Asthma can be regarded as a complex syndrome of reversible airway obstruction characterized by bronchial hyperirritability following exposure to various stimuli. Some of the stimuli include extrinsic allergens, viral respiratory infections, and various factors that stimulate irritant receptors in the airways, (eg, vigorous exercise, cold air, cigarette smoke, and air pollutants). The threshold for bronchial hyperreactivity varies among asthmatic individuals and, from time to time, in the same individual. Infection, exercise, exposure to specific allergens, climatic factors, and nonspecific irritants can lower this threshold, and antiasthmatic medications can raise it. If sensitivity to specific allergens can be demonstrated, avoidance of these allergens or, in selected instances, immunotherapy with specific allergens can raise the threshold for the reaginic (IgE) induced hyperreactivity.

Advances of clinical pharmacology and pulmonary physiology have significantly improved the management of asthma in children and adolescents. Application of these advances requires consideration of the frequency and severity of reversible airway obstruction, the chronicity of symptoms between acute episodes, the various specific factors that may trigger the irritable airways of asthma, and the persistance of airway obstruction based on measurements of pulmonary function. The management of asthma is directed toward the reversal of the altered physiology and the prevention of subsequent symptoms and signs of the disease.

The pathophysiology of the airway obstruction includes contraction of bronchial smooth muscle, edema of bronchial mucosa, and excess secretions caused by stimulation of the mucous glands of the respiratory tract. These factors cause either partial or complete obstruction and result in impaired ventilation and pulmonary gas exchange. Partial obstruction of the airways results in increased airway resistance, decreased flow, air trapping, and hypoxemia. Areas of complete obstruction may result in atelectasis, which can be confused radiologically with pneumonia.

Age is not a factor in the diagnosis. The traditional euphemisms of asthma in infancy (eg, recurrent bronchiolitis or bronchitis, asthmatic bronchiitis, and wheezy bronchitis) may only delay appropriate treatment until the patient is older and the presentation more classical. More than 50% of children with asthma have an onset of symptoms during the first two years of life, and at least 25% of these children had an onset of symptoms before they were 1-year-old. In infants and younger children with asthma, mucosal edema and mucus secretions may predominate over bronchospasm. These patients may appear to respond less well to bronchodilator medication. However, earlier notions that infants have no functioning bronchial smooth muscle to cause bronchospasm are not true, and the apparent bronchodilator unresponsiveness of infants with asthma is relative and not absolute.

MANAGEMENT OF ACUTE EPISODES OF REVERSIBLE AIRWAY OBSTRUCTION

The type and intensity of treatment should be determined by the severity of symptoms and the degree of airway obstruction. When acute episodes of mild intensity occur intermittently, bronchodilator medications can be used as needed for relief of symptoms and improvement in pulmonary function. Either theophylline or adrenergic drugs may be used. More severe and/or frequent episodes will require physician intervention.

Theophylline is the primary bronchodilator used in the United States today. If theophylline is to be used only for acute symptoms, rather than as a continuous medication, an initial loading dose of 5 to 7.5 mg/kg as an oral solution, chewable tablet, or plain, uncoated tablet will raise the serum concen-
combination by 10 to 15 µg/ml.³ For children unable to retain oral medication, a rectal solution at the same dose provides similarly rapid and reliable absorption.⁴ Aminophylline suppositories, however, are contraindicated because absorption is erratic and has been associated with theophylline intoxication. Subsequent safe dosage recommendations for short-term use when serum theophylline concentration will not be used to guide dosage is based on age (Table 1). Oral theophylline should be continued for at least 24 hours after the asthmatic symptoms subside. Inasmuch as some degree of bronchospasm persists for days after symptoms subside, longer periods of therapy are often recommended. Combination products containing theophylline with the suboptimal β-adrenergic agent, ephedrine, and a CNS depressant should be avoided. Flexibility in theophylline dosing is limited by the other preparations, which are poor choices for therapy.

