T. Understanding the psychologic factors in asthma. Geriatrics 1973;54-62.
5. Parker G, Lipscombe P. Parental overprotection in asthma. Psychosom Res 1979;23:295-9.
6. Yellowless PM, Halucy RS. Psychological aspects of asthma and the consequent research implications. Chest 1990;97: 628-34.

K. OCCUPATIONAL ASTHMA

Summary statements

- Occupational asthma may be induced or aggravated by variable periods of exposure to fumes, gases, dusts, or vapors.
- Symptom patterns of occupational asthma are variable and range from acute symptoms at work to late-onset responses after work.
- Specific causes of occupational asthma include immunologic, irritant, and direct pharmacologic stimuli. Many patients with immunologically induced occupational asthma have IgE-mediated sensitization to a variety of animal- and plant-derived proteins that provoke their symptoms.
- Preexisting atopy may constitute an increased risk factor for asthma caused by many occupational proteins but not by most low molecular weight chemicals.
- Other obstructive airway diseases, such as chronic bronchitis, bronchiolitis obliterans, and emphysema, may mimic occupational asthma.
- Some low molecular weight chemicals may also induce IgE-mediated clinical sensitization.
- After careful review of past medical records and a detailed history and physical examination, the diagnosis of occupational asthma can be accomplished by a combination of pulmonary function testing, skin tests, and blood tests. Inhalation challenge should be performed when warranted.
- Removal of either the patient or the precipitant from the workplace environment is the most effective long-term treatment strategy.
- Some workers have persistent asthma for years after they are removed from the offending occupational agent.

Occupational asthma may be defined as variable airflow obstruction and, in most cases, bronchial hyperresponsiveness attributable to inhalation of specific agents contained in fumes, gases, dust, or vapors in the workplace.[1] The response to these exposures may induce asthma either on an immunologic or nonimmunologic basis.

The diagnosis of occupational asthma may be relatively easy or difficult. A variety of diagnostic modalities may be required to confirm or refute the diagnosis. Attempts should be made to characterize the severity of cough, wheeze, and/or dyspnea and the timing of symptom-free intervals between such symptoms. It should be determined whether the patient has had previous asthma or has concomitant chronic bronchitis or emphysema, which may make the diagnosis of occupational asthma more difficult.

Symptom patterns

In patients suspected of having occupational asthma, work-related respiratory complaints may include the following: (1) intensification of symptoms within minutes or hours after starting work and resolution of these symptoms at home; (2) marked improvement on weekends and vacations; (3) isolated late-onset symptoms 4 to 6 hours after

TABLE I. Examples of occupational allergens: Animal- and plant-derived proteins

Class	Occupations	Allergen sources
Animal-derived proteins	Animal workers	Epidermal, hair, saliva, and proteins; hog trypsin
	Detergent workers	*Bacillus subtilis* enzymes
	Bait handlers	Insect emanations
	Food processing workers	Animal protein allergens (e.g., shellfish, eggs)
	Poultry workers	Fowl mites
	Silk workers	Silkworm moths, larvae
	Granary workers	Grain mites
Plant-derived proteins	Bakers	Wheat and rye flour dust, cottonseed
	Farmers	Soybean dust
	Food processors	Coffee bean dust, enzymes (e.g., papain and bromelain), buckwheat, spices
	Shipping and dock workers	Castor beans, soybeans
	Food, printing, hair dressers, saponin workers	Karaya, tragacanth, guar, quiaja
Miscellaneous	Tobacco workers	Tobacco leaf
	Pharmaceutical workers	Psyllium

leaving the workplace; (4) dual reactions characterized by immediate bronchospasm and resolution of symptoms within 2 to 5 hours followed by a late response in the evening; and (5) chronic symptoms without apparent relationship to exposure. The development of respiratory symptoms usually occurs after a latent period of exposure that, in the case of immunologically induced reactions, could reflect sensitization.[2] Occupational asthma occurs within weeks to months after exposure, but in some industries, workers have been exposed to occupational allergens for as long as 10 years before symptoms develop. This variability emphasizes the complexity of making a diagnosis. Thus many cases are mistakenly attributed to adult-onset or so-called intrinsic asthma. Conversely, it is noteworthy that asthma occurring in the workplace may appear in individuals with preexisting but nonsymptomatic asthma as a result of nonoccupational irritants or allergens. In addition to immediate, late-onset, and dual asthmatic responses, some patients have symptoms that occur repetitively on a nocturnal basis even on days away from work. Such patients may also be misdiagnosed as having a nonoccupational basis for their symptoms. Persistence of asthma for long periods after removal from the offending agent has been described in several well-documented surveys of occupational asthma.[3]

Specific precipitants

Specific mechanisms of occupational asthma are linked to both immunologic and nonimmunologic causes. Nonimmunologic causes include irritant effects of toxic chemicals (e.g., sulfur dioxide, ozone), direct pharmacologic effects (e.g., cotton bracts, organophosphates), or activation of complement pathways.[4] A special type of nonimmunologic asthma is the reactive airways dysfunction syndrome that has been described after a single or several exposures to agents contained in high levels of irritating vapors, fumes, dust, or smoke.[5] Immunologic causes include a wide array of organic substances such as proteins, glycoproteins, and high molecular weight polysaccharides. A selective list of these agents is shown in Table I. A number of low molecular weight chemicals have also been documented as immunologic causes of occupational asthma. A partial list of these agents is shown in Table II.

Identification of specific agents causing occupational asthma may not be possible in some cases. Further help may be required from industrial hygienists, toxicologists, and chemists who are familiar with the precise composition of materials present in the workplace.[6]

Risk factors

The presence of preexisting atopy is associated with an increased risk of occupational asthma caused by many of the high molecular weight occupational agents. However, atopy does not appear to be as much of a prerequisite for most cases of immunologic asthma induced by low molecular weight chemical substances. A notable exception to this is the association of atopy with occupational asthma induced by tetrachlorophthalic anhydride.[7] Smoking is a variable risk factor.

TABLE II. Examples of occupational allergens: Chemicals

Class agents	Occupations	Causative chemical
Acid anhydrides	Epoxy resin workers	Phthalic anhydride, trimellitic anhydride, hexahydrophthalic anhydride
Precious metal salts	Platinum refining workers	Ammonium tetrachloroplatinate
Diisocyanates	Polyurethane foam workers, foundry workers, auto painters	Toluene diisocyanate, diphenylmethane diisocyanate, hexamethylene diisocyanate
Metallic salts	Metal plating workers, refinery workers	Nickel sulfate, potassium chromate, vanadium
Soldering fluxes	Electronic workers	Colophony resins (abietic, pumaric acids)
Wood dust	Western and Eastern red cedar workers	Wood dust (plicatic acid)
Antibiotics	Pharmaceutical workers	Penicillin, spiramycin, tetracycline
Miscellaneous	Pharmaceutical and beauty workers	Sulfonechloramide, piperazine Hydrochloride, phenylglycine acid Chloride persulfate salts, ethylenediamine

It appears to increase the odds of asthma developing in certain chemical industries, but it does not play a role in asthma induced by diisocyanates or Western red cedar.[3, 4, 7] Preexisting bronchial hyperresponsiveness, race, or gender are not risk factors.

Differential diagnosis

Diseases that may mimic asthma should be considered. These include fixed obstructive disorders such as chronic bronchitis, emphysema, bronchiolitis obliterans, various mixed restrictive/obstructive lung diseases with obstructed small airways, and even congestive heart failure.[6, 8, 9] In addition, patients may complain of work-related symptoms for secondary gain.

Immunologic findings

Most immunologically induced occupational asthma cases are caused by IgE-mediated respiratory sensitization to a wide variety of animal- and plant-derived proteins.[4, 10] For these substances, skin testing is the most sensitive method for detecting specific IgE antibodies to confirm bronchial sensitization. In some cases, serologic assays of specific IgE antibodies may also be used to screen worker populations at risk for sensitization to occupational allergens. The detection of antibody responses to low molecular weight materials depends on the reactivity of the chemical. Suitable tests for chemical antigens must first be established by conjugation of the antigen to a human protein such as human serum albumin.[11] The presence of IgG antibodies may indicate (1) the degree of exposure to a specific substance, (2) IgG-mediated cytotoxic or immune complex disease (e.g., pulmonary hemorrhages and acquired hemolytic anemia in trimellitic anhydride workers), or (3) possibly a protective immune response against the development of clinical sensitivity.[12]

Removal from exposure

If respiratory symptoms develop in a worker when exposed to recognized triggers such as chemicals or organic protein substances, avoidance may confirm the diagnosis if symptoms decrease. Moreover, improvement of lung function may parallel clinical improvement when the worker is removed from exposure to the suspected agent. Reexposure will be associated with objective worsening of the patient's respiratory status, as confirmed by reappearance of symptoms in association with wheezing and deterioration of pulmonary function. However, it is now established that some workers may have persistent asthma for years after removal from the offending occupational agent.[3]

Pulmonary function testing

Because of the variable nature of occupational asthma, pulmonary function tests may be normal if the patient is tested at times of remission (i.e., on an off-work day or preshift in the case of acute reactions). Thus a single, normal pulmonary function evaluation cannot be used to exclude the diagnosis of occupational asthma. The measurement of preshift and postworkshift ventilatory function (either FEV_1 or peak expiratory flow rate) may be valuable in determining the presence of immediate or dual asthmatic responses.[2]

Inhalation challenge

Inhalation challenge with a suspected agent, performed by experienced personnel in a properly controlled laboratory environment, may be required to provide additional support or informa-

tion to confirm the diagnosis.[13] Bronchial hyperresponsiveness to methacholine or histamine provides important supportive information when it is unclear whether the patient's symptoms are due to asthma. Provocation responses to these agents will, in most cases, correlate with the diagnosis of asthma. Serial measurements of bronchial hyperresponsiveness may be indicated when it is not possible to determine a specific occupational cause of asthma. A baseline methacholine or histamine challenge is done at a time when the patient is completely asymptomatic. The patient then returns to the workplace for a week, after which a repeat assessment of bronchial hyperresponsiveness is performed. An increase in hyperresponsiveness suggests that occupational factors may be involved. Sometimes challenges with specific occupational agents must be done when it is absolutely necessary to prove the cause. Such tests are of special help in the following situations: (1) investigation of new agents causing occupational asthma, (2) instances where there may be multiple substances in the workplace that may be suspected, and (3) for medical/legal purposes.

A negative challenge with methacholine or histamine does not exclude a diagnosis of occupational asthma, as has been documented in some workers with toluene diisocyanate asthma.

Inhalation challenge should be done under carefully controlled conditions because the test is designed to reproduce symptoms and could result in a severe exacerbation unless proper precautions are followed (see section on specific challenge tests). Because of the technical limitations of certain types of bronchial challenge tests, a negative test result does not entirely exclude the possibility of occupational asthma.[13]

Former workers

The retrospective diagnosis of occupational asthma may not always be clearcut. In such cases skin tests, serologic tests, and inhalation challenges may provide supportive information.[14] However, allergic antibodies wane with time, so such tests are clearly time-dependent.

Treatment and prevention

The pharmacologic treatment of occupational asthma is similar to naturally occurring asthma. If exposure to the offending agent is not terminated, workers may become refractory to the usual pharmacologic measures and may then become corticosteroid dependent. Immunotherapy plays a limited role in laboratory animal workers and veterinarians who develop occupational asthma after exposure to specific animals. In certain workplace situations, industrial hygiene and engineering renovations may prevent subsequent cases of occupational asthma. Occasionally special self-contained breathing masks or whole-body suits may be used for short periods. The most effective method of preventing persistence of occupational asthma is to make a prompt diagnosis and remove the worker from further exposure as soon as possible.

