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The Clinical Challenge of Acute Asthma: Diagnosis, Disposition, and Outcome-Effective Management: Year 2001 Update

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The patient typically will present with anxiety, shortness of breath, and acute respiratory distress, and the physician will have to respond with prompt, definitive intervention. This is a common scenario for acute exacerbations of chronic asthma, a clinical condition that is routinely managed in the emergency department (ED). Nationwide, it is estimated that more than 17 million people suffer from asthma,[1] a protean condition that includes patients with minor respiratory symptoms as well as individuals on the verge of respiratory collapse.

Nationally, asthma accounts for more than 1.8 million visits to EDs and its incidence exceeds 4% of the United States population.[2] Despite significant advances in our understanding of the mechanisms and predisposing factors—as well as the introduction of new pharmacotherapeutic options such as leukotriene antagonists—the prevalence and morbidity and mortality rates associated with asthma continue to climb.

Current data show that the annual rate of ED visits for asthma increased by 20% between 1992 and 1995. More alarmingly, the death rate from asthma dramatically increased, with the annual asthma mortality rate increasing 56% from the period 1979-1980 to 1993-1995.[2] There is some information, however, suggesting that prevalence rates have stabilized in most populations, except among African-American females.[3]

From an emergency perspective, the management of asthma has become increasing multi-modal, and requires that the emergency physician become familiar with a wide range of pharmacologic options, among them, inhaled and systemic corticocosteroids, beta-agonists, leukotriene antagonists, and other agents. Traditionally, emergency and primary care physicians relied heavily on beta-agonists as the drugs of choice for treatment of asthma exacerbations. With advances in molecular biology and a more detailed understanding of the inflammatory pathways that are responsible for bronchoconstriction, however, new approaches have proven successful for reducing airway reactivity both for chronic maintenance therapy and acute exacerbations.

With these issues in focus, this clinical review provides an update of new developments in asthma management. Typical features of the clinical presentation are discussed, and signs and symptoms that help identify patients with acute asthma exacerbations and that differentiate asthma from other pulmonary processes are summarized. A concise, practical framework is offered for

identifying and stratifying asthma episodes by severity and initiating prompt, appropriate treatment. Finally, because the therapeutic landscape is changing so rapidly, this article will update the emergency physician about optimal treatment strategies for the management of acute and chronic asthma.

— The Editor

Introduction

Definition and Epidemiology. Asthma is a chronic inflammatory disorder resulting in widespread narrowing of the airways; it is characterized by the clinical symptoms of wheezing, dyspnea, chest discomfort, and cough. *(See Table 1.)* Typically, the condition leads to airway hyper-reactivity which occurs in response to a variety of nonspecific stimuli, and presents as a reversible or variable airway obstruction. The lung parenchyma remains normal, although some degree of sub-basement membrane fibrosis may occur.[4]

In the United States, asthma accounts for more than 470,000 hospitalizations annually, and more than 5,000 people die from exacerbations of asthma each year. Hospitalization rates are highest among African-Americans and children, with death rates highest among African-Americans between the ages of 15 and 24.[5] Asthma is the most common chronic disease of childhood, affecting more than 5.3 million children.[1]

Worldwide, the prevalence of asthma is increasing. Furthermore, studies have shown that asthma is more common in Western countries and less common in developing countries. Its prevalence increases in developing countries as they become more Westernized or communities become more urbanized.[6] In the United States alone, the costs associated with asthma exceed $6.2 billion, with 43% of these expenditures resulting from ED visits, hospitalizations, and death.[7]

Risk Factors. Traditionally, risk factors for asthma mortality have been thought to include a history of sudden, severe exacerbations, prior intubations, and admission to an intensive care unit (ICU). Additionally, use of more than two canisters per month of a short-acting beta-2 agonist, current systemic corticosteroid use, difficulty with perceiving airway obstruction, and medical or psychiatric co-morbidity have been linked to an increased risk of death from asthma. Certainly, not all patients meeting these criteria require ICU placement or admission. However, physicians should take these aspects of the history into account, along with the response to ED treatment when making a disposition decision.

Inner-city children and adults share a disproportionately high risk for asthma-related morbidity and mortality.[8] Epidemiological studies have highlighted several contributing factors: lack of insurance and decreased immunization rate, lack of access to quality health care, and an indoor/outdoor environment with exposure to triggers such as dust, pollen, smoke, and pollution.[8,9] Additionally, studies have pointed to a possible causal relationship between the use of illicit drugs (particularly inhaled cocaine and heroin) and asthma.[10,11] At the molecular level, research into the genetics of asthma has unveiled several candidate genes that may contribute to asthma susceptibility.[12-14]

Clinical Pathophysiology

Mechanisms causing airway obstruction in asthma are multifactorial, and not completely understood. As an intrinsic airway disease, obstruction is due to an abnormality in the airway itself, as contrasted with extrinsic disease such as emphysema. In emphysema and chronic obstructive pulmonary disease (COPD), obstruction results, in part, from loss of external support of the airways, as well as from airway reactivity. The principal response to airway inflammation is partial obstruction of the airway lumen, which becomes obstructed by excessive secretions; alternatively, the airway wall thickens from edema and smooth muscle hypertrophy. Airway inflammation results in the release of mediator factors that produce the hallmark features of asthma: airway edema, epithelial injury, and infiltration by leukocytes (particularly eosinophils). Small decreases in overall airway diameter manifest as significant clinical changes in ventilation. These changes can easily be measured with spirometry or flow volume curves.