β-Adrenergic agents may be used as either primary bronchodilators or adjuncts to theophylline. In contrast to theophylline, there are no reliable dose-response curves and serum drug level determinations for these agents. Metaproterenol, the only oral preparation approved for pediatric use, may be administered as a syrup or tablet at a dosage of 10 mg for children older than 6 years, whose weight is less than 30 kg. Lower doses are indicated for infants and toddlers. For larger children the dosage is 20 mg. Oral terbutaline is available only as tablets of 2.5 to 5 mg and is not currently recommended for use in patients less than 12 years old. Both drugs may be repeated at four- to six-hour intervals.

Metaproterenol, isoproterenol, isoetharine, and albuterol are available in metered-dose inhalers. All may be used for acute episodes in a dosage of two to three inhalations delivered with maximal time allotted between doses so that the initial bronchodilation of the first inhalation allows for enhanced effectiveness of the additional dose. Parents and patients should be warned of the dangers of overuse, a particular problem in the adolescent. Abuse may result in decreasing effect and “rebound” bronchospasm. Overuse has been associated with fatalities.⁵ The newer sympathomimetic bronchodilators with prolonged effect such as metaproterenol, terbutaline, fenoterol, and albuterol have not been associated with rebound bronchospasm, but some degree of tolerance has been observed (i.e., decreasing effect with continuous use). Patient education, selection, and monitoring can minimize overuse and abuse.

If oral or dose-metered bronchodilators are used initially for an acute episode of asthma without adequate response, injected or nebulized sympathomimetic bronchodilators delivered with oxygen are indicated. Aqueous epinephrine (1:1,000) or terbutaline, 1 mg/ml, in doses of 0.01 ml/kg (up to 0.3 ml) can be given by subcutaneous injection. Epinephrine can be used twice more at 15- to 20-minute intervals; terbutaline can be repeated in 30 minutes if no adverse effects occur. Terbutaline appears to have greater potency and longer duration of action at equivalent doses.⁶ Epinephrine may be followed by a longer acting suspension of epinephrine (Susthine 1:200) in a single dose of 0.005 ml/kg, with a maximal dose of 0.2 ml. Isoproterenol (0.5%) or isoetharine (1%) can be delivered nebulized with oxygen using doses of 0.25 to 0.5 ml diluted in 2 ml of saline. This regimen can be used to replace subcutaneous epinephrine or terbutaline. Metaproterenol (5%) can be similarly used but is not approved for children less than 12 years of age. Terbutaline and albuterol have not been approved for aerosol use by the Food and Drug Administration. A compressor device is the method of choice for aerosol delivery of these agents. Nebulization with oxygen limits the risk of hypoxemia, which may complicate aerosol therapy. Corticosteroids should be considered when response to optimal bronchodilator therapy is inadequate.⁷ The physician should be prudent in the use of corticosteroids, but he/she should not wait until the child's symptoms are so severe that hospitalization may be necessary. Prednisone (1 to 2 mg/kg per day, given as a single morning dose or divided every 12 hours) generally is adequate, and its short-term use (seven to ten days) has not been associated with toxicity. The appropriate institution of a brief course of corticosteroids during severe exacerbations may avert the need for hospitalization. The patient receiving chronic steroid therapy, either orally or by aerosol, should be placed on high-dosage bursts of prednisone for acute exacerbations of asthma. Maintenance corticosteroid dosage should be resumed when symptoms and signs of the acute exacerbation are relieved.
MANAGEMENT OF STATUS ASTHMATICUS
AND RESPIRATORY FAILURE

The hallmark of status asthmaticus is severe, persistent wheezing and dyspnea refractory to bronchodilators. Respiratory failure can occur in a patient with severe status asthmaticus. Treatment requires intensive medical care, which is best administered in an intensive care unit or other appropriately staffed facility.