REFERENCES

1. Bernstein DI. Guidelines for the diagnosis and evaluation of occupational lung disease. J ALLERGY CLIN IMMUNOL 1989;84(suppl):701-844.
2. Smith AB, Castellan RM, Lewis D, et al. Guidelines for the epidemiologic assessment of occupational asthma. J ALLERGY CLIN IMMUNOL 1989;84(suppl):794-805.
3. Chan-Yeung M. Occupational asthma. Am Rev Respir Dis 1986;133:666-703.
4. Bernstein IL. Occupational asthma. In: Kaplan AP, ed. Allergy. New York: Churchill Livingstone, 1985:1-30.
5. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Chest 1985;88:376-84.
6. Bernstein IL. Occupational asthma. Clin Chest Med 1981; 2:255.
7. Venables KM, Newman-Taylor AJ. Exposure-response relationships in asthma caused by tetrachlorophthalic anhydride. J ALLERGY CLIN IMMUNOL 1990;85:55-8.
8. Murphy SMF, Fairman RP, Lapp NL, et al. Severe airway disease due to inhalation of fumes from cleaning agents. Chest 1976;69:372-6.
9. Epler GR, Colby TV. The spectrum of bronchiolitis obliterans. Chest 1983;83:161-2.
10. Grammer LC, Patterson R, Zeiss CR. Guideline for the immunologic evaluation of occupational lung disease. J ALLERGY CLIN IMMUNOL 1989;84(suppl):805-14.
11. Bernstein DI, Zeiss CR. Guidelines for preparation and characterization of chemical-protein conjugate antigens. J ALLERGY CLIN IMMUNOL 1989;84(suppl):820-2.
12. Lushniak BD, Reh CM, Gallagher JS, et al. Indirect assessment of exposure to diphenylmethane diisocyanate (MDI) by evaluation of specific immune responses to MDI-HSA in foam workers. J ALLERGY CLIN IMMUNOL 1990;85:251.
13. Cartier A, Bernstein IL, Burge PS, et al. Guidelines for bronchoprovocation on the investigation of occupational asthma. J ALLERGY CLIN IMMUNOL 1989;84(suppl):823-9.
14. Biagini RE, Bernstein IL, Gallagher JS, Moorman WJ, Brooks S, Gann PH. Factors affecting diverse reaginic immune responses to platinum and palladium metallic salts. J ALLERGY CLIN IMMUNOL 1984;74:794-801.

L. ASTHMA IN THE SCHOOL SETTING

Summary statements

- Asthma must be identified early to optimize treatment that can decrease school absenteeism and increase opportunities for participation in physical activity.

- Asthma can be effectively treated in most children by the use of readily available inhaled medications.
- Every effort should be made to normalize physical activity in children with asthma.
- Education programs for patients, parents, and teachers should be encouraged to provide better management of asthma in the school setting.

Asthma and other allergic disease account for one third of chronic medical conditions occurring in childhood and affect one of five school children.[1] It is estimated that 3 million children younger than 15 years of age in the United States have asthma.[2] A survey of the prevalence of asthma in Connecticut showed that more than 7% of the school population suffered from or had a history of asthma and/or chronic bronchitis.[3] Overall, the prevalence of childhood asthma in 1988 was thought to be 4.3%.[4] Some of the problems for parents, teachers, and children with asthma include poor school performance, excessive school absences, adverse effects of asthma medications on learning and behavior, use of medications at school, and difficulties with physical exercise. It has been estimated that some limitation of activity occurs in 30% of asthmatic children, contrasted with 5% of nonasthmatic children.[5]

School performance

Ongoing asthma symptoms may cause children with asthma to fatigue easily, to have reduced attention span, and to have impaired concentration. Loss of sleep or interrupted sleep from nocturnal asthma may aggravate the situation in the classroom. As a result, chronic asthma per se, excluding the influences of medication and school absenteeism, has the potential for adversely affecting school performance. In support of this contention, some studies have shown that children with allergies and asthma have lower levels of academic performance.[6-8] However, information on academic performance in these studies has been obtained through teacher or parent questionnaire or interview. A study with standardized academic achievement tests indicated that overall the academic capability of children with asthma was average to above average. In this study, factors that were associated significantly with low performance were low IQ, low socioeconomic status, older age, and the presence of emotional and behavioral problems.

School absenteeism

Asthma is the most common chronic childhood disease that results in school absence. Twenty percent of all school days lost in elementary and high school are related to asthma.[1] It has been noted that children with asthma have an approximately 50% higher absenteeism rate than do nonasthmatic children.[9] The absenteeism rate decreases as the child becomes older. In one study, 12% of children with asthma had more than 30 days of school absence, and this subgroup of children scored appreciably worse on a teachers' assessment of their educational, social, and psychological adjustment.[10] It is likely that school absenteeism plays a role in creating learning difficulties in some children with asthma, although other facts, such as low socioeconomic status and/or the presence of emotional and behavioral problems, must not be overlooked.[11] Of equal importance is school absenteeism because of failure of asthma diagnosis and treatment.

Therefore it is extremely important that any evaluation of a child with asthma include questions about the extent of missed school and possible academic difficulties. Aggressive management of chronic asthma is an important factor in minimizing absenteeism. The availability of new and highly effective treatments for asthma should allow almost all children to attend school without excessive absenteeism. When inadequate control of asthma results in school absence, referral to an asthma specialist is indicated. Continued poor performance after asthma control is achieved should prompt questions about emotional and behavioral problems.

Appointments with physicians and for immunotherapy should be scheduled at times other than regular school hours. Children who require hospitalization for asthma may fall behind in their schoolwork, but this can be minimized by communication between parents and teachers. Schoolwork can be brought to the hospital or to the child's home during recuperation. Many children with asthma are kept out of school unnecessarily because of unwarranted fear by the parents or the school about the child's asthma. School nurses should be taught about asthma management and how to use peak flow meters for a more thorough and objective assessment of asthma severity and to detect undiagnosed exercise-induced asthma (EIA). Parents and school personnel should be educated about warning signs of asthma exacerbation. Asthma medications should be kept at school to treat acute exacerbations, and it should be made

clear to parents and educators that the student's asthma is not contagious. These measures lessen the possibility that the child with asthma will needlessly be kept at home.

Many schools are attempting to give additional educational assistance to chronically ill children who are prone to school absence and learning difficulties. The Education for All Handicapped Children Act of 1975 (PL94-142) is a federal law that mandates special support services to students who are physically handicapped or "other health impaired." Asthma falls under classification of "other health impaired."[12] The degree of implementation of PL94-142 is highly variable throughout the country. Certain school districts have established excellent programs that provide extra tutoring and assistance to help children with chronic asthma who are having academic problems. Specific areas of academic weakness are identified and corrected. The managing physician should be aware of PL94-142 and insist that the school implement its provisions to assist the child with asthma who is missing school or falling behind academically.

Effects of asthma medications

Theophylline. A potential problem for the child with asthma is the effect of medication on school performance. In the past several years various investigators have reported negative psychological and behavioral changes in children resulting from the administration of theophylline.[13-17] However, other studies have been unable to detect any problem in learning or behavior in children taking theophylline.[18, 19] The Food and Drug Administration recently concluded, in agreement with its Pulmonary–Allergy Drugs Advisory Committee, that insufficient data exist at this time to state that theophylline produces an adverse effect on the school performance of children.[20]

Nevertheless, individual intolerance to the central nervous system effects of theophylline occurs, and physicians should alert parents of children taking theophylline about possible behavior and learning problems. If such problems develop at home or at school, the patient's management should be reevaluated.

β_2 adrenergic agonists. β_2-Adrenergic agonists are usually prescribed for use by inhalation (see below). However, some children are not able to use a metered dose inhaler effectively because of the coordination required and may need a spacer, breath-activated device, or an oral formulation of these medications. In children especially sensitive to this class of medication, nervousness or tremor may occur. Tremor, most often occurring in the hands, may affect the child's penmanship or other fine motor skills. Although tremor may decrease with continued use of β_2-agonists (tolerance), it may be necessary to (1) change from an oral to an inhaled formulation, (2) lower the dose, (3) try another medication in this category that may be less tremorgenic, or (4) use a β-agonist only when acute asthma occurs.

Oral corticosteroids. Oral corticosteroids have also been implicated in the development of psychologic and neurologic adverse effects in adults.[21] However, only limited information is available about the consequences of oral corticosteroids on the central nervous system in children. An early study of children receiving prolonged corticosteroid treatment reported restlessness, depression, and insomnia.[22] In another study, parents noted significant increases in mood instability, tearfulness, argumentative behavior, and tiredness in children taking prednisone.[23] Investigations have shown reduced verbal memory in children with asthma a few hours after taking oral corticosteroids, but symptoms subsided within a day.[24] A follow-up study examining children between 8 and 16 years of age with severe asthma revealed that patients receiving high doses of corticosteroids had reduced ability to recall information and experienced more anxiety and depressive symptoms.[25] Thus, children taking oral corticosteroids, particularly at high doses, may be at risk for learning and behavior problems in school because of these mood and memory changes. However, the corticosteroid effect noted so far on mental performance has been subtle.

Use of inhaled medications in school. Another frequently encountered problem is a reluctance by school officials to allow the use of medications at school. School policy usually dictates that all medication taken at school must be authorized by the child's physician. However, such policy often requires that the medication be kept in a school office rather than freely available to the student. This can be inconvenient, disruptive to the student's schedule, and cause unnecessary delay in treating asthma symptoms appropriately. With the availability of time-released oral theophylline and β-agonists, students rarely need to go to the office to obtain oral asthma medication. However, inhaled β-agonists or cromolyn should be readily available for treating acute asthma symptoms and for preventing exercise-induced bronchospasm. It should not always be necessary for the student to

go to a special place to use their inhalers; instead, children who are judged to have sufficient maturity should be allowed to retain the inhaler in their possession. Children should be allowed to take medication in settings that do not cause embarrassment.

Use of inhaled medications in school children with asthma

Children with asthma frequently have sudden or abrupt symptoms caused by exercise. However, in the majority of cases, asthma triggered in this manner can be prevented by inhaled bronchodilators or sodium cromolyn. The most desirable means of utilizing these measures to allow normal physical activities at recess and during physical education is to make inhaled medications sufficiently accessible so that children do not have to leave their classmates or go elsewhere in the school for their use. For children whose parents and physician judge them to have sufficient maturity to control these medications, it is essential that they retain use of inhalers in their possession. School policies requiring the inhaler be kept in an office or nurse's station, even for children judged to be responsible to use the medication appropriately, result in interference in the medical care of the patient. Most children will not use their medication if it must be kept in an office. School officials should discuss with parents or physicians any questions regarding appropriateness of use and responsibility for care of inhaled medication, i.e., indiscriminate use or permitting other students to obtain possession. Otherwise, school personnel should cooperate in the best interest of the patient's medical care by permitting the student to have possession of the inhaler. Since there is no indication that these medications have any potential for abuse in nonasthmatic patients, it cannot be argued that this policy presents any danger to other students. Nonetheless, it is reasonable to expect the student requiring the medication to be sufficiently responsible to retain control over the device and be sufficiently discreet in its usage so as not to draw undue attention to treatment.