Current research suggests that the increased airway reactivity and inflammation in individuals with asthma results from a predis-

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Table 1. Differential Diagnosis in Asthma

ADULTS
Chronic obstructive pulmonary disease (COPD)
Foreign body aspiration
Allergic reaction
Congestive heart failure (CHF)
Neoplasms
Toxic inhalation
Tracheal stenosis
PEDIATRICS
Tracheobronchitis
Foreign body aspiration
Tracheomalacia
Bronchopulmonary dysplasia
Cystic fibrosis
Allergic reaction

Table 2. Evaluation of the Patient with Asthma: History

GENERAL
- Age
- Gender

MEDICATION USE AND COMPLIANCE
- Steroids
- Leukotriene antagonists
- Theophylline

MEDICAL HISTORY
- Cardiovascular disease

PAST EPISODES
- ICU admissions
- Number of emergency department visits in last year
- Any history of pneumothorax

CURRENT EPISODE
- Onset
- Time course (crescendo pattern)
- Characterization of symptoms
  - Dyspnea
  - Fever
  - Chest tightness
  - Wheezing
  - Cough or sputum production
- Prior treatment
- Recent upper respiratory infection (URI) symptoms
- Occupational exposures

FAMILY HISTORY
- Other family members with asthma
- Other pulmonary disease
- History of atopy (eczema, dermatitis)

SOCIAL HISTORY
- Tobacco history or second-hand exposure
- Drug history, especially inhaled drugs/inhalants

posing event early in life. Consequently, the patient develops airway hyper-reactivity, which is precipitated by the release of inflammatory mediators when the patient is exposed to specific trigger factors. Many stimuli have been shown to cause increases in airway responsiveness, including viral upper respiratory tract infections, irritant gases, and inhaled antigens.

Once airways are primed with heightened reactivity, environmental exposures or certain stimuli cause symptomatic bronchoconstriction. Specific trigger factors that precipitate asthma exacerbations include inhaled antigens, exercise, cold air, irritant gases, dust, animal dander, beta-blockers, metabisulfite, cigarette smoke, emotional stress, and aspirin.[15] Up to 15% of asthmatics will experience bronchoconstriction when exposed to aspirin; cross reactivity with other nonsteroidal anti-inflammatory drugs (NSAIDs) also may occur. Given the high relapse rate following treatment for acute asthma, it may be helpful to educate patients about these asthma triggers.

Clinical Features

Phases of Asthma Exacerbations. Clinically, patients experience an early or immediate response, and a late or delayed response. In the early response, degranulation of mast cells from IgE-antigen binding to mast cells leads to bronchial smooth muscle contraction and mucous hypersecretion. This phase of the response lasts 1-2 hours and is the target of initial, acute interventions with beta-agonists in the ED.

The delayed phase begins simultaneously and manifests clinically 4-6 hours after exposure to the allergen, but can last for several more hours. Granulocytes, and especially eosinophils, infiltrate the airway wall. There is associated airway hyperresponsiveness and increased bronchial constriction. Steroids and leukotriene antagonists are used to diminish the late phase of exacerbations.

History. Components of the history that may be important for evaluating the patient with asthma are listed in Table 2. Primary questioning should focus on determining risk factors for severe asthma exacerbations and for death, while simultaneously trying to identify, if possible, a precipitant for the attack. Specific points include the extent of the patient's disease, a medication history, current or previous use of steroids, and ICU admissions or a history of intubations for asthma. Of special note is the finding that a history of ICU admissions and/or intubations are risk factors for respiratory failure.[63]

A typical triad of presenting symptoms in a patient with an asthma exacerbation includes cough, wheezing, and dyspnea, although all three may not be present. The patient also may experience feelings of tightness in the chest. Increased symptoms at night are common, with coughing or wheezing waking the patient from sleep. Children, in particular, can experience increased nocturnal symptoms because their airway patency decreases at night.

Patients with longstanding disease often can communicate their subjective impression of the severity of their current episode, along with the time course of previous episodes. However, studies also have shown that up to 15% of asthma patients, 24-27% of elderly patients, and many patients who had near-fatal asthma exacerbations could not perceive their severity of obstruction.[16-18] For reasons that are not fully explained, men tend to underestimate the severity of bronchoconstriction.

Physical Examination. Physical examination of the asthmatic includes rapid evaluation of the patient's general appearance, including anxiety level, mental status, and the level of respiratory

Table 3. Evaluation of the Patient with Asthma: Important Aspects of the Physical Examination

GENERAL APPEARANCE
• Anxiety
• Mental status
• Level of respiratory distress:
Retractions
Accessory muscle use
VITAL SIGNS
• Temperature
• Heart rate
• Respiratory rate
• Pulse oximetry
• Blood pressure (pulsus paradoxus)
PULMONARY
• Hyperresonance
• Prolonged expiratory phases (increased I:E)
• Air flow
• Wheeze distribution
• Any focal findings
ASSOCIATED FINDINGS
• Ear, nose, and throat (increased nasal secretions, sinusitis, mucosal swelling)
• Cardiac (S_3, S_4, diffuse apical impulse, murmurs)
• Skin (dermatitis, eczema, atopy, urticaria)
• Extremities (edema, cyanosis, clubbing)
• Upper airway (inspiratory stridor, localized wheeze, dysphonia)
• Lymphadenopathy

distress. *(See Table 2.)* Altered mental status, severely labored breathing, and accessory muscle use are signs of impending or actual respiratory failure. Tachypnea and tachycardia commonly occur, but are poorly correlated with disease severity.