Initial arterial blood gas levels should be used to establish a base line for the degree of hypoxemia and acid-base balance in all patients in status asthmaticus. Frequent monitoring of blood gases is essential unless rapid improvement is clinically apparent. Humidified oxygen should be given to maintain normal arterial oxygen saturation. Hydration and electrolyte status should be evaluated, and deficits corrected, and sufficient maintenance fluid should be administered. Underhydration may increase the viscosity of mucus plugs, but overhydration may result in pulmonary edema. Also, inappropriate antidiuretic hormone production may accompany status asthmaticus.

When the arterial pH is below 7.3 and the base deficit is greater than 5 mEq/liter, intravenous sodium bicarbonate (bicarbonate dose in milliequivalents = 0.3 x body weight in kilograms x base deficit) may be helpful to correct the metabolic component of the acidosis. Respiratory acidosis is corrected by appropriate drug therapy to increase alveolar ventilation; assisted ventilation may occasionally be required.

In a patient with status asthmaticus, a therapeutic serum concentration of theophylline should be obtained rapidly with a loading dose of aminophylline (85% theophylline). The loading dose should be 5 to 7.5 mg of aminophylline per kilogram diluted in 25 to 50 ml of saline administered intravenously over a period of about 20 minutes. As a general guideline, 1 mg of aminophylline per kilogram of body weight will raise the serum concentration by 2 µg/ml. Thus, 5 mg of aminophylline per kilogram will raise the serum concentration an average of 10 µg/ml (range of approximately 7 to 16 µg/ml). If an initial serum theophylline level cannot be obtained, the loading dosage of theophylline should be modified on the history of theophylline dosing. After the loading dose, a constant maintenance infusion of aminophylline of 0.85 mg/kg/hr for children 1 to 9 years old, 0.65 mg/kg/hr for children 6 to 16 years old, and 0.45 mg/kg/hr for adults usually will maintain serum concentrations of approximately 10 µg/ml. The initial maintenance infusion should be reduced by 50% if there is significant fever, liver disease, or heart failure. Average theophylline dosage for infants less than 1 year old relates to age and can be estimated by a regression formula: dose (milligrams per day) = 0.3 x age in weeks + 8.

Measurement of serum theophylline levels is essential for optimal use. Clearance is significantly prolonged in neonates, and individual serum concentrations at all ages will range widely because of variable clearance of theophylline. Theophylline concentrations should be measured at the time of admission and at 1, 6, 12 and 24 hours after admission (or at any time that theophylline toxicity is suspected on the basis of symptoms such as headaches, CNS irritability, or gastrointestinal [GI] upset). The theophylline infusion is best administered by constant infusion pump, but it may be administered by a controlled intravenous drip using a Volutrol (Cutter Laboratories, Inc, Berkeley, CA) if no more than two hours of medication is accessible to the drip chamber at any time. If the plasma concentration of theophylline falls below 10 µg/ml, an additional loading dose should be administered to produce a serum concentration of 10 to 15 µg/ml. If constant infusion cannot be maintained safely, equivalent doses may be given as boluses administered over a period of 30 minutes at six-hour intervals (eg, 5 to 6 mg/kg every six hours will result in a mean serum concentration that matches the steady-state serum concentration achieved with a 1 mg/kg/hr constant infusion). Aerosolized sympathomimetic agents should be administered with aminophylline, using the doses discussed.

Intravenous corticosteroids are indicated for status asthmaticus because they facilitate recovery from hypoxemia and may increase the action of adrenergic drugs on β-adrenergic receptors. An initial loading dose of hydrocortisone hemisuccinate, dexamethasone phosphate, or betamethasone phosphate equivalent to 1 to 2 mg of prednisone per kilogram should be administered intravenously, followed by an equivalent dosage over the next 24 hours by continuous infusion (Table 2), or it may be repeated in divided doses at four- to six-hour intervals. Tapering the dose for the sake of adrenal function is unnecessary if steroid therapy is short-lived, but small airway bronchospasm may persist for more than one week requiring a longer course. Both the use of five days of high dose oral prednisone at 1 to 2 mg/kg in a single morning dose and a seven- to ten-day regimen of prednisone starting at 1 to 2 mg/kg and tapering by 5 mg each morning have been successful.

