

SUGGESTED ADDITIONAL READING

In addition to the guidelines developed by the NHLBI and the NAEP, the Joint Council of Allergy and Immunology (a joint organization representing the two major national organizations in allergy and immunology) has developed and released a useful compendium relating to practice parameters in asthma. This 160 page document was published in the November issue of the *Journal of Allergy and Clinical Immunology* primarily to represent a description of the standard of care for asthma for this subspecialty; a very useful 14 page compilation of the summary statements has been included as an appendix to this Grand Rounds protocol. It has been reprinted with permission (Susan Patterson) from Mosby-Year Book, Inc., St. Louis, MO and the American Academy of Allergy, Asthma and Immunology. This is a highly distilled and well-referenced guide to important points relating to the diagnosis and management of asthma.

Additionally, an updated set of guidelines is under development by the NHLBI and is expected to be released in late November, 1996 and published and distributed in early 1997.

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. Deter-

mination 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 (P_{aO_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 (P_{aCO_2}) rises from initially low levels to "normal" levels. Therefore a P_{aCO_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 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.
- 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 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 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 $\mu\text{g/ml}$; patients with more severe disease may require concentrations greater than 10 $\mu\text{g/ml}$ for effective control of symptoms. Although patients may experience significant adverse reactions at less than 10 $\mu\text{g/ml}$, as the serum concentration increases, the frequency and severity of toxicity increase. With levels less than 15 $\mu\text{g/ml}$ 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, carbamazepine, 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 perme-

ability, 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 E₂ 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 idiosyncrasies.
- 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 (SO₂)-induced airflow obstruction in asthmatic patients, and cromolyn sodium has also been shown to block SO₂-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.