Most exacerbations begin with expiratory wheezing, but with more severe bronchoconstriction this can progress to both inspiratory and expiratory wheezing. Air movement may range from mildly decreased to almost absent. When a patient develops severely diminished airflow, wheezing becomes diminished or disappears entirely. Wheezing also may be absent in patients with mild asthma. The variability of physical findings suggests the need for objective measurements of pulmonary function.

Children may demonstrate nasal flaring or intercostal and suprasternal retractions in serious asthma exacerbations. In children, it is common for an exacerbation to begin with a cough that progresses to wheezing, tachypnea, and dyspnea. With severe obstruction, the child may assume a hunched-over, tripod-like sitting position with hyperexpansion of the thorax. In addition, the child may complain of abdominal pain, presumably due to the strenuous use of abdominal muscles and the diaphragm during an exacerbation. With a severe obstruction, the increased work of breathing may cause diaphoresis.

In general, although physical findings can help approximate patient acuity, several studies have shown that a physician's examination is neither accurate in assessing the degree of airway obstruction[19] nor for predicting whether the obstruction is reversible.[20] Pulse oximetry has shown promise for monitoring the severity of acute exacerbations, although the literature is inconclusive as to its utility in predicting the course of asthma attacks.[21] In the pediatric population, decreased oxygen saturation often is an early sign of severe airway obstruction and does predict the need for hospitalization.[22] A pulse oximetry of less than 91% usually implies a severe attack.

Several authors have studied cumulative asthma scores, consisting of weighed aspects of the patient's history and physical findings as tools to predict the course of an exacerbation.[23-25] Although the precise clinical benefit of asthma scores has yet to be demonstrated, studies to date have shown no improvement in predicting outcome when compared with physician judgment.

Pulmonary Function Testing. Measurements of peak expiratory flow rates (PEFR) provide a simple, reliable, objective modality for assessing the respiratory status of patients with asthma, as well as the efficacy of treatment.[26] A PEFR is easily obtained on inexpensive equipment, can quantify the degree of diminished airflow, and provides a reproducible measure of the severity of airflow obstruction.

Overall, FEV_1 and PEFR measured by spirometry more accurately predict severity of the exacerbation when compared with physician physical examination. Consequently, most guidelines for asthma management focus on the percent of predicted pulmonary function as the most reliable means of stratifying the severity of episodes.[27] Predicted values vary by race, age, gender, and height. Inexpensive spring loaded peak flow meters are inaccurate in their midrange and tend to lose accuracy after several hundred uses. The PEFR is more effort-dependent than measurement of FEV_1. The advantage of measuring FEV_1 by spirometry is that it provides a graphic record, allows comparison to baseline studies from the pulmonary function lab, and is less effort-dependent. In addition, the spirometer is easily calibrated.

In the ED, the initial FEV_1 or PEFR is helpful for risk-stratifying patients into various categories of airway obstruction. Repeat assessment after treatment is important to monitor progress and guide the aggressiveness of therapy. Values of less than 30% of predicted point to an increased likelihood of significant hypoxemia or hypercarbia.[28] Most patients with a pre-discharge PEFR of less than 50% of predicted value after treatment and observation should be admitted or observed.

Diagnostic Studies. Arterial blood gas (ABG) analysis is not usually performed, but it can help assess the degree of respiratory compromise when intubation is being considered. Importantly, as a screening tool neither pretreatment nor post treatment ABG values correlate strongly with pulmonary function testing, and neither is useful for predicting the course of an exacerbation[29] although an FEV_1 or PEFR of less than 30% of predicted values may indicate significant hypercarbia or hypoxemia. *(See Tables 3 and 4.)*

Typically, chest radiographs show treatable abnormalities in a small percentage of patients and are not routinely indicated. Hyperinflation occurs during acute attacks, but may become chronic if airway obstruction is longstanding. The chest x-ray may provide additional information and help narrow the differential in patients with hypoxia, fever, focal lung findings, or symp-

Table 4. Laboratory Testing for Asthma

PULMONARY FUNCTION (PEFR or FEV_1)	Initially and after treatment in all patients
CHEST RADIOGRAPH	Consider if focal findings or signs of pneumonia (fever, purulent sputum) are present, or if uncertain of diagnosis
ELECTROCARDIOGRAM	Not routinely indicated; May consider for patients with known cardiac history
COMPLETE BLOOD COUNT	Not routinely indicated
ELECTROLYTES	Not routinely indicated
THEOPHYLLINE LEVEL	Prior to bolus administration of aminophylline or tachyarrhythmias in patient on therapy
ARTERIAL BLOOD GASES	Very severe obstruction that is not responsive to therapy or during mechanical ventilation

toms that do not improve with bronchodilator therapy.