If hypoxemia and/or hypercapnea (PO2 < 50 mm Hg in 100% inhaled O2 or Pco2 > 50 mm Hg) occurs, the patient should be treated for respiratory failure in an intensive care unit capable of providing assisted ventilation to children. Signs associated with respiratory failure include persistent tachycardia, persistent dyspnea, "quiet" chest with decreased
breath sounds indicating hypoventilation, cyanosis, notable use of accessory respiratory muscles, and pulsus paradoxus of 15 mm Hg or greater; but the final diagnosis is established by arterial blood gas levels.

Intravenous isoproterenol by constant infusion has been advocated to avoid the use of mechanical ventilation. This procedure should only be undertaken by those experienced in the use of isoproterenol because of the potential for inducing serious arrhythmias and possible myocardial necrosis. When this drug is used, the possibility of a subsequent need for assisted ventilation must be appreciated.

Assisted ventilation should be considered for any child with a rising arterial Pco2, and it is unavoidable if the arterial Pco2 is continuing to rise above 55 mm Hg. Mechanical ventilation requires an experienced team, including a physician familiar with intubation and the use of the volume ventilator, a respiratory therapist, and skilled nurses. This team must be cognizant of dangers such as faulty intubation, accidental extubation, postintubation laryngeal edema or stenosis, oral and/or dental trauma, pneumomediastinum, pneumothorax, and sometimes profound subcutaneous emphysema. Nasotracheal intubation is more comfortable and results in more secure placement of the tube, although oral tracheal intubation can be used when necessary. The patient should be given 100% oxygen during intubation, and secretions should be suctioned regularly. A nasogastric tube should be used with continuous suction to avoid distention of the stomach. The patient should be sedated after intubation to improve synchronization of respiration with the ventilator. Skeletal muscle-paralyzing agents, such as curare and pancuronium bromide, are used frequently. Whereas curare is sometimes preferred for intubation because of its short half-life, which minimizes the period of respiratory muscle paralysis if intubation fails, pancuronium bromide is preferable for longer periods because, unlike curare, it lacks cardiac effects and histamine release potential. The risk of accidental extubation must be appreciated and avoided when the patient is paralyzed.

**MANAGEMENT OF CHRONIC ASTHMA**

The goals of the long-term management of chronic asthma include the prevention of daily or frequently recurring symptoms and the prevention of acute exacerbations. It is desirable to achieve normal pulmonary function, but the risk-benefit ratio must be weighed if chronic corticosteroid therapy is necessary to achieve this goal.

Theophylline is generally the most effective non-corticosteroid drug for the suppression of symptoms of chronic asthma. This drug, administered in doses that maintain serum concentrations between 10 and 20 μg/ml, reduces the frequency and severity of acute symptoms and minimizes exercise-induced bronchospasm. Rapid-release tablets and liquid preparations may be used successfully, but sustained-release formulations of theophylline decrease fluctuations in serum concentrations and allow eight- to 12-hour dosing intervals. Of those sustained-release formulations currently marketed, not all have reliable and consistent absorption. In addition, most formulations are not available in dosage sizes that allow adequate flexibility to individualize the dose required for optimal effect and safety. Slo-Phyllin Gyrocaps are available in 60-, 125-, and 250-mg bead-filled capsules, which can be opened and sprinkled over a spoonful of soft food without any apparent effect on their absorption characteristics. As currently formulated, Theo-Dur tablets offer the advantage of longer duration of action and the potential for 12-hour dosing for most patients, if they are able to swallow the tablet whole. Theodur is available as 100-, 200-, and 300-mg scored tablets and thus allows 50-mg increments in dosing when the 100-mg tablet is halved. The sustained-release theophylline market is in a state of flux, and changes in formulation are sometimes made without announcement or even notification in the package labeling. Furthermore, data related to rate and completeness of absorption are not routinely submitted to the FDA before marketing of new theophylline products, and the various preparations may not be interchangeable.