Physical exercise

Exercise can be an important cause of asthma symptoms in children. In school this problem occurs usually during physical education (PE) class, during practice for a specific sport, or on the playground. PE teachers and coaches may not realize that a student has asthma or that excessive exercise may induce bronchospasm in some students who are otherwise healthy. If so, affected students may be penalized or pushed beyond their capacity to exercise, thus precipitating asthma, or may be inappropriately transferred to an adaptive PE class. With few exceptions, most children with asthma are able to participate fully in regular PE, provided the instructor adequately understands the potential limitations of the patient and that when indicated, medication is allowed before or after exercise. As stated by the American Academy of Pediatrics Committee on Children with Disabilities regarding children with asthma, "Every effort should be made to minimize restrictions and to invoke them only when the condition of the child makes it necessary."[26] Long distance running (e.g., running laps) poses the greatest problem; activities with repeated short bursts of running are better tolerated by the child with asthma. Permission for the student to premedicate with either an inhaled β-agonist, cromolyn, or both, usually permits full participation in strenuous physical activity. Physicians managing children with asthma rarely need to permanently excuse a child from PE class or enroll them in an adaptive PE class because of asthma. A small number of children with asthma use their illness to avoid activity. They have learned to manipulate overprotective parents and unwary physicians. PE classes and exercise are beneficial for children with asthma, and any decision to modify a school PE program should only be made after consultation between the physician, parent, child, and school. Ideally, a trusting relationship should exist between the student and the PE instructor. The student should be allowed to determine his or her asthma control and either modify his or her exercise activity or take medication before or after exercise.

"Warmup" exercises may reduce EIA[27] (see Section on EIA). Such exercises recommended for athletes with asthma include a 10- to 20-minute warmup period that may incorporate short sprints, jumping, and/or gymnastic activities in which the intensity can be controlled by the patient. This enables the patient to discover his or her own exercise tolerance level and limits. All the above issues should be incorporated into a continuing education program for teachers, coaches, and other school personnel. Physicians should become actively involved in these programs.

Conclusions

Most children with asthma have symptoms of asthma before they enter school, and many continue to have asthma throughout adolescence. It is possible that conflicts may develop between students with asthma, their parents, and school officials that could interfere with normal school activities. However, aggressive asthma management by a physician knowledgeable in the care of asthma and cooperative management through education of patients and their parents allows students with asthma to attend school regularly and participate in all activities. Occasionally minor modifications in school policy (e.g., allowing the child to keep an inhaler in his or her desk) or the environment (e.g., removal of furry pets from the classroom) may be necessary. Poor academic or physical performance by the student with asthma should prompt an investigation into the possible role of school absenteeism, asthma medications, or emotional and behavioral problems.

REFERENCES

1. Schiffer CJ, Hunt EE. Illness among children. Washington, DC: Department of Health, Education, and Welfare, 1963; Children's Bureau publication No. 405.
2. US Department of Health, Education, and Welfare. Asthma and the other allergic diseases; NIAID. Washington, DC: National Institutes of Health, 1979; publication No. 79-387:7.
3. O'Neil SL, Barysh N, Setear SJ. Determining school programming needs of special population groups: a study of asthmatic children. J School Health 1985;55:237-42.
4. Weitzman M. Recent trends in the prevalence and severity of childhood asthma. JAMA 1992;268:2673-6.
5. Taylor WR, Newacheck PW. Impact of childhood asthma on health. Pediatrics 1992;90:657-61.
6. Rawls DJ, Rawls JR, Harrison CW. An investigation of six- to eleven-year-old children with allergic disorders. J Consult Clin Psychol 1971;36:260.
7. Havard JG. Relationships between allergic conditions and/or learning disabilities. Dis Abs Intern 1975;35:69.
8. Freudenberg N, Feldman CH, Clark NM, et al. The impact of bronchial asthma on school attendance and performance. J School Health 1980;50:522.
9. Parcel GS, Gilman SC, Nader PR, Bunce H. A comparison of absentee rates of elementary school children with asthma and nonasthmatic schoolmates. Pediatrics 1979;64:878-81.
10. Anderson HR, Bailey PA, Cooper JS, Palmer JC, West S. Morbidity and school absence caused by asthma and wheezing illness. Arch Dis Child 1983;58:777-89.
11. Gutstadt LB, Gillette JW, Mrazek DA, Fukuhara JT, La Brecque JF, Strunk RC. Determinants of school performance in children with chronic asthma. Am J Dis Child 1989;143:471-5.
12. Special Education Department, San Diego City Schools, A handbook for parents of special children. San Diego, 1988.
13. Furukawa CT, Shapiro G, Du Hamel T, Weimer L, Pierson WE, Bierman CW. Learning and behavior problems associated with theophylline therapy. Lancet 1984;1:621.
14. Furukawa CT, et al. Cognitive and behavioral findings in children taking theophylline. J ALLERGY CLIN IMMUNOL 1988;81:83.
15. Rachelefsky GS. Behavior abnormalities and poor school performance due to oral theophylline usage. Pediatrics 1986;78:1113.
16. Kasenber DF, Bloom L. Potential neuropsychological side effects of theophylline in asthmatic children. Pediatr Asthma Allergy Immunol 1987;1:165.
17. Nelson LA, Schwartz JI. Theophylline-induced age-related CNS stimulation. Pediatr Asthma Allergy Immunol 1987; 1:175.
18. Rappaport L. Effects of theophylline on behavior and learning in children with asthma. Am J Dis Child 1989;143: 368.
19. Joad JP. Extrapulmonary effects of maintenance therapy with theophylline and inhaled albuterol in patients with chronic asthma. J ALLERGY CLIN IMMUNOL 1986;78:1147.
20. Theophylline and school performance. US Food Drug Administration Drug Bull 1988;18:32.
21. Jick H. What to expect from prednisone. Drug Therapy 1975:85.
22. Estrada de la Riva G. Psychic and somatic changes observed in allergic children after prolonged steroid therapy. South Med J 1958;51:865.
23. Harris JC. Intermittent high dose corticosteroid treatment in childhood cancer: behavioral and emotional consequences. J Am Acad Child Psychiatry 1986;25:120.
24. Suess WM, Stump N, Chai H, Kalisker A. Mnemonic effects of asthma medication in children. J Asthma 1986;23:291-6.
25. Bender BG, Lerner JA, Poland JE. Association between corticosteroids and psychological change in hospitalized asthmatic children. Ann Allergy 1991;66:414-9.
26. Committee on Children with Disabilities and Committee on Sports Medicine. The asthmatic child's participation in sports and physical education. Pediatrics 1984;74:155.
27. Godfrey S. Clinical variables of exercise-induced bronchospasm. In: Dempsey JA, Reed CE, eds. Muscular exercise and the lung. Madison: University of Wisconsin Press, 1977:247.

M. SPECIAL PROBLEMS IN ASTHMA MANAGEMENT DUE TO SOCIOECONOMIC, GEOGRAPHIC, AND CULTURAL FACTORS

Summary statements

- Asthma may present special problems in management related to living conditions, geographic location, availability of and access to health care professionals and health care facilities, socioeconomic status of the patient, and cultural differences in orientations to disease.
- Exposure to outdoor and indoor respiratory pollutants and allergens may be intensified in relation to socioeconomic and geographic factors.
- Inaccessibility to specialists who care for asthma may lead to episodic care, lack of follow-up, inadequate patient education, and

possibly increased asthma mortality in urban African-Americans.

- Inaccessibility to specialists who care for asthma can be the result of difficult geographic or economic conditions, lack of health care coverage, and structured health care plans ("gatekeeper" concept).
- The selection of medications for the treatment of specific patients with asthma should take into consideration the education of the patient, the patient's mental status, the economic status of the patient, cultural approaches to the use of medications, and accessibility to medical care while providing the best approach to treatment possible for that individual patient.

Asthma may present special problems in management related to living conditions, geographic location, availability of and access to health care professionals and health care facilities, socioeconomic status of the patient, and cultural differences in orientation to disease. The incidence of asthma is increased in African-American children and children from poor familes.[1, 2] Exposure to outdoor and indoor respiratory pollutants and allergens may be intensified in relation to socioeconomic and geographic factors. Patients in urban environments tend to be exposed to especially high concentrations of respiratory particles and other irritants such as sulfur dioxide (So_2), ozone, and the oxides of nitrogen.[3] Kerosene space heaters, which frequently are used in inadequately heated homes, can emit So_2 and No_2 in amounts sufficient to exacerbate asthma.[4] High sulfur dioxide and nitrogen dioxide emissions and other pollutants may be generated by wood burning stoves and have been associated with increases in respiratory illness in some studies.[5, 6] Exposure to side stream cigarette smoke, which is implicated as a risk factor for lower respiratory diseases,[6-8] particularly in children, may be intensified under crowded living conditions and has been implicated as a risk factor for asthma in patients of low socioeconomic status.[9]

The level of exposure to indoor allergens such as cockroach and housedust mite, resulting in sensitization, may be particularly high in inner city areas and among individuals of low income.[10, 11] The risk for the development of asthma and/or acute episodes of asthma may be increased wth heavy exposure to allergens such as dust mite, cockroach, and animal allergen.[12-17] The elimination and control of these indoor allergens are frequently impossible. The disadvantaged, often without social or economic alternatives, find it difficult to leave an environment of intense exposures.

Inaccessibility to any type of physician and particularly specialists who care for asthma may also be a particular problem for some patients. This is especially true for the poor in the inner city, who frequently are forced to rely on hospital outpatient services, such as emergency rooms, as a primary source of care. Patients in rural areas may also find care by asthma specialists impossible because of lack of availability and the possibility that patients may have to travel great distances for asthma care.[18] As a consequence, care is episodic and asthma education and follow-up are inadequate, although when concerted efforts are made to maximize continuity of care and asthma education in inner city patients, the need for emergency health care can be reduced significantly.[19, 20] Patients forced to rely on hospital outpatient services also tend to wait long periods for care and may have transportation problems that delay the onset of appropriate therapy and result in greater severity of disease.[21] Indigent patients who reside disproportionately in large urban inner city areas suffer not only greater asthma morbidity, as measured by frequency of hospitalizations,[22, 23] and emergency room visits but also appear to have higher mortality rates.[24] There are indications that certain racial groups in urban areas, such as African-Americans, are at particularly high risk for asthma mortality. This appears to be related at least in part to low socioeconomic status.[25]

Although inaccessibility to health care beause of poor economic conditions and lack of health care coverage has been related to increased asthma mortality and morbidity, inadequate accessibility to physicians with the expertise necessary for proper care of asthma can be a significant problem even among patients who have health care insurance.[26] Many health care plans limit access to specialists by a "gate-keeper" or other provisions. Denial of health care insurance because of chronic illness, such as asthma that is "preexisting," is also an impediment to continuing care. Inaccessibility to asthma specialists has been related to greater asthma morbidity, including more emergency room and hospital visits and poorer symptom control, than when the patient is treated by specialist physicians expert in the treatment of asthma.[27, 28]

Because asthma is a chronic disorder in which therapy depends on identification and avoidance of the environmental stimuli that drive the pathologic process, it is important to identify the causative

factors for each patient. Successful therapy also depends on proper education of the patient and family with periodic reinforcement and adjustment of therapy. Continuity of care through the same health care providers is important and may be critical to the success of such therapy. Obstacles to adequate care include the diffiulty that the health care system poses in conjunction with socioeconomic and geographic factors. Even when care is potentially available, the inconvenience of obtaining that care is often so great as to make acquiring it extremely difficult and at times impossible.[29] Asthma care must be made sufficiently convenient to minimize loss of time from work or school while maximizing the continuity of care. With the increasing number of single parent and dual-career families, the convenience of health care is an increasingly important issue. Also, elderly patients who have difficulty traveling may require periodic care at home. In other words, potentially accessible care must be made practically accessible to maximize the opportunity for caregiving and care receiving on a long-term basis.