Complete blood count (CBC) is rarely helpful, although eosinophilia and/or leukocytosis are typical findings in asthma exacerbations. Leukocytosis alone represents a nonspecific finding, especially since beta-agonist administration and corticosteroids can cause white cell de-margination. For patients taking theophylline preparations, and especially in elderly patients, theophylline levels should be obtained prior to bolus administration of aminophylline. Patients older than age 60 demonstrate decreased clearance of the drug, and have a 16-fold increased risk for theophylline toxicity.[30] Theophylline toxicity usually occurs as serum levels exceed 20 mcg/mL particularly in patients with preexisting neurologic or cardiac disease.[31]

Patient Management

The primary, initial pharmacological treatment for acute asthma is beta-agonist therapy, usually by inhalation, although other routes are sometimes used. A number of agents are available, each of which possesses varying degrees of beta selectivity. It should be emphasized that beta-agonists also are available in oral formulation, but that this route is not indicated for initial stabilization in the ED. *(See Tables 5 and 6.)*

Beta-Agonists. Two agents generally are used for parenteral beta-agonist treatment, epinephrine and terbutaline. In the past, these drugs commonly were administered by subcutaneous injection. However, a series of investigations have demonstrated that inhaled beta-agonists are as effective as subcutaneously injected agents. On occasion, epinephrine and terbutaline still are used for patients with acute asthma, particularly in patients who have very severe obstructions or for those who cannot or will not tolerate nebulizers. There is only limited evidence suggesting that patients who do not respond to inhaled agents will have a subsequent response to injected epinephrine.[32] Intravenous administration of beta-adrenergic agents is common is some countries, although its use in the United States primarily has been in the pediatric population.

Several studies have compared intravenous with nebulized albuterol in patients with either respiratory failure or very severe airway obstruction. These trials have suggested that intravenous administration is associated with a higher incidence of side effects, without producing significant clinical advantages.[33,34]

As mentioned, there are a variety of agents available for inhalation, each varying with respect to beta-2 selectivity and duration of action. The onset of action of such agents as terbutaline, isoetharine, metaproterenol, and albuterol is very rapid.[35] Isoetharine, in particular, produces significant bronchodilatation within 10 minutes of administration but it must be diluted to avoid reactions to the preservative agent, bisulfite. There is no convincing evidence suggesting the superiority of one of agent over the other in terms of efficacy or safety, although there have been some reports suggesting that isoetharine has a greater incidence of side effects than albuterol.[3] Moreover, the extended duration of action of agents such as fenoterol and albuterol may lead to some benefits over isoetharine.[28] Although salmeterol is effective for maintenance therapy, it should not be used for the treatment of acute exacerbations of asthma, and patients should be cautioned not to use salmeterol for home rescue therapy.

Beta-agonists can be given by metered dose inhaler with a spacer, small-volume nebulization, or dry powder inhalation. These variable routes of administration lead to similar degrees of airway improvement, assuming they are used properly.[37-39] The advantage of using either dry powder or a metered dose inhaler with a spacer is that it reinforces patient education about proper medication administration.

There may be differences in the personnel cost to set up nebulizers or monitor a patient's use of metered dose inhalers, which may vary between institutions.[40] The efficiency of drug delivery by nebulization can be enhanced by using an acorn type nebulizer, diluting the drug to a 3 mL volume, and driving the ventilator with a 6-8 L/min flow rate from either a compressed air source or wall oxygen outlet.[41]

Intermittent positive-pressure breathing (IPPB) treatments have fallen out of favor, although occasionally there are patients who may receive a modest benefit from this treatment.[42] There does not seem to be any advantage when comparing specific metered dose inhalation with a spacer, tri-powder inhalation, intermittent nebulization, or continuous nebulization in adults.[43] Albuterol is given by continuous nebulization in some centers. While some studies have found an advantage to continue infusion, others have either not demonstrated a difference or found that continuous nebulization led to a higher incidence of side effects.[44-46] There may be cost saving with respect to personnel time with one method or the other, depending on the institution.

The National Asthma Education Prevention Program (NAEPP) recommends the following dosing schedule for albuterol: 2.5 mg administered every 20-30 minutes, increasing to doses of 5 mg every 20-30 minutes for patients with severe obstruction. Although recommended, there is little evidence to support the superiority of this dosing scheme.[47] In children, repeated, low

doses of albuterol lead to less fluctuation in FEV_1 over the course of several hours compared to larger, hourly doses.[48] In another pediatric study, higher dose albuterol (0.15 mg/kg) lead to greater bronchodilation compared to lower dose albuterol (0.05 mg/kg).[49] Studies in adults have found that higher dose treatment does not substantially improve bronchodilation over lower dose treatment but that it does lead to a higher incidence of side effects.[50,51]

While these studies suggest that the method of administration may not be critical, recent studies suggest that two factors may determine initial response to albuterol: initial response and the cumulative dose of albuterol. Some studies have found that patients who do not respond to an initial administration of 5-7.5 mg of albuterol will not respond to further dose increases and require hospital admission.[52] Dose ranging studies suggest that a cumulative dose of between 5-7.5 mg of albuterol results in adequate bronchodilation in patients who will be responsive to ED therapy.[53-56] Patients who do not respond to these doses require hospital admission. On an equivalent basis, it appears that administration of 2.4 mg of albuterol by metered dose inhaler produces adequate bronchodilation.[54] It is unclear whether these threshold doses of albuterol should be administered by repeated nebulization every 20 minutes or whether administration of a single, large dose of albuterol will lead to equivalent bronchodilation.

These studies, which are consistent with recommendations of the NAEPP, concluded that patients who are going to respond to albuterol will do so relatively early in their ED course, usually within the first hour in most cases. Conversely, failure to respond to the initial courses of albuterol suggests that the patient will have continued bronchoconstriction for hours to days, unless other therapies are employed.