Cromolyn sodium, administered by inhalation as a dry powder into the lungs via a turbuinhalar device, is another agent for the management of chronic asthma. This drug appears to prevent release of the chemical mediators of bronchospasm from sensitized mast cells exposed to specific antigens. However, its benefit in nonimmunologically mediated asthma suggests that other undefined mechanisms of action may be involved. This drug has no other bronchodilator effect and is useful only...
as a preventative measure when used on a regular basis. In a collaborative, compatible study with theophylline, asthma control with cromolyn was satisfactory. Cromolyn has an outstanding safety record. The most frequent side-effect observed is cough from inhalation of the powder; this is rarely sufficient to prevent routine use, and no ill pulmonary effects have been observed from long-term inhalation of the powder.

β-Adrenergic sympathomimetic agents (metaproterenol, terbutaline, albuterol) are prescribed for asthma not controlled by theophylline and/or cromolyn. Many physicians prefer maintenance therapy only with optimal theophylline and/or cromolyn because of concern that tolerance may occur with long-term adrenergic use. Metaproterenol and tablets may be used in dosages of 10 to 20 mg every four to six hours. Terbutaline tablets (2.5 to 5.0 mg) may be used every six to eight hours in children older than 12 years. Inhaled metaproterenol, and albuterol, two inhalations, may offer more bronchodilation and avoid systemic side effects such as tremor and irritability, but patients and parents must be warned about potential abuse. Inhaled β-agonists are particularly effective in blocking exercise-induced bronchospasm if it is not controlled by theophylline or cromolyn.

When the patient has chronic, intractable symptoms, continuous use of corticosteroids may be needed. The long-term use of daily corticosteroids, especially when multiple doses are used each day, results in adrenal suppression, growth retardation, the risk of posterior-subcapsular cataracts, hyper tension, and osteoporosis. However, when used in single doses on alternate mornings, the long-term use of corticosteroids is possible with minimal risk of these side effects. Inhaled beclomethasone dipropionate, a corticosteroid delivered by a metered-dose inhaler, is an alternative to alternate-day prednisone. Both alternate-day prednisone and inhaled beclomethasone dipropionate are only preventative measures and do not clear acute symptoms as effectively as higher dose daily steroids. Daily steroids generally have been used to eliminate symptoms and normalize pulmonary function at the onset of the maintenance regimen. Alternate-day prednisone is the continuous corticosteroid regimen of choice for children too young to use the beclomethasone metered-dose inhaler effectively. It is the initial treatment of choice for children in whom compliance problems are anticipated because a single dose every other morning is simple to administer. The alternate-day prednisone regimen also costs less than aerosolized beclomethasone. Initial doses of alternate-day prednisone need to be higher than twice the daily dose. Serious side effects are rare, but some patients gain excessive weight on alternate-day prednisone, even when there are no other adverse effects. Inhaled beclomethasone dipropionate is a good alternative in these patients. Most experience with inhaled beclomethasone dipropionate in children has been at daily doses of 400 µg. However, some children have required higher doses for control, and limited experience indicates that doses up to 800 µg/day have an acceptable safety level. Patients not responding well to one of these corticosteroid regimens may do better on the other. The use of the two corticosteroid regimens together results in an additive effect on hypothalamic-pituitary-adrenal suppression. If bursts of daily prednisone are required by patients who have received continuous doses of inhaled beclomethasone dipropionate or alternate-day prednisone, the previous chronic corticosteroid regimen should be resumed as soon as possible after relief of the exacerbation. If the patient is asymptomatic while receiving chronic steroids, doses should be decreased at two-week intervals to determine the lowest dose possible without exacerbation.