Pharmacotherapeutic agents are an important component in the treatment of acute and chronic asthma, and treatment regimens should be made as simple and understandable as possible (within the framework of adequate therapy) in order to maximize compliance. This is especially important when dealing with less educatable patients and families as well as elderly patients with deteriorating mentation. Similarly, the means of obtaining safe and effective medications must be convenient. The capability of the patient or family to obtain certain types of medication for economic or other reasons should be taken into account in determining therapy. Differences in cultural and individual orientations can account for resistance to different forms of medications. For example, the use of oral, inhaled, or injected medications each has different degrees of acceptance among different cultures as well as individual patients.

In summary, health care systems need to be both available and user friendly. Whereas this is true for the care of all patients under all circumstances, it is of particular importance among patients with asthma and other chronic disorders in whom socioeconomic and geographic factors as well as living conditions may pose even greater obstacles to proper care than usual.

REFERENCES

1. Weitzman M, Gortmaker S, Sobel A. Racial, social and environmental risks for childhood asthma. Am J Dis Child 1990;144:1189-94.
2. Swartz J, Gold D, Dockery DW, Wass ST, Speizer FE. Predictors of asthma and persistent wheeze in a national sample of children in the United States: association with social class, perinatal events, and race. Am Rev Respir Dis 1990;142:555-62.
3. Dockery DW, Speizer FE, Stram DO, Ware JH, Spengler JD, Ferris BG Jr. Effects of inhalable particles on respiratory health of children. Am Rev Respir Dis 1989;139:587-94.
4. Cooper JA, Malek D, eds. Proceedings of the International Conference on residential solid fuels, environmental impacts and solutions. Beaverton, Oregon Graduate Center, 1982.
5. Honecky RE, Osborne III JS, Akpom CA. Symptoms of respiratory illness in young children and the use of wood-burning stoves for indoor heating. Pediatrics 1985;75:587-93.
6. Samet JM, Marbury MC, Spengler JD. Health effects and source of indoor air pollution. Am Rev Respir Dis 1987; 136:1486-508.
7. Bonham GS, Wilson RW. Children's health in families with cigarette smokers. Am J Public Health 1984;71:290-3.
8. Tager IB. Health effects of "passive smoking" in children. Chest 1989;96:1161-4.
9. Martinez FD, Cline M, Burrows B. Increased incidence of asthma in children of smoking mothers. Pediatrics 1992;89: 21-6.
10. Linvia O. Environmental and social inferences on skin test results in children. Allergy 1983;38:513-6.
11. Menon P, Menon V, Hilman B, Stankus R, Lehrer SB. Skin test reactivity to whole body and fecal extracts of American *(Periplaneta americans)* and German *(Blatella germanica)* cockroaches in atopic asthmatics. Ann Allergy 1991;61: 573-7.
12. Sporik R, Holgate ST, Platts-Mills TAE, Cogswell J. Exposure to house-dust mite allergen *(Der p I)* and the development of asthma in childhood: a prospective study. N Engl J Med 1990;323:502-7.
13. Platts-Mills TAE, de Weck AL. Dust mite allergens and asthma—a worldwide problem. J ALLERGY CLIN IMMUNOL 1989;83:416-27.
14. Sears MR, Hoerbison GP, Holdaway MD, Hewitt CJ, Flannery EM, Silva PA. The relative risks of sensitivity to grass pollen, house-dust mite and cat dander in the development of childhood asthma. Clin Exp Allergy 1989;19:419-24.
15. Kang B, Vellody D, Homburger H, Yungingoo J. Cockroach cause of allergic asthma: its specificity and immunologic profile. J ALLERGY CLIN IMMUNOL 1979;63:80-6.
16. Harving H, Korsgaard J, Dake R, Beck HI, Bjerring P. House-dust mites and atopic dermatitis: a case-control study on the significance of housedust mites as etiologic allergens in atopic dermatitis. Ann Allergy 1990;65:25-31.
17. Pollard SM, Chapman MD, Fiocco GP, Rose G, Platts-Mills TAE. Epidemiology of acute asthma: IgE antibodies to common inhalant allergens as a risk factor for emergency room visits. J ALLERGY CLIN IMMUNOL 1989;83:875-7.
18. Mok H, Johnston P, Abbey H, Talamo RC. Prevalence of asthmatics and health service utilization of asthmatic children in an inner city. J ALLERGY CLIN IMMUNOL 1982;70: 367-72.
19. Clark NM, Feldman CH, Evans D, Levinson MJ, Waselewski Y, Mellins RB. The impact of health education on frequency and cost of health care use by low income

children with asthma. J ALLERGY CLIN IMMUNOL 1986;78: 108-15.
20. Wissow LS, Warshow M, Bor J, Baker D. Case management and quality assurance to improve care of inner city children with asthma. Am J Dis Child 1988;142:748-52.
21. Weissman JS, Stern R, Fielding S, Epstein AM. Delayed access to health care: risk factors, reasons and consequences. Ann Intern Med 1991;114:325-31.
22. Gergen PJ, Weiss KB. Changing patterns of asthma hospitalization among children: 1979 to 1987. JAMA 1990;264: 1688-92.
23. Perrin JM, Homer CJ, Berwick DM, et al. Variations in rates of hospitalization of children in three urban communities. N Engl J Med 1989;320:1183-7.
24. Sly RM. Mortality from asthma in children 1979-1984. Ann Allergy 1988;60:433-43.
25. Wissow LS, Gittelsohn AM, Moyses S, Starfield B, Miessman M. Poverty, race and hospitalization for childhood asthma. Am J Public Health 1988;78:777-82.
26. Cartland JDC, Yudkowsky BK. Barriers to pediatric referral in managed care systems. Pediatrics 1992;89:183-92.
27. Bucknall CE, Robertson C, Moran F, Stevenson RD. Differences in hospital management. Lancet 1988;2:748-50.
28. Zeiger RS, Heller S, Mellon MH, Wald J, Falkoff R, Schatz M. Facilitated referral to asthma specialist reduces relapses in asthma emergency room visits. J ALLERGY CLIN IMMUNOL 1991;87:1160-8.
29. Perrin JA, Valvona J, Sloan FA. Changing patterns of hospitalization for children requiring surgery. Pediatrics 1986;77:587-92.

N. ASTHMA IN CHILDREN

Summary statements

- Asthma is the most common chronic condition of childhood. The prevalence and severity of childhood asthma have increased substantially in recent years. Age-related differences in diagnostic and therapeutic considerations in childhood require special attention.
- Asthma can begin in infancy, although rarely in the first few months of life. Wheezing is a common symptom encountered in infancy through the first 2 to 3 years of life and may be a transient phenomenon in this age group. Many children develop persistent or recurrent wheezing, i.e., asthma. Persistent asthma that begins early is likely to be more severe.
- Atopy in the child, parental atopy or asthmatic history and maternal smoking are risk factors for persistent and recurrent asthma. Low lung function and maternal smoking are risk factors for transient wheezing.
- The history and physical examination, the mainstay of the diagnosis of asthma in all age groups, can present special problems in infants and young children. The diagnosis and estimation of asthma severity must depend more on the history and response to therapy as assessed by inconstant third-party observations than more continuous and objective assessments possible in the older child and adult. Information from observers in and out of the home is important. Education of parents and other caretakers regarding assessment of possible signs and symptoms, their severity, and possible incitants can aid in diagnosis and therapy.
- Recurrent symptoms of prolonged cough, often with shortness of breath, with or without wheezing, suggest asthma. Demonstration of a favorable clinical response to bronchodilator therapy and, when measurable, bronchodilation as demonstrated by pulmonary function testing helps confirm the diagnosis. A positive family history for allergic disease or asthma, although not essential, tends to support a diagnosis of asthma.
- It is important to realize that asthma may coexist with other conditions. Alternative or additional diagnoses should be considered when the history is atypical or the response to good medical management is poor.
- Any aspect of the history that is atypical for asthma, e.g., a history of sudden onset of symptoms; coughing or wheezing with feedings; neonatal requirement for ventilatory support; or symptoms of stridor, may suggest the need to consider alternative diagnoses.
- A large number of conditions can result in symptoms suggestive of asthma. The most common nonasthmatic conditions in childhood that involve obstruction of the large airways include a foreign body in the trachea, bronchus or esophagus, and laryngotracheomalacia. Obstruction involving both the large and small airways is most commonly due to viral bronchiolitis and cystic fibrosis.
- The differential diagnosis of the child with wheezing can be approached on an age-related basis. Infants are at a higher risk for congenital abnormalities and some infectious conditions. Aspiration of a foreign body and cystic fibrosis may occur in any age group but most commonly present early in life. Gastroesophageal reflux with pulmonary involvement may occur at any age. Vocal cord dysfunction and hyperventilation syndrome merit consideration mainly in the adolescent age group.
- General observations that may be helpful in the evaluation of the infant or young child include assessment of clubbing of fingers or

toes (suggesting cystic fibrosis, other chronic lung disease such as bronchiectasis, congenital heart disease, and hepatobiliary disease rather than asthma), activity level, and status of growth and nutrition.

- In addition to physical findings pertinent to all age groups, the evaluation of respiratory effort and of speech—hoarseness, stridor, and the ability to speak or cry normally—is particularly helpful in the infant and young child, especially during symptomatic episodes.
- Objective measurement of pulmonary function is important whenever possible not only in confirming the clinical diagnosis but also in monitoring asthma. Expiratory spirometry should be used as soon as the child is old enough to cooperate. Peak flow monitoring and pulmonary function measurements can generally be done by age 6 or 7 years of age and peak flow can be measured in some children as young as 3 to 4 years of age.
- A chest x-ray film should be obtained at least once in any child with asthmatic symptoms sufficient to require hospitalization.
- A sweat chloride test should be considered in any child who has had several exacerbations of asthma requiring in-hospital treatment or who has had a history of recurrent pneumonia, in order to rule out cystic fibrosis.
- Children with recurrent wheezing who have repeated bronchopneumonia confirmed by x-ray films should have an immunologic evaluation, including quantitative immunoglobulins and possibly specific antibody titers.
- The determination of specific IgE antibody by skin or in vitro tests is useful to evaluate potential allergic trigger factors in children with asthma or when a history suspicious of atopic etiology is obtained. Testing for specific IgE antibodies can be done even in infancy, but it is most commonly useful in children over 2 years old.
- Treatment of the child with asthma includes *all* of the following: (1) environmental control; (2) use of appropriate medications; (3) immunotherapy when indicated; (4) education of patient, family, and caregivers; and (5) close monitoring and follow-up. Responsibility for treatment may apply to all environments in which the child spends a significant amount of time, such as preschool, school, and day care.
- Environmental control for the child includes limiting exposure to cigarette smoke and other irritants, as well as to house dust mite, cockroach, mold, animal, and pollen allergens. The greatest effort should be spent in relation to the bedroom, where children spend a major part of their time.
- Pharmacologic management of the child with asthma includes the use of short-acting β_2-adrenergic bronchodilators as needed to relieve acute symptoms and anti-inflammatory agents routinely to control chronic symptoms. Anti-inflammatory agents for use in children include cromolyn sodium and inhaled corticosteroids. Nedocromil sodium is approved for use beginning in adolescence. Theophylline and oral long-acting β_2-adrenergic agents are used as adjunctive therapy. Systemic corticosteroids are used in short bursts (usually days) for acute severe asthma; long-term use is reserved for severe, chronic asthma not adequately controlled with inhaled corticosteroids at approved higher doses and bronchodilators.
- Aerosolized preparations are preferred for the child as these generally induce fewer side effects; however not all agents are available for use or have not been approved for use by the Food and Drug Administration in this age group. β-Agonists, ipratropium bromide, and cromolyn sodium can be delivered by nebulizer; nebulized corticosteroids are not available in the United States. Spacers with a face mask can be helpful for delivery of medications through metered dose inhalers in very young children.
- Present data are inadequate to establish if inhaled corticosteroids pose a risk for a more complicated course with varicella or other viral infections in children. The use of acyclovir, varicella immune globulin, or both should be considered in children who have a negative varicella history and/or antibody titer and who are or recently have been taking systemic corticosteroids and are exposed to varicella.
- Immunotherapy can be safe and effective for children with well-defined allergies whose clinical symptoms correlate with the sensitivities identified on allergy testing.
- Exercise-induced bronchospasm is common in children. Pretreatment with β-agonists and/or cromolyn sodium can prevent symptoms; β-agonists are also useful in reversing exercise-induced symptoms. Optimal control of chronic asthma by anti-inflammatory therapy

can also decrease the frequency and intensity of exercise-induced asthma.