Albuterol is a mixture of two enantiomers, the R form and the S form, of which only the R form is active as a bronchodilator.[57] In laboratory studies, the S enantiomer of albuterol can increase bronchial reactivity.[58] The R enantiomer alone is commercially available, as levalbuterol and has been approved for patients with chronic, stable asthma. In that patient population, it has been demonstrated to be at least as safe and efficacious as racemic albuterol.[59,60] Levalbuterol has not yet been approved for acute asthma. A pilot study has been reported in abstract form that suggests levalbuterol is safe and efficacious for the treatment of acute asthma.[61] Some authors have questioned the superiority of levalbuterol over racemic albuterol for acute asthma, raising concerns that the recommended dose for chronic, stable asthma may be inadequate for patients with acute asthma.[62] A large, multicenter trial currently is under way to test the hypothesis that levalbuterol is superior to racemic albuterol for the treatment of acute asthma.

Oxygen Therapy. Most patients with acute asthma do not require supplemental oxygen therapy. However, patients with very severe airway obstruction, significant respiratory distress, chronic underlying cardiopulmonary disease, or hemoglobin desaturation may require oxygen supplementation. Pulse oximetry, in conjunction with pulmonary function testing, can aid in the decision to administer oxygen. The normal pulse oximetry should be above 94-95%. Treatment with beta-agonists may modestly decrease the oxygen saturation, as a result of an increase in ventilation perfusion mismatch.

Studies in pediatric patients have suggested that a pulse oximetry of less than 91% after treatment may indicate the need for admission.[63] It has been commonly thought that younger asthmatic patients do not develop hypercarbia as a result of 100% oxygen administration such as may occur in patients with COPD. Recent evidence, however, suggests that very severely obstructed asthmatic patients may develop modest degrees of hypercarbia with 100% oxygen administration.[64]

Corticosteroids. Corticosteroids have been recommended for patients who do not respond to a first course of albuterol. Inasmuch as asthma is an inflammatory disease, administration of corticosteroids to ED patients with an asthma exacerbation has become routine. Interestingly, this practice is based on the results of a few selected studies, many of which were small and single-center in design. Some studies have found that steroids have no effect on the ED course of acute asthma.[65,66] Others have found that steroid administration decreases the hospitalization rate, although it does not always do so in conjunction with an improvement in airway obstruction.[67,68] Two recent meta-analyses have been performed on the acute effects of steroid administration.[69,70] These meta-analyses reflect that most of the studies have been done with small sample sizes, and that the evidence that corticosteroids acutely improve pulmonary function is less than compelling.

On the other hand, other studies have found that short courses of steroids improve pulmonary function and limit the risk of relapse following acute asthma treatment. In one trial, an eight-day tapering course of steroids markedly decreased the need for a repeat ED visit.[71] In another investigation, a short course of prednisone decreased the relapse rate, lowered dyspnea scores, and reduced beta-agonist use for three weeks after the ED visit.[72] While these two studies used eight-day courses of tapering steroids, another author found no difference in the relapse rate in patients who had an eight-day course of steroids followed by either a one- or seven-week taper.[73] Other studies, however, have shown that a taper may not be needed in patients who are not chronically steroid dependent.[74] Others also have demonstrated that there does not appear to be a rebound effect with acute deterioration of lung function when steroids are abruptly discontinued.[75]

In the past, steroids routinely were administered parenterally. It appears now that oral prednisone in doses of 40-60 mg is as efficacious as intravenous methylprednisolone, and that there are no differences in either hospitalization rates or improvements in pulmonary function.[76,77] Steroids have been administered in a variety of doses, and different types of steroids used. There does not appear to be a clearcut benefit for very high doses of steroids, although a few studies have demonstrated that very low doses may not be useful.[78-83] Children may not like the taste of oral steroids and, as a result, may benefit from long-acting intramuscular injections of methylprednisolone. This route of administration also has been demonstrated to be beneficial for adults.[84]

Some trials have found that inhaled steroids can be useful during the ED treatment of asthma.[85] Although these studies are small, they have shown that patients who are treated with inhaled steroids have improved pulmonary function over the course of

Table 5. Drugs for Acute Management of Asthma

DRUG	ROUTE	DOSE	ADVANTAGES	DISADVANTAGES
ADRENERGIC				
Epinephrine	SQ	0.3-0.5 mg repeated q20 min to 1 mg	Does not require patient cooperation	Pain at injection site, Needle exposure
BETA ADRENERGIC				
Terbutaline	SQ	0.25-0.5 mg repeated q30 min to total of 0.5 mg over 4 hours	Does not require patient cooperation	Pain at injection site, Needle exposure
	MDI	200 mcg/spray 2 inhalations q20 min	Mimics home therapy	Staff time to demonstrate proper use
Albuterol	Nebulization	0.5 cc in 3-6 cc normal saline q20 min	Duration of action 4-6 hr	Requires nebulizer setup
	MDI	90 mcg/spray 1-2 puffs q20 min	Mimics home therapy	Should be used with a spacer
Metaproterenol	Nebulization	0.3 cc in 3-6 cc normal saline	Duration of action 4-6 hr	Less B_2 specific than albuterol
	MDI	1-2 puffs q20 min 0.65 mg per actuation	Duration of action 4-6 hr	Less B_2 specific than albuterol
Pirbuterol	MDI	0.2 mg/actuation 1-2 puffs q20 min	Maximum onset of action 30-60 minutes	Only available as MDI
Bitolterol	MDI	370 mcg/spray 1-2 puffs q20 min	Rapid onset of action, duration 8 hours	Only available as MDI
STEROIDS				
Prednisone	Oral	Typically 40-60 mg po	Inexpensive	Hours for onset of action
Methyl-prednisolone	IV	Typically 80-120 mg	Intravenous	No advantage over oral therapy
OTHER AGENTS				
Magnesium sulfate	IV	1-2 g over 20 minutes	Some studies show benefit	Typically only beneficial in severe asthma
Aminophylline		5.6 mg/kg loading dose then 0.9 mg/kg/hr maintenance	Modest bronchodilation	Must check levels before administration and adjust dose for medications and chronic illnesses
Ipratropium	MDI	18 mcg/spray 1-2 puffs with beta-agonists	Modest bronchodilation	Not all studies have demonstrated effect
	Nebulization	0.02% solution with beta-agonist	Modest bronchodilation	Not all studies have demonstrated effect