Immunotherapy, the injection of allergenic extracts so that sensitivity to inhalant allergens will be decreased, has long been used in the management of allergic asthma. Studies and clinical experience support the fact that injections of allergenic extracts decrease sensitivity to inhalant allergens when a specific antigen is used in sufficient doses. If the physician judges, on the basis of history and skin tests, that a major component of the patient’s asthma is caused by an allergy to inhaled allergens, injection therapy with specific pollen or house dust, in increasing concentrations, is beneficial and may reduce allergic symptoms. Mold immunotherapy remains unstudied. Bacterial and food vaccines have been amply discredited.

SUMMARY

Advances in the knowledge of clinical pharmacology and pulmonary physiology have significantly improved the management of asthma in children and adolescents. Acute episodes of asthma can be treated with oral bronchodilators if the episodes are mild, but inhaled sympathomimetic drugs are more effective and may have fewer side effects. Effective therapy for status asthmaticus consists of intravenous aminophylline and corticosteroids and aerosolized sympathomimetic drugs. Theophylline, in a dose that maintains serum concentrations between 10 and 20 µg/ml, or cromolyn is the drug of choice for managing asthma when symptoms are continuous or recur frequently. Theophylline appears to be more convenient to use than inhaled cromolyn sodium, after the proper dose is established. However,
cromolyn has no risk of overdosage and does not require the measurement of serum concentrations essential for theophylline efficacy and safety. β-Adrenergic agents are useful adjuncts or alternatives to therapy with theophylline or cromolyn. Treatment by short courses of corticosteroids may be needed at intervals for patients with chronic or labile asthma. Continuous use of corticosteroids will be required for the relatively few patients whose asthma cannot be controlled with other medications. Alternate-day prednisone or inhaled beclomethasone dipropionate offer two alternatives for continuous therapy with corticosteroids which are relatively free from adverse effects of chronic steroid administration. Immunotherapy for inhalated pollens, house dust, or molds may be useful in selected patients whose allergy is clearly exacerbating to their asthma.

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REFERENCES

BIBLIOGRAPHY
ERRATA

In the article “Milk Feeding Patterns in the United States during the First 12 Months of Life” by Martinez et al (Pediatrics 68:863–868, 1981), corrections should be made in Table 5 (p 865) and Table 6 (p 866). In Table 5, Income, 1980 ≥$15,000 should read 46.6 (not 38.1). In Table 6, values for Income, In Hospital should read as follows: <$15,000, 50.5 (not 39.9); $15,000–24,999, 57.1 (not 53.9); ≥$25,000, 62.2 (not 58.8).

In the article “Management of Asthma” by the Section on Allergy and Immunology of the American Academy of Pediatrics (Pediatrics 68:874–879, 1981) corrections should be made on p 876, fourth paragraph, as follows: Line 15, sentence should read: After the loading dose, a constant maintenance infusion of aminophylline of 0.85 mg/kg/hr for children 1 to 9 years old, 0.65 mg/kg/hr for children 9 to 16 years old, and 0.45 mg/kg/hr for adults usually will maintain serum concentrations of approximately 10 μg/ml. Line 23, sentence should read: Average theophylline dosage for infants less than 1 year old relates to age and can be estimated by a regression formula: dose (milligrams per kilogram per day) = 0.3 × age in weeks + 8.

In the letter “Aspirin Fatalities—The New Taxonomy” by McIntire and Angle (Pediatrics 69:249, 1982), in the second paragraph, the last sentence should read: Eight of the 11 deaths occurred at the victim’s residence, implying delayed recognition and underutilization of poison control center facilities.

In the letter “Echocardiography in Aspergillus Endocarditis” (Pediatrics 69:252, 1982) the authors’ names are as follows: Martin B. Kleiman, MD, Randall Caldwell, MD, Donald Girod, MD, and Roger Hurwitz, MD.
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Pediatrics 1981;68:874

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