- Children with asthma need to have their medications conveniently available at school. Designated school personnel and children with asthma need to understand the use of each medication. The physician and parent are responsible for providing simple instructions for medication use.

Asthma is the most common chronic condition in childhood and has an enormous associated morbidity.[1, 2] In 1990, children between 5 and 17 years old missed more than 10 million days of school, and had 160,000 hospitalizations, 860,000 emergency room visits, and 1,254,000 physician visits because of asthma.[3] The prevalence and severity of childhood asthma have been increasing. Hospital admissions for asthma increased 4.5% from 1979 to 1987, with the greater increase occurring in children less than 5 years old.[4] Moreover, 0.5% of admissions required cardiopulmonary resuscitation or intubation.[5] Possible explanations for these findings have included increased exposure to indoor allergens and air pollutants from more energy-efficient homes with poorer air exchange and increased humidity, increase in adverse drug effects, and poor availability and use of medical care.[6, 7] Increases in day care use with increased exposure to viral infections, maternal smoking exposure, and a larger cohort of low birth weight infants surviving with increased risk of obstructive lung diseases are also possible factors.[8]

Diagnostic considerations

Asthma can begin in infancy, although rarely in the first few months of life. Age-related differences in diagnostic and therapeutic considerations in children, as well as differences in growth and development related to the course of asthma require special comment.[9, 10]

Wheezing, a hallmark of asthma, is an extremely common symptom encountered in infancy through the first 3 years of life and reportedly occurs in as many as 35% of children.[11] In most of these children, this phenomenon appears to be transient (a single or a small number of wheezing episodes) and does not recur later in childhood. In perhaps one third of children who wheeze in this age group, wheezing persists at least into later childhood. Other children develop persistent or recurrent wheezing, after the first 3 years.[11, 12] Atopy (parental asthma, other atopic disease in the child, allergic [IgE] sensitization), and maternal smoking are risk factors for persistent and recurrent asthma; low lung function and maternal smoking are risk factors for transient wheezing.[7, 13] Bronchiolitis caused by respiratory syncytial virus (RSV) and other viruses occurs in transient or persistent early wheezers. It is not clear whether wheezing bronchiolitis represents a marker for asthmatic disease in early wheezers or whether it may be responsible for the development of chronic asthma in some patients.[14, 15]

Asthma commonly is underrecognized, underdiagnosed and undertreated in children.[2, 16] Chronic or prolonged coughing without wheezing, associated with upper respiratory tract infections, may also be the presenting symptom of asthma. It frequently is misdiagnosed as recurrent or chronic bronchitis, wheezy bronchitis, or recurrent pneumonia or may be called asthmatic bronchitis.

The history and physical examination, which are the mainstay of the diagnosis of asthma in all age groups, can present special problems in children, particularly in the infant and very young child.[10] Gathering of historical information and objective data is hampered by the need to rely on occasional observations from second or third parties rather than the perception and description of symptoms by the patient. Various observers—parents, other relatives or guardians, baby sitters, preschool or school personnel—often spend a great deal of time with children but may not report or be cognizant of symptoms when they occur outside of their sphere of observation. For instance, exercise-induced bronchospasm may occur as a subtle or obvious phenomenon in school and yet may not be observed by parents who are unaware of the symptoms at home. Observer assessments of severity as well as frequency of symptoms are also difficult and variable. Objective measures of airflow obstruction (peak flow, FEV_1, and other spirometric measures) are commonly assessable in the 6-year-old child, less commonly in the 5-year-old child, and only occasionally in younger children. Therefore assessment of airway obstruction in the very young child must rely on historical suspicion, physical examination, and response to therapy.

Information about physical signs such as overt wheezing (as opposed to chest rattling from mucus or inspiratory stridor) or wheezing heard with a home stethoscope, color, chest retractions, respiratory effort, and respiratory rate can be invaluable in helping establish a diagnosis and assessing severity, as well as response to therapy. Parents, guardians, and other observers such as school

TABLE. Differential diagnosis of asthma in children

Infants	Children
Bronchopulmonary dysplasia	Foreign body
Laryngotracheobronchomalacia	Cystic fibrosis
Immunodeficiency syndrome	Gastroesophageal reflux
Laryngotracheobronchitis	Laryngotracheobronchitis
Congenital malformation (vascular ring, TE fistula)	Croup
Cystic fibrosis	Ciliary defects
Foreign body	Vasculitis syndrome (Churg-Strauss)
Gastroesophageal reflux	Hyperventilation
Congenital heart disease	Habit cough
Chronic respiratory infection (chlamydia, respiratory syncytial virus, adenovirus, pertussis)	Laryngeal dysfunction
Bronchiolitis	Bronchiectasis
	α-antitrypsin deficiency
	Mechanical obstruction (lymph nodes, etc.)
	Chronic sinusitis (chronic cough)

Modified from Smith L. Childhood asthma: diagnosis and treatment. Curr Probl Pediatr 1993;271-305.

personnel need to be appropriately educated about obtaining important historical information on possible symptoms and signs of asthma. This is especially important because of the episodic nature of the disease and the frequent absence of diagnostic signs and symptoms in remission periods when the physician is called on to evaluate the child. Measures of lung function and response to bronchodilator therapy, exercise, or other asthmatic challenges such as methacholine or histamine are valuable aids in assessing asthma in older children, as they are in adults.[17, 18]

History

Recurrent symptoms of cough, wheeze, and shortness of breath suggest asthma. In addition, asthma should be strongly suspected in children who experience recurrent bouts of pneumonia or "chronic bronchitis."[19] Some authors propose that any child regardless of age with recurrent (3 or more) episodes of wheezing and/or dyspnea should be considered as having asthma until proved otherwise.[24] Because wheezing is a symptom of intrathoracic airway obstruction, other conditions can result in wheezing (Table).[20]

Chronic cough lasting more than 6 weeks and often persisting after a viral infection of the upper respiratory tract should make one suspicious of asthma in childhood.[21-23] Many of these children never wheeze; others have classic symptoms of wheezing later in the disease. Children with cough-variant asthma may show airflow limitation by spirometry with reversibility by bronchodilators. Many will show evidence of airway hyperresponsiveness to methacholine challenge.[24] Response to asthma treatment, bronchodilators, or anti-inflammatory drugs is the best diagnostic indicator of cough-variant asthma.[25] Chronic sinusitis with or without asthma may also cause prolonged coughing in childhood.

Differential diagnosis

A positive family history for allergic disease and/or asthma, essentially normal growth and development and a history of intermittent cough and/or wheeze tend to support the diagnosis of asthma. Because asthma is so common, it is important to realize that it may coexist with other conditions listed in the Table. Suspicion of the possibility of an alternative or additional diagnosis should be entertained when the history is atypical or the response to good medical management is suboptimal. An atypical history may include: (1) onset of symptoms in the neonatal period, (2) history of ventilatory support in the neonatal period, (3) intractable wheezing that is unresponsive to bronchodilators, (4) wheezing associated with feeding; vomiting, (5) the sudden onset of coughing or choking, (6) steatorrhea, and/or (7) stridor. Additional or alternative diagnoses should also be considered if there is (1) failure to thrive, (2) clubbing, (3) a cardiac murmur, (4) no reversibility of airflow obstruction after administration of a bronchodilator,

and/or (5) a focal or persistent finding on chest radiograph.[16] A large number of conditions can result in symptoms suggestive of asthma. The most common nonasthmatic childhood conditions that involve obstruction of the large airways include foreign body in the trachea, bronchus, or esophagus and laryngotracheomalacia. Obstruction involving both the large and small airways most commonly occurs from viral bronchiolitis and cystic fibrosis.[26]

The differential diagnosis of the child with wheezing can be approached on an age-related basis (Table). In infants, consideration should be given to congenital abnormalities and RSV and other viral infections that can induce wheezing. children. Aspiration of a foreign body and cystic fibrosis may occur in any age group but most commonly presents in the first years of life. Gastroesophageal reflux with pulmonary involvement may occur at any age. Any aspect of the history that is atypical for asthma, such as a history of sudden onset of symptoms, coughing or wheezing with feedings, neonatal requirement for ventilatory support, or symptoms of stridor, may suggest the need to consider alternative diagnoses.

Sudden cough, gagging, localized wheezing (although there may be more generalized "reflex" wheezing) and diminished breath sounds may be evident in foreign body aspiration, whereas laryngotracheomalacia may be characterized by stridor or noisy respiration from birth[27]; however, expiratory wheezing may occur in this condition. Bronchiolitis usually occurs during the first 2 years of life with a peak incidence at approximately 6 months of age. Cystic fibrosis is usually associated with more persistent symptoms, recurrent or persistent infiltrates on chest x-ray film, an abnormal stool history, and is often accompanied eventually by clubbing and failure to thrive.[28] Vocal cord dysfunction[29, 30] and hyperventilation syndrome[31] merit consideration in the differential diagnosis, mainly in the adolescent age group. Chronic sinusitis may cause prolonged cough and needs to be distinguished from cough-variant asthma.

Physical examination

The physical examination in a child with suspected asthma is best done in a comfortable setting to minimize anxiety and maximize cooperation of the child and parent(s). For the young child, for example, an examination performed in a warm room on an examination table (on mother or father's lap) with good visibility of the head, neck, and chest is desirable. It can be useful to give an infant a bottle during the examination to evaluate feeding capability.

In addition to physical findings pertinent to all age groups, the evaluation of respiratory effort and speech—hoarseness, stridor, and ability to speak or cry normally—is particularly helpful in the infant and young child especially during symptomatic episodes. Deep breathing, which may be difficult to induce in young children, can bring out wheezing not heard on normal breathing.

Other general observations that may be helpful in evaluation of the infant or young child include assessment of clubbing of fingers or toes that suggests cystic fibrosis, bronchopulmonary dysplasia, bronchiectasis, congenital heart disease, or hepatobiliary disease; activity level, and status of growth and nutrition.