three hours.[86] More importantly, recent studies have found that adding inhaled steroids to courses of oral steroids decreases the relapse rate in patients who are discharged following ED treatment for asthma.[87,88] Studies in children have found that inhaled steroids cannot be substituted for oral steroids.[89]

There have been concerns about the effects of long term treatment with high-dose inhaled steroids on growth rate in children. It appears that there is either no long-term effect on adult height in children treated with inhaled steroids or a transient, small reduction in growth velocity.[90,91] If used long-term, inhaled steroids have been shown to decrease asthma hospitalization time and mortality rate.[92-94] Unfortunately, a recent study has found that many patients with unstable asthma are not on inhaled corticosteroids in spite of indications for their use.[95] Measures aimed toward enhancing compliance with outpatient, inhaled steroid therapy programs cannot be overemphasized.

Leukotriene Antagonists. One of the more recent and important developments in the pharmacological arena of asthma management has been the approval of the leukotriene receptor antagonists for the management of chronic, stable asthma. Studies evaluating such leukotriene antagonists as zileuton, zafirlukast, and montelukast have demonstrated that, over the course of several months, there is a decrease in asthma symptoms, beta-agonist use, and improvement in pulmonary function.[96,97] Several studies suggest that these drugs may be useful for the ED therapy of acute asthma. Within one hour of administration of either 100 mg or 250 mg of oral montelukast, significant improvement in pulmonary function was observed.[98] Intravenous administration of montelukast leads to an even greater improvement in pulmonary function compared to oral administration.[99] A previous multicenter study that has been published in abstract form evaluated more than 600 patients who received zafirlukast in addition to steroids and a beta-agonist. The zafirlukast-treated group had a significant reduction in dyspnea and improvement in pulmonary function. During the follow-up period, the zafirlukast-treated group had a decreased relapse rate.

A recent trial evaluated the efficacy of the anti-leukotriene montelukast for treatment of acute asthma using an intravenous formulation (which is not yet commercially available). This group

Table 6. Additional Agents for Post ED Asthma Therapy

DRUG	ROUTE	DOSE	COMMENTS	TYPICAL COST
INHALED STEROIDS				
Triamcinolone	MDI	2 puffs bid-qid	Rinse mouth after use	$52 per cannister
Beclomethasone	MDI	2 puffs bid-qid	Rinse mouth after use	$52 per cannister
Budesonide	MDI	1-2 puffs bid	Rinse mouth after use	$108 per cannister
Fluticasone	MDI varying strengths	1-2 puffs bid	Rinse mouth after use	$44-91 per cannister
LEUKOTRIENE ANTAGONISTS				
Zafirlukast	Oral	20 mg bid	Caution with hepatic disease	$58 for 1-month supply
Montelukast	Oral	10 mg qd	4 or 5 mg dose in children	$71 for 1-month supply
OTHER AGENTS				
Cromolyn	MDI nebulizer	2 puffs qid 20 mg minutes before exercise	Use 10-60 minutes before exercise	$56/month
Nedocromil	MDI	2 puffs qid	Tailor dose to clinical effect	$40/month
Sustained release theophylline	Oral	Start 200-300 mg bid and adjust based on levels	Monitor theophylline levels	$20/month
Levalbuterol	Nebulizer	0.63-1.25 mg q6-8 h	Not currently approved for acute therapy	$176/month
Salmeterol	MDI	2 puffs bid	Not for rescue therapy	$65/month

hypothesized that intravenous montelukast would produce a rapid improvement in FEV_1 when given as adjuvant therapy for acute asthma. This multicenter, randomized, double-blind, placebo-controlled, parallel group trial included adults (ages 15-54) with acute asthma who failed to improve with initial beta-agonists and oxygen received either intravenous montelukast or placebo as a single bolus infusion, in addition to standard therapy. FEV_1 was measured prior to (baseline) and at predetermined intervals following administration of study drug. Testing included baseline FEV_1 as covariate.