Laboratory aids in diagnosis

An objective measurement of pulmonary function is important in confirming the clinical diagnosis of asthma. In the child who is too young to perform pulmonary function tests, the clinical history, and response to therapy and physical examination remain the only means of diagnosing asthma. The effort dependent nature of the forced expiratory maneuver makes this test generally inaccurate or unreliable in very young children. Expiratory spirometry is an essential part of the evaluation and management of children with asthma and should be used as soon as the child is old enough to cooperate. An improvement of 12% to 20% or greater in FEV_1 after inhalation of bronchodilator in children who are able to perform reliable pulmonary function tests is a classic indicator of asthma.[32, 33] This improvement may not be demonstrable until vigorous bronchodilator or anti-inflammatory treatment has occurred. In some cases it may be necessary to demonstrate a 15 to 20% fall in FEV_1, for example, after exercise. Assessment of peak flow rates at home also can aid in determining whether symptom complaints are due to airflow limitation as well as in assessing severity of obstruction on a day-to-day or occasional basis.

Lung function can be measured by a variety of techniques in infants and very young children.

Bronchial reactivity in infancy is high compared with later childhood and adulthood.[34] It has been hypothesized that young children with asthma retain a level of responsiveness that in normal children decreases with age.[35] Evaluation of airway responsiveness in infants and young children, however, is confounded by various factors that include changes in airway and body size with age and measurement methodologies that differ at different ages, as well as a variation in the amount of bronchoconstrictor that is effectively inhaled for bronchial challenges.[36] In addition, wheezing in young children is not necessarily associated with bronchial hyperresponsiveness. Consequently, at this time, measurements of pulmonary function and bronchial responsiveness in infants and young children are considered investigational tools.[36]

The necessity of obtaining an x-ray film in children with typical histories, physical examinations, other laboratory findings of asthma, and excellent response to asthma therapy, especially in mild disease, is unclear. A chest x-ray should be considered for a child admitted for the first time for asthma, if one has not been obtained previously. A chest x-ray or other radiographic study such as barium swallow or computed tomographic scan may be needed in evaluating patients with signs or symptoms suggestive of possible alternative diagnoses as alluded to in the differential diagnosis of asthma.

Cystic fibrosis can be readily diagnosed with a sweat chloride test.[28] It is important that this test be done at a center where it is frequently performed; errors are common if the test is not performed accurately and often leads to a false diagnosis and undue family stress. Any child who has had several exacerbations of asthma requiring in-hospital treatment or who has a history of recurrent pneumonia documented by x-ray should be considered a candidate for a sweat chloride test. Genetic testing also can be done to verify disease.[37] Other findings that can be associated with cystic fibrosis include gastrointestinal symptoms, such as chronic diarrhea, failure to thrive, and nasal polyposis in a child less than 12 years of age.

Increased numbers of eosinophils are frequently associated with asthma, even in the absence of any apparent allergic component. Children with asthma may have eosinophilia.[38]

A Water's view with or without an upright lateral view sinus x-ray film can be useful in identifying or ruling out sinusitis in the young child. Sinus x-ray films are more reliable in assessing disease after the first year of life,[39] but their sensitivity is questionable.[40] The computed tomographic scan can provide more anatomical information,[41] but sedation is often required in young children to obtain an accurate examination. It may be important to consider the possibility of chronic sinusitis as a complicating factor contributing to chronic or difficult to control asthma in children.[42] However, it may be that chronic sinus inflammation is concomitant with but independent of the patient's asthma.

Children with recurrent upper or lower respiratory tract infections related to immune deficiency can also present with recurring wheezing. An immunologic evaluation beginning with quantitative immunoglobulins and specific antibody titers may be necessary.[43]

Exposure to allergens in children can lead to the development and continuation of asthma and can also trigger acute asthmatic episodes. A search for IgE antibody to environmental allergens is important when either an atopic etiology is suspected on historical grounds or in moderate and severe disease even in the absence of a specifically suspicious history. Although IgE antibody can be detected at any age, even in infancy, it is probably most commonly useful in children over 2 years of age. Both inhalant and ingested allergens[44] have been shown to trigger asthmatic responses in young children, although asthma as the sole manifestation of food allergy is unusual. Measurement of total IgE is of limited usefulness (see Parameter on Diagnostic Testing for more detailed discussion of this issue).

Management of asthma in the young child

Management of the young child with asthma includes (1) controlling the environment, (2) use of appropriate medications, (3) immunotherapy when appropriate, (4) education of patient, family, and caregivers, and (5) close monitoring and follow-up. The goal of therapy is the same in all age groups, namely, to achieve sufficient control that there are (ideally) no symptoms or minimal symptoms that interfere with the normal daily functioning of the child. This includes the normal ability to participate in exercise, minimal need for rescue therapy, normal or near-normal lung function, and avoiding adverse effects of therapy.

Environmental controls are extremely important

in the control and prevention of asthma, especially for young children of atopic families and children with reactive airway disease. Chronic exposure to certain indoor allergens is a risk factor for the development of chronic asthma and for triggering acute symptoms. There is, therefore, an important opportunity to diminish and possibly prevent the chronicity and severity of asthma by controlling the environment, especially in young children who spend most of their existence in a limited environment. By analogy to observations in adults who develop asthma from occupational stimuli, the earlier the recognition and elimination of environmental causes of disease, the greater the likelihood of asthma amelioration and disappearance of disease.[45] It is important, to a reasonable extent, to attempt to avoid triggers of bronchospasm and environmental factors in order to limit the opportunity for sensitization to antigens, such as house dust mite, cockroaches, molds, and animal dander.[46-49] House dust mite controls can result in delay of sensitization in children and improvement in individuals who already have symptoms.[47, 48]

Because children spend a large proportion of their time in the bedroom, this area should be the primary target for allergen control and kept as allergen free as possible with impermeable encasings for mattresses and pillows, washable bedding, limited exposure to stuffed animals and pets kept outside the home environment altogether or at a minimum outside the bedroom at all times. Sensitization to animal allergens can occur at a very young age and domestic animals, especially cats, are highly sensitizing. Animal exposure should be limited especially in atopic families. For animals that are not eliminated from the environment, it may be of some help to wash the animal at least once a week, especially cats, because the antigen is derived from glandular secretions in the skin as well as the saliva[49] and appears to wash off easily. It seems to be regenerated rapidly, however. Ideally, exposure of children sensitized to animals should be avoided at preschool, school, and other child care environments. Foods implicated in causing asthma should be avoided, but it is essential to ensure nutritional dietary adequacy.

Asthmatic patients (atopic or nonatopic) may experience an increase in symptoms by irritants such as cigarette smoke, fireplace or wood burning stoves, "fumes," air pollutants,[50] strong odors, household sprays, and in some cases poorly ventilated gas cooking stoves. Young children are sensitive to environmental exposure to cigarette smoke.[51] Decrease in lung function has been correlated with the number of cigarettes smoked in the environment, as well as a noted increase in upper and lower respiratory tract infections.[52-54] Moreover, the level of lung function is decreased in relation to environmental exposure to cigarette smoke in children.[55] Fireplace smoke and gas stove use in the home has also correlated with worsening asthma in some studies.[56, 57] Education about appropriate environmental controls should include day care providers and family members.

Well-controlled studies on the effectiveness of immunotherapy in very young children are virtually nonexistent. Nevertheless, immunotherapy for this age group can be effective. At the same time, there have been recommendations for very conservative use in preschool children based mainly on possible safety considerations.[58, 59] Immunotherapy has been shown to be effective in reducing the symptoms of asthma and bronchial hyperresponsiveness in children.[60, 61] Sensitization and exposures can vary significantly over time, particularly in the young growing child, and thus programs need to be frequently reassessed. Whether immunotherapy begun early in life can accelerate loss of sensitivity or prevent sensitization anew is not known.[62] The reader is referred to the section of this document, which discusses allergen immunotherapy in the asthmatic patient.

Pharmacologic management of infants and children follows the same basic principles concerning the use of bronchodilators and antiinflammatory agents as in adults. However, drug delivery is often more difficult in the young child, because the delivery system may not be appropriate for the child's age and the drugs or form of delivery may not have Food and Drug Administration approval for use in the younger age group.

Very young children, including infants, can respond to bronchodilators.[63, 64] Nebulizing of solutions is a very useful drug delivery system for the young child.[65, 66] Aerosolized bronchodilators can be given by nebulizer with a mask or mouthpiece or by metered dose inhaler with a spacer as the child gets older. A spacer device attached to a mask also can be used to deliver medication to young children. The effectiveness of inhalational medication in young children,

however, may be uncertain and inconsistent because of variable and inadequate drug delivery. The Rotahaler inhalation device may be useful in children who have difficulty coordinating a metered dose inhaler. Oral liquid albuterol or metaproterenol is frequently used on an as-needed basis for symptom relief in the young child, but the inhalational route is preferred when possible. It is important to monitor the use of inhalational bronchodilators in children not only to ensure proper technique and compliance but to avoid excessive or otherwise inappropriate use. This is difficult outside the home and may present special problems at school, particularly with adolescents. Oral or inhaled long-acting β-agonists are considered as adjunctive therapy to inhaled maintenance anti-inflammatory therapy. Inhaled long-acting β-agonists are not approved for use in patients less than 12 years old.

Ipratropium bromide, a derivative of atropine, has synergistic bronchodilating activity with β-agonists.[67] It is available in aerosolized and nebulized solution but is not approved for use in young children; nor has it been approved for use in the treatment of asthma by the Food and Drug Administration. It has been used effectively in other countries for the treatment of acute or chronic asthma in children and adults.[68, 69]

Anti-inflammatory agents include the nonsteroidal agents, cromolyn sodium and nedocromil sodium, and corticosteroids. There is increasing evidence that early use of inhaled corticosteroids, i.e., soon after initial diagnosis, is associated with more favorable lung function later. Comparable information with early use of other anti-inflammatory agents is not available. Consideration of inhaled corticosteroid use as first-line anti-inflammatory therapy even in the very young child[70] has gained an advocacy by many physicians, especially European pediatric asthma experts. Inhaled corticosteroids and cromolyn sodium are considered alternative first-line anti-inflammatory therapy for persistent asthma in infants and young children by the international work group for Global Strategy for Asthma Management and Prevention.[71] Because of continuing concern about adverse long-term effects possibly associated with prolonged use of inhalational corticosteroids in the young child, a more conservative approach of attempting asthma control with cromolyn sodium before considering inhaled corticosteroid therapy is still advocated by many U.S. asthma experts.

Inhaled corticosteroids are not presently available in a nebulized formulation in the United States. Inhaled corticosteroids offer a major advantage over regular daily oral corticosteroids for all age groups but especially for the growing child. Effects on growth are a concern with high doses and possibly with currently recommended doses of inhaled corticosteroids in children,[72] although much of the currently available evidence indicates that they are relatively safe.[73, 74] Effects on growth are significantly less with inhaled corticosteroids than with oral preparations and uncontrolled asthma itself is associated with growth retardation, confounding assessment of reports of decreased rates of growth over relatively short terms of observation. Inhaled corticosteroids are used in preference to long-term systemic (oral) corticosteroids because, in general, asthma can be controlled more readily with inhaled corticosteroids at doses associated with significantly less side effects. Nevertheless, short courses of oral corticosteroids are often necessary to control exacerbations of asthma. Consideration should be given to prompt use of oral corticosteroids for treatment of exacerbations in children with a history of recurrent severe exacerbations. In severe asthma, oral corticosteroid maintenance therapy may be required. If so, every attempt should be made to use an alternate-day morning dosage schedule.

Concerns have been raised about varicella and corticosteroids.[75, 76] There are reports of children dying of varicella while receiving systemic corticosteroids.[77] Data presently available, albeit limited, suggest that inhaled corticosteroids when used in recommended doses do not increase the risk of a more complicated clinical course with varicella or other viral infections.[78] The use of acyclovir and/or varicella immune globulin should be considered in children with a negative varicella history and/or antibody titer who receive systemic corticosteroids and are exposed to varicella.[79, 80] Whether varicella vaccine is useful is not known.

Cromolyn has an excellent safety record and is available in a nebulized form, making it an attractive choice for first-line chronic anti-inflammatory therapy for asthma in early life. It does not cross react with other medications or cause significant central nervous system side

effects. However, efficacy may not be obtained for weeks or months, and it needs to be used on a regular basis (recommended two to four times a day) for maintenance. Nedocromil is not available in a nebulized formulation. Neither drug appears to be as potent as inhaled corticosteroids.

Theophylline is available in liquid and long-acting oral preparation–sprinkle form for treatment of young children with asthma past the period of infancy. Long-acting formulations are advantageous because theophylline metabolism is more rapid in young children than in older children and adults. Theophylline blood levels must be monitored in children as should concomitant drug usage, which may influence theophylline metabolism. Improvement in symptoms can result from serum levels as low as 5 to 15 μg/ml.[81] Peak levels below 16 μg/ml should be considered for safety reasons. A small percentage of children may experience central nervous system disturbances including difficulty concentrating, overactive behavior, nervousness, and insomnia at these levels.[81-83] Various factors, including medications, diet, and viral infections, can alter theophylline metabolism.

The use of antihistamines is not contraindicated in children with asthma.

Medications should be used in **step-wise sequence** depending on the severity of asthma:

- Inhaled short-acting β_2-adrenergic agonists are used as needed for rescue and symptomatic relief of asthma at all levels of severity. This may be the only medication required for mild asthma, including prevention of exercise-induced bronchospasm (EIB). Cromolyn sodium may be used alone or in conjunction with β_2-agonists to prevent EIB.
- Sodium cromolyn or inhaled corticosteroids are added for first-line maintenance anti-inflammatory therapy of mild to moderate disease in the young child; in the older child, cromolyn, nedocromil, or inhaled corticosteroids are added. Some experts advocate the use of inhalational corticosteroids as first-line anti-inflammatory therapy in young children (discussed previously). Methylxanthines, and/or ipratropium bromide and/or long-acting oral β_2-agonists can be added to obtain additional control or to decrease corticosteroid dose requirements.[84, 85]
- Higher doses of inhaled corticosteroids, or if necessary oral corticosteroids, are added with more persistent and severe disease.[16, 86, 87] Long-acting inhaled β_2-agonists can be considered in children 12 years and older.

Therapy should also be based on the age of the child in regard to medication delivery, schedules, tolerance, compliance, and care available.[88] Once adequate control is achieved for a suitable period of time (e.g., 1 to 3 months), therapy should be decreased to the lowest amount necessary to keep symptoms under control, temporarily increasing medication dosage regimens when needed for an appropriate length of time. Maintenance inhalational corticosteroid dose requirements appear to be much lower than those required for obtaining control of asthma initially.[70, 89]

Children with asthma who require daily medication should adhere to the prescribed regimen regardless of their daytime situation. The greater the convenience of the dosing regimen, e.g., a twice-daily regimen compared with drug administration three or four times a day, the greater the likelihood of compliance. Efforts should be made to keep medication regimens at home if possible. It may be necessary to carefully instruct responsible individuals to properly administer medications to the asthmatic child who is in day care. Medication for breakthrough symptoms, such as inhaled β-agonists, should be on hand and readily available for children either in day care or in preschool in the event that they should require medication for an acute unanticipated episode of asthma or before planned exercise. The physician and parent are responsible for providing simple instructions for medication use, understandable by caretakers and the child if appropriate for his or her age.

Symptom monitoring in the young age group is often difficult. However, children as young as 3 years old can sometimes be taught to measure pulmonary function by office spirometry, and to use a peak flow meter. The use of peak flow monitoring is recommended as part of routine asthma management, especially in moderate to severe asthma. With use of peak flow values it is possible to evaluate daily "pulmonary status," AM to PM variations in airflow (that are exaggerated in uncontrolled asthma), effectiveness of

medication, ongoing medication requirements, and severity of asthma exacerbations.

Home assessment of peak flows can help guide management decisions. A variety of algorithms have been promoted for utilizing peak flow information including the traffic light zone analog, which is relatively simple to understand.[90] Values 50% to 80% of normal suggest that treatment needs to be intensified. Values lower than 50% alert the patient and family to seek medical care. Although this maneuver is effort dependent and can be more difficult when children are sick and uncooperative, it is a very valuable tool because early symptom recognition is often difficult for caregivers (parents, relatives, and/or school personnel) or even the older child.

Peak flow monitoring should be supplemented by evaluation of symptoms of cough, nighttime wheezing, wheezing with activity, and general activity level. An early sign of respiratory difficulty for many children can be a modification in activity e.g., the quiet child. The use of peak flow monitoring does not eliminate the periodic need for more complete assessment of pulmonary function.

Care of acute asthma exacerbations in the young child may often be more complex than in the older child.[91, 92] The airways are smaller and less change in the radius of the airway results in a more significant change in airway resistance. Mucus plugging and bronchospasm can quickly result in respiratory compromise. Furthermore, in the infant the muscles and bony structure are not well developed, both of which can directly affect pulmonary compliance. Young children have frequent respiratory viral illnesses. Viral infections are implicated in up to 50% of episodes of wheezing in young children.[93] Respiratory viruses can increase airway inflammation, bronchial hyperresponsiveness,[94] damage airway epithelium and can cause downregulation of β-adrenergic receptor function.[95] Bacterial infections, except for sinusitis, rarely cause wheezing. Chlamydial infection has been associated with increased wheezing.[96, 97]

Exercise-induced bronchospasm is very common and can occur at any age.[98] Eighty percent to 90% of children with asthma experience bronchospasm after exercise.[99] Pretreatment with β-agonists and/or cromolyn sodium is recognized as effective for the prevention of exercise-induced bronchospasm. In the school age child there are often complications regarding drug availability because of restrictions in drug usage in some schools. Children with asthma should be allowed to have in their possession inhaled medications at school. In some cases the physician may need to insist that this be accomplished.

Educational programs are available for parents and older children and both need to understand and accept a treatment plan for effective management. Camp programs are available through the American Lung Association, AAFA (the Asthma and Allergy Foundation of America) and local hospitals, clinics and organizations. The goal of such programs is to teach children and their caregivers about asthma as well as to provide a safe normal camp experience. Parameters have been established for the care of children who attend camp programs.[100]

Educational materials for educational programs are available. Parental/community educational programs and support groups are also available in many communities.

REFERENCES

1. Taylor WR, Newacheck PW. Impact of childhood asthma on health. Pediatrics 1992;90:657-62.
2. Amirav I, Burg F. The need to educate health professionals about childhood asthma. Arch Pediatr Adolesc Med 1994;148:1339-43.
3. Weiss KB, Gergen PI, Hodgson TA. An economic evaluation of asthma in the United States. N Engl J Med 1992;326:862-6.
4. Weiss KB, Wagener DK. Changing patterns of asthma mortality identifying target populations at high risk. JAMA 1990;264:1683-7.
5. Gergen PI, Weiss KB. Changing patterns of hospitalization among children: 1879-1987. JAMA 1990;264: 1683-92.
6. Tepper RS, Morgan WJ, Cota K, et al. Physiological growth and development of the lung during the first year of life. Am Rev Respir Dis 1986;134:513-9.
7. Martinez FD, Morgan WJ, Wright AL, et al. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. N Engl J Med 1988; 319:1112-7.
8. Chan KN, Noble-Jamieson CM, Elliman A, et al. Lung function in children of low birth weight. Arch Dis Child 1989;64:1284-93.
9. Blessing-Moore J. Asthma affects all age groups but requires special consideration in the pediatric age group especially in children less than five years of age [Editorial]. J Asthma 1994;31:415-8.
10. Tinkelman D, Conner B. Diagnosis and management of asthma in the young child. J Asthma 1994;31: 419-25.
11. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. N Engl J Med 1995;332:133-8.