The trial revealed no differences in baseline characteristics between the groups. Mean baseline FEV_1 was 1.66 L (47% of predicted; N = 191). Over the first hour following administration of study drug, patients receiving placebo were refractory to subsequent treatment (average change in FEV_1 = 0.05 L; 95% CI = -0.06, 0.16). In contrast, montelukast caused a rapid improvement in FEV_1 (average change in FEV_1 over 20 minutes = 0.18 L; 95% CI = 0.04, 0.26). At 60 minutes, this difference was 0.22 L, an improvement of 13.6% from baseline. Least squares (LS) mean change differences in FEV_1 between montelukast and placebo were statistically significant ($P < 0.05$) at all time intervals. Beta-agonist use and corticosteroid use were not increased in the montelukast group. No significant drug-related adverse events were identified. These investigators concluded that intravenous montelukast causes rapid bronchodilation and is well-tolerated as adjuvant therapy in the management of acute asthma.

Magnesium. Magnesium has been shown to be useful for the treatment of severe, acute asthma both in adults and in children.[100-102] Magnesium should not be considered routine therapy for all patients with acute asthma. A large trial found that, overall, magnesium was effective only in the subgroup of patients with severe airway obstruction.[103] This is consistent with the results of a meta-analysis which found that, overall, there is a non-significant improvement in peak flow with a significant effect only in patients with severe obstruction.[104] Intravenous doses of 1.5-2 g usually are sufficient.

Aminophylline. In stable asthmatic patients, aminophylline therapy leads to improved pulmonary function. However, routine use of this drug is complicated by the narrow therapeutic window and its interaction with a number of other medications, including erythromycin, cimetidine, and antiarrhythmics. Concerns about aminophylline toxicity have lead to some recommendations to decrease the upper limit of the therapeutic range to 15 mcg/mL. Some studies have demonstrated a modest improvement in pulmonary function in patients treated with both aminophylline and albuterol.[105] The addition of aminophylline may lead to a decrease in hospitalization rate.[106] It should be stressed that even over the short course of ED treatment, aminophylline may increase the risk of side effects.[107] Unfortunately, most studies evaluating the use of aminophylline have been small, single-center studies. Overall, it appears that aminophylline may have a role to play in patients who are unresponsive to other therapies; however, there is inadequate evidence to judge the efficacy of aminophylline for routine asthma therapy.

Ipratropium. Older studies evaluating the effect of ipratropium have not found an advantage to adding this therapy to beta-agonist treatment.[108] In contrast, other studies have found that it is effective in patients with severe obstruction.[109] Most of the studies that have been performed evaluating the use of ipratropium have been small, with only a few studies enrolling more than 100 patients. When all of these studies were combined into a meta-analysis, the addition of ipratropium was shown to lead to a modest improvement in pulmonary function and a decrease in the hospitalization rate.[110] The typical dose is 0.5 mL of the 0.02% solution or 2 puffs from a metered dose inhaler, and repeated as needed with the albuterol dosing.

Antibiotics. Most patients with acute asthma do not require antibiotic therapy because most infection-mediated asthma exacer-

bations probably are associated with viral respiratory infections, although this is difficult to demonstrate using serologic studies. Asthmatics, however, are susceptible to sinusitis, which may be subclinical in nature. Patients with evidence of lower respiratory tract infection or with clinical signs and symptoms of sinusitis may benefit from antibiotic therapy. When initiated, antibiotic therapy should cover both typical agents such as *Hemophilus influenzae* and *Streptococcus pneumoniae,* as well as atypical agents such as *Mycoplasma* or *Chlamydia.* For outpatient management of lower respiratory tract infections, therapy with agents such as azithromycin is recommended.

Antihistamines. Antihistamines are not generally thought of as medications for asthma therapy. Because of the frequent association between asthma and symptoms of rhinitis, there may be some role for adjunctive antihistamine therapy. In one study of patients with mild to moderate asthma and allergic rhinitis, an extended course of cetirizine decreased symptoms of chest tightness, wheezing, dyspnea, and nocturnal asthma symptoms.[111] A meta-analysis of a number of antihistamines, however, found that only the above study with cetirizine demonstrated a significant effect of antihistamines.[112]

Heliox. Heliox (a mixture of oxygen and helium) has occasionally been used for therapy in patients with respiratory failure.[113-115] In a small, randomized study, a 70%/30% mixture led to a significant improvement in pulmonary function and dyspnea scores compared to oxygen alone.[116] Other studies, however, have not demonstrated an advantage to heliox use.[117,118] Currently, there is inadequate evidence to recommend the routine use of heliox. Where available, it may be considered for patients with respiratory failure.

Mechanical Ventilation. Assisted ventilation is indicated for patients with respiratory failure or impending failure who are not responsive to therapy. Nasal BiPAP is an appropriate treatment choice for cooperative patients. In order to be eligible, the patient must have normal mentation, and normal facial anatomy. Morbidly obese patients frequently fail therapy. BiPAP usually is started with inspiratory pressures of around 8 cm-H_2O and expiratory pressures of 3 cm-H_2O. The settings are increased based on pulse oximetry and arterial blood gas analysis. Patients who fail to improve over 30-60 minutes require intubation.