12. Wilson NM. The significance of early wheezing. Rev Clin Exp Allergy 1994;24:522-9.
13. Morgan WJ, Martinez FD. Risk factors for developing wheezing and asthma in childhood. Pediatr Clin North Am 1992;39:1185-203.
14. Glezen WP. Antecedents of chronic and recurrent lung disease: childhood respiratory trouble. Am Rev Respir Dis 1989;140:873-4.
15. Cypcar D, Busse WW. Role of viral infections in asthma. Immunol Allergy Clin North Am 1993;13:745-67.
16. Canny GJ, Levison H. Childhood asthma: a rational approach to treatment. Ann Allergy 1989;64:406-16.
17. Hopp RJ, Townley R, Brennan B, Dave N. Bronchial challenge techniques in children; methacholine, histamine, hyperventilation and osmolar. In: Hillman BC, ed. Pediatric respiratory disease: diagnosis and treatment. Philadelphia: WB Saunders, 1993:131-6.
18. Lemen RJ. Pulmonary function testing in the office, clinic, and home. In: Chernick RM, ed. Kendig's disorders of the respiratory tract in children. Philadelphia: WB Saunders, 1993:147-54.
19. Taussig JM, Smith SM, Blumenfield K. Chronic bronchitis in childhood: what is it? Pediatrics 1981;67:1-5.
20. Smith L. Childhood asthma: diagnosis and treatment. Curr Probl Pediatr 1993:271-305.
21. Corrao WH, Brannon SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. N Engl J Med 1979;300:633-7.
22. Cloutier MM, Loughlin GM. Chronic cough in children: a manifestation of airway hyperreactivity. Pediatrics 1981; 67:6-12.
23. Kih YY, Chae SA, Min KU. Cough variant asthma is associated with a higher wheezing threshold than classic asthma. Clin Exper Allergy 1993;23:696-702.
24. Galvez RA, McLaughlin FJ, Levisin H. The role of methacholine challenge in children with chronic cough. J ALLERGY CLIN IMMUNOL 1987;79:331-5.
25. Johnson D, Osborn LM. Cough variant asthma: a review of the clinical literature. J Asthma 1991;28:85-90.
26. Ellis EF. Asthma in infancy and childhood. In: Middleton E, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, eds. Allergy: principles and practice. St Louis: Mosby, 1993:1225-62.
27. Sly RM. Asthma. In: Behrman RE, ed. Nelson text book of pediatrics. Philadelphia: WB Saunders, 1992: 587-96.
28. Hilman B, Lewiston N. Clinical manifestations of cystic fibrosis in pediatric respiratory disease. Edited by: Hilman B, ed. 1994:661-73.
29. Christopher KI, Wood RP, Eckert C, et al. Vocal cord dysfunction presenting as asthma. N Engl J Med 1983;308: 1566-70.
30. Goldman J, Mores M. Vocal cord dysfunction and wheezing. Thorax 1991;46:401-4.
31. Fanunk D, Hodgens B, Hanna D. Hyperventilation syndrome in children and adolescents: a review with implications for research and practice. Int Pediatr 1991: 2:269-75.
32. American Thoracic Society. Standardizations of spirometry: 1987 update. Am Rev Respir Dis 1987;136:1285.
33. Cherniack RM. Pulmonary function testing. Philadelphia: WB Saunders, 1992:221-4.
34. Murphy TM, Leff AR. Airway reactivity and respiratory smooth muscle tone. In: Chernick RM, Mellins RM, eds. Basic mechanisms of pediatric respiratory disease. Philadelphia: BC Decker, 1991:221-36.
35. Dave NK, Hopp RJ, Biven RE, Degan J, Bewtra AK, Townley RG. Persistence of increased nonspecific bronchial reactivity in allergic children and adolescents. J ALLERGY CLIN IMMUNOL 1990;86:147-53.
36. Tepper RS. Airway reactivity. Workshop: early childhood asthma. What are the questions? Am J Respir Crit Care Med 1995;151:s19-20.
37. Klinger KW. Genetic aspects of cystic fibrosis. In: Hillman BC, ed. Pediatric respiratory disease: diagnosis and treatment. Philadelphia: WB Saunders, 1993:652-60.
38. Wardlaw AJ, Kay AB. Eosinophil. In: Weiss EB, Stein M, eds. Bronchial asthma: mechanisms and therapeutics, 3rd ed. Boston: Little Brown, 1993:258-70.
39. Matt B. Sinusitis. In: Loughlin GM, Eigen H, eds. Respiratory disease in children: diagnosis and management. Baltimore: Williams & Wilkins, 1994:551-9.
40. Lusk RP, Logan RH, Muntz AR. The diagnosis and treatment of recurrent and chronic sinusitis in children. Ped Clin North Am 1989;36:1411-21.
41. Zinreich SJ, Kennedy DW, RosenBaum AE, et al. Paranasal sinuses: CT imaging requirements for endoscopic surgery. Radiology 1987;163:769-75.
42. Rachelefsky GS, Data RM, Siegel SC. Chronic sinus disease with associated reactive airways disease in children. Pediatrics 1984;73:526-9.
43. Umetsu DT. Immunodeficiency and lung disease. In: Hilman B, ed. Pediatric respiratory disease. Philadelphia: WB Saunders, 1993:703-16.
44. Novembre E, DeMartino M, Vierucci A. Foods and respiratory allergy. J ALLERGY CLIN IMMUNOL 1988;81: 1059-65.
45. Chan-Yeung M, Lam S, Koener S. Clinical features and natural history of occupational asthma due to western red cedar *(Thuja plicata)*. Am J Med 1982;72:411-5.
46. Platts-Mills TAE, DeWeck AL. Dust mite allergens and asthma a worldwide problem (International Workshop). J ALLERGY CLIN IMMUNOL 1989;83:416.
47. Platts-Mills TAE, Tovey ER, Mitchell EB, et al. Reduction of bronchial hyperreactivity during prolonged allergen avoidance. Lancet 1982;2:675-8.
48. Arshad SH, et al. Effect of allergen avoidance on the development of allergic disorders in infancy. Lancet 1992; 339:1493-7.
49. DeBlay F, Chapman MD, Platts-Mills TAE. Airborne cat allergens. *Fel D 1)* environmental control with the cat in situ. Am Rev Respir Dis 1991;431:1334-9.
49. Spieksma FT. Domestic mites: their role in respiratory allergy. Clin Exp Allergy 1991;21:655.
50. Pierson WE, Koenig JQ. Respiratory effects of air pollution on allergic disease. J ALLERGY CLIN IMMUNOL 1992; 90:557-66.
51. Haliken S, Host A, Husby S, et al. Recurrent wheezing in relation to environmental risk factors in infancy. Allergy 1991;46:507-14.
52. Murray AB, Morrison BJ. Passive smoking and the seasonal difference of severity of asthma hyperresponsiveness in nine-year old children. J ALLERGY CLIN IMMUNOL 1986;77:575-81.
53. Evans D, Levison MJ, Feldman CH, et al. The impact of passive smoking on emergency room visits of urban children with asthma. Am Rev Respir Dis 1987;135:356-72.
54. Murray AB, Morrison BJ. The effect of cigarette smoke from the mother on bronchial hyperresponsiveness in nine-year old children. J ALLERGY CLIN IMMUNOL 1986; 77:575-81.
55. Haby MM, Peat JK, Woolcock AJ. Effect of passive

smoking, asthma and respiratory infections on lung functions in Australian children. Pediatr Pulmonol 1994;18: 323-9.
56. Honiky RE, Osborne IS III, Apkom CA. Symptoms of respiratory illness in young children and the use of wood burning stoves for indoor heating. Pediatrics 1985;75:587-93.
57. Mella RJ, Florey CV, Altman LK. Association between gas cooling and respiratory disease in children. Br Med J 1977;2:149-62.
58. Malling HJ, Weeke B, eds. Position paper: immunotherapy. Allergy 1993;48(suppl 14):9-35.
59. Ownby DR, Adinoff AD. The appropriate use of skin testing and allergen immunotherapy in young children. J ALLERGY CLIN IMMUNOL 1994;94:662-5.
60. Aas K. Controlled trial of hyposensitization to house dust. Acta Pediatr Scand 1971;60:264-8.
61. Van Bever HP, Stevens WJ. Suppression of the late asthmatic reaction by hyposensitization in asthmatic children allergic to house dust mites. Clin Exp Allergy 1989: 19:399-404.
62. Bousquet J, Michel FB. Specific immunotherapy in asthma: is it effective? J ALLERGY CLIN IMMUNOL 1994;94:1-11.
63. Bentur L, Kerem R, Canny GJ, et al. The response to beta$_2$ agonists in children under the age of 2 years with acute asthma. Ann Allergy 1990;65:122-6.
64. Bentur L, Canny GJ, Shields MD, et al. Controlled trial of nebulized albuterol in children younger than 2 years with acute asthma. Pediatrics 1992;89:133.
65. Kerem E, Levison H, Schuh S, et al. Efficacy of albuterol administered by nebulizer versus spacer device in children with acute asthma. J Pediatr 1993;123:313-7.
66. Newhouse MT. Are nebulizers obsolete for administering asthma medication to infants and children? Pediatr Pulmonol 1993;15:271-2.
67. DeStefano G, Bonetti S, Bonizatto C, et al. Additive effect of albuterol and ipratropium bromide in the treatment of bronchospasm in children. Ann Allergy 1990;65:260-2.
68. Wade TA. Comparison of ipratropium solution, fenoterol solution, and their combination administered by nebulizer and face mask in children with acute asthma. J ALLERGY CLIN IMMUNOL 1988;82:1012-8.
69. Grandordy BM, Thomas V, de Lauture D, Marsac J. Cumulative dose-response curves for assessing combined effects of salbutamol and ipratropium bromide in chronic asthma. Eur Respir J 1988;1:531-5.
70. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respir Med 1994;88:373-81.
71. International Consensus Report on Diagnosis and Treatment of Asthma. National Heart, Lung, and Blood Institute. June, 1992: Publ No. 92-3091.
72. Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic mild to moderately severe asthma in children. Pediatrics 1993; 22:64-77.
73. Konig P, Hillman L, Cervantes C, et al. Bone metabolism in children with asthma treated with inhaled beclomethasone dipropionate. J Pediatr 1993;122:219-26.
74. Pedersen S, Agertoft L. Effect of long-term budesonide treatment on growth, weight and lung function in children with asthma. Am Rev Respir Dis 1993;147:A265.
75. Dowell SF, Bresse JS. Severe varicella associated with steroid use. Pediatrics 1993;22:223-8.
76. Reiches NA, Jones J. Steroids and varicella: commentary. Pediatrics 1993;22:223-8.
77. Kasper WJ, Howe PM. Fatal varicella after a single course of corticosteroids. Pediatr Infect Dis J 1990;2: 729-32.
78. Welch MJ, Segal A, Tokey R, Szefler S, Simons FE. Inhaled corticosteroids (ICS) and viral infections [Abstract]. J ALLERGY CLIN IMMUNOL 1993;23:198.
79. Starr SE. Varicella in children receiving steroids for asthma: risks and management. Pediatr Infect Dis J 1992;11:419-20.
80. American Academy of Allergy and Immunology position statement: inhaled corticosteroids and severe viral infections. J ALLERGY CLIN IMMUNOL 1993;92:223-8.
81. Hendeles L, Weinberger M, Szefler S, Ellis E. Safety and efficacy of theophylline in children with asthma. J Pediatr 1992;120:177-83.
82. Furakawa DT, Du Hamel TR, Weimer L, et al. Cognitive and behavioral findings in children taking theophylline. J ALLERGY CLIN IMMUNOL 1988;81:83-8.
83. Lindgren S, Lokshin B, Stromquist A, et al. Does asthma or treatment with theophylline limit children's academic performance? N Engl J Med 1992;327:926-30.
84. Reisman J, Guldes-Debalt M, Kagin F, et al. Administration by inhalation of salbutamol and ipratropium in the initial management of severe acute asthma in children. J ALLERGY CLIN IMMUNOL 1988;81:16-20.
85. Achuh S, Johnson DW, Callahan S, Canny GJ, Levison H. Efficacy of continuous ipratropium in severe asthma. Pediatr Res 1994;35:A873.
86. Warner JL, Gotz M, Landau LI, Levison H, et al. Management of asthma: a consensus statement. Arch Dis Child 1989;64:1065-79.
87. Van Bever HP, Stevens WJ. Pharmacotherapy of childhood asthma, an inflammatory disease. Drugs 1992;44:36-46.
88. McCarthy TP, Lenney W. Management of asthma in pre-school children. Br J Gen Pract 1992;42:329-434.
89. Haahtela T, Jfirvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. N Engl J Med 1994;331:700-5.
90. National Asthma Education Program: Expert Panel on the Management of Asthma. Sheffer AL, Chairman. Guidelines for the diagnosis and management of asthma. J ALLERGY CLIN IMMUNOL 1991;88:425-34.
91. Provisional Committee on Quality Improvement: Practice parameter: The office management of acute exacerbations of asthma in children. Pediatrics 1994;93:119-26.
92. Lapin CD, Cloutier MM. Outpatient management of acute exacerbations of asthma in children. J Asthma 1955;32:5-20.
93. Pattersmore PK, Johnston SI, Bardin PG. Viruses as precipitants of asthma symptoms. J Epidemiol Clin Exp Allergy 1992;11:325-36.
94. Bardin PG, Johnston SL, Pattemore PK. Viruses as precipitants of asthma symptoms. II: Physiology and mechanisms. Clin Exp Allergy 1992;22:809-22.
95. Bjornsdorrie US, Busse WW. Respiratory infections and asthma. Med Clin North Am 1992;76:895-915.
96. Hammerschlag MR. Is that pulmonary infection due to *Chlamydia pneumonia*? J Respir Dis 1992;13:1385-400.
97. Hahn DL, Dodge RW, Golubjatnikov R. Association of *Chlamydia pneumoniae* (TWAR) infections with wheez-

ing, asthmatic bronchitis and adult onset asthma. JAMA 1991;266:225-30.
98. Anderson S. Exercise-induced asthma. In: Middleton E, et al., eds. Allergy: principles and practice. 4th ed. St Louis: Mosby, 1993:1343-67.
99. Siegel SC, Rachelefsky CS. Asthma in infants and children. J ALLERGY CLIN IMMUNOL 1965;76:1-15.
100. Consortium on Children's Asthma Camps. Parameters of care for asthma camps. American Lung Association, 1994.
101. Blessing-Moore J, ed. Self management programs for childhood asthma. Clin Rev Allergy 1987;5:191-3.
102. Blessing-Moore J. Self management programs in pediatric respiratory disease. In: Hillman B, ed. Pediatric respiratory disease, diagnosis and treatment. Philadelphia: WB Saunders, 1994.