Disposition

Most patients respond well to therapy. Generally, the disposition of patients should follow the National Institutes of Health (NIH) recommendations based on peak flows after treatment. The decision to hospitalize the patient should be based on pulmonary function and clinical assessment, taking into account the severity of airflow obstruction, symptoms, and prior exacerbations; medication use over the course of the exacerbation; access to medical care; and the home conditions.[27]

Patients, who continue to have severe airway obstruction with pulmonary function of less than 50% of predicted values, may require admission. Hypercarbia or mental status changes indicate a need for admission to an ICU for continued beta-agonist therapy, intravenous steroids, and monitoring for respiratory failure. Patients who demonstrate improvement with therapy with peak flows of 70% or more may be discharged home. Patients with moderate to severe asthma or unstable asthma may benefit from long-term, daily peak flow monitoring.[119] Patients with asthma should be instructed to abstain from smoking or exposure to environmental tobacco, to avoid exposure to allergens to which they are sensitive, and to try to minimize exercise when levels of air pollution are high. Finally, the patient's self-management and rescue plan should be reviewed.

In patients with peak flows that remain between 50% and 70% of that predicted after therapy, the disposition decision is tailored to the patient's individual clinical characteristics and social circumstances. Repeated presentation to the ED may signal a failure of the patient's home management or worsening disease. Hospitalization can be used to optimize the patient's regimen and provide further education.

In all patients discharged from the ED, close medical follow-up after an acute asthma attack is important. Patients should have prompt reevaluation with their primary care physician or other medical personnel, usually three days after discharge.

Summary

Initial assessment of patients with acute asthma should be aimed toward determining the severity of the acute attack, the precipitating cause of the attack, and the patient's risk of respiratory failure. Little diagnostic testing is required for most asthmatic patients. Aminophylline levels should be measured in patients on chronic therapy. Pulse oximetry may be useful for assessing the severity of the attack and the need for supplemental oxygen therapy. Measurements of pulmonary function, including either peak flow or the FEV_1, may be used to assess the severity of the episode and monitor the patient's progress through his or her ED stay.

Therapy is initiated with inhaled beta-agonist, typically albuterol, in the range of 2.5-5 mg by nebulized inhaler. Alternatively, this medication may be administered by other dry powder or with a meter dose inhaler along with a spacer. Oxygen therapy is occasionally necessary, especially in patients demonstrating significant desaturation.

Although there is only modest evidence to suggest that they effect the course of the ED treatment, oral steroids, such as prednisone in a dose of 40-60 mg, are typically administered if there is not rapid and near complete improvement with the first dose of nebulized albuterol. Patients with very severe obstruction or those who are not responding to the standard therapy may benefit from adjunctive therapy, including ipratropium, aminophylline, or magnesium. The role of other therapies, such as heliox and noninvasive positive pressure ventilation, remain under study.

Patients who meet criteria for discharge, relief of dyspnea and improvement in pulmonary function at least greater than 50% of predicted normal, should have their outpatient medication regimen adjusted. Patients should be on a spacer for use with their meter dose inhaler and receive a demonstration of its use. Salmeterol may be used to decrease the frequency of rescue therapy in addition to its use in patients who have prominent nocturnal symptoms. Ipratropium generally is considered first-line therapy for patients with elements of COPD, although it is not routinely used for younger patients with asthma. Patients should be discharged with a short

course of oral steroids, usually in the range of 5-14 days. A taper usually is not necessary for therapy lasting less than two weeks.

Inhaled corticosteroids should be started at the same time and patients should be kept on inhaled steroids for weeks to months following an acute exacerbation. In patients who are already on maximal therapy, consideration should be given to adding theophylline. Theophylline also may be considered in patients who cannot or will not use a meter dose inhaler or in those who have prominent nighttime symptoms. Leukotriene antagonists also may be added to decrease patients' steroid dependence. Patients with difficult-to-control asthma may benefit from a referral to an asthma specialist.

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Physician CME Questions

81. Asthma is a chronic inflammatory disorder resulting in widespread narrowing of the airways and is characterized by which of the following clinical symptoms?
    A. Wheezing
    B. Dyspnea
    C. Chest tightness
    D. Cough
    E. All of the above

82. Specific trigger factors that precipitate asthma exacerbations include which of the following?
    A. Inhaled antigens
    B. Cold air
    C. Dust
    D. Cigarette smoke
    E. All of the above

83. Which of the following tests should be performed on most patients with an acute asthma exacerbation?
    A. Chest radiograph
    B. White blood count
    C. Peak flow measurement
    D. Theophylline level

84. All of the following about inhaled beta-agonists are true *except:*
    A. Isoetharine, in particular, produces significant bronchodilatation within 10 minutes of administration but it must be diluted to avoid reactions to the preservative agent, bisulfite.
    B. Salmeterol should *not* be used in acute exacerbation due to its delayed onset of action.
    C. The variable routes administration lead to similar degrees of airway improvement, assuming they are used properly.
    D. Inhaled agents are as effective as oral agents.

85. Which of the following suggests a need for admission?
    A. Post-treatment pulmonary function of less than 50% of predicted value
    B. Patient presenting with a fever
    C. A pulse oximetry of 92% of initial evaluation
    D. Ongoing steroid use before arrival

86. Magnesium may be useful in asthma treatment when:
    A. the initial pulmonary function is < 30% of predicted value.
    B. the patient has severe obstruction.
    C. the patient is on chronic steroids.
    D. there is a history of alcohol abuse.

87. In order to use nasal bipap, all of the following must be present *except:*
    A. normal mentation.
    B. normal facial anatomy.
    C. marked respiratory acidosis.
    D. a cooperative patient.

88. In the patient with asthma, a physical presentation including which of the following would signal impending or actual actual respiratory failure?
    A. Altered mental status
    B. Severely labored breathing
    C. Accessory muscle use
    D. All of the above

In Future Issues: Drugs of Abuse