State of the Art

The Assessment and Management of Adults with Status Asthmaticus

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Summary

Asthma is a disease characterized by wheezing, dyspnea, and cough resulting from airway hyperreactivity and variable degrees of reversible airflow obstruction (1). Current paradigms emphasize the role of airway wall inflammation in the pathogenesis of this disease (2, 3), which, in conjunction with smooth muscle-mediated bronchoconstriction and intraluminal mucus, results in airflow obstruction. Fortunately, most patients with asthma do not have debilitating disease, and symptoms are easily controlled with a limited number of medications and education. But in others, the disease paints a much more malignant picture of daily breathlessness and persistent, severe functional impairment—a picture not dissimilar from patients with emphysema and fixed airflow limitation.

All patients with asthma are at risk of developing a severe asthma attack that places them at risk of developing respiratory failure—a disorder referred to as status asthmaticus (SA). Asthma attacks can occur at any time and at any pace. Some patients develop sudden and unexpected increases in airflow obstruction resulting primarily from bronchial smooth muscle-mediated bronchospasm. This syndrome, aptly termed sudden asphyxic asthma, may be quite different from more slowly progressive forms of airflow obstruction (4). Recent studies have demonstrated that patients dying of sudden exacerbations of asthma have diminished eosinophils and increased neutrophils in the airway submucosa (5), and less intraluminal mucus (6), compared with patients with slower onset disease. The more common story is the patient who develops progressive symptoms over days before finally presenting to the emergency department in respiratory distress. In these patients, airway wall inflammation and edema play a significant role. Yet many patients miss the opportunity to treat effectively worsening airway inflammation, opting instead to increase their use of beta-agonists as the sole treatment strategy (7).

No matter the tempo, patients with SA have a life-threatening illness (8, 9) that can result in ventilatory failure and death.

The purpose of this article is to review the clinical assessment and management of these critically ill patients. We emphasize four key areas of management: (1) assessment of disease severity, (2) use of pharmacologic agents to treat airflow obstruction, (3) intubation and mechanical ventilation, and (4) strategies to prevent recurrent episodes of status asthmaticus.

CLINICAL ASSESSMENT

Patients in SA are typically anxious, breathless, fatigued, sitting upright in bed, and preoccupied with the task of breathing. Their distress is heightened by the loud, bright, and noisy critical care setting, which further interferes with the gathering of useful clinical information. In the face of these distractions, a swift and directed assessment of disease severity and risk of clinical deterioration is crucial. This generally requires an analysis of several factors, including the medical history, physical examination, bedside measurements of airflow obstruction, response to initial therapy, arterial blood gas measurements, and radiographic...
studies. This multifactorial analysis is necessary because no single clinical measurement has been found to predict outcome reliably (10).

Medical History
Several features of past severe attacks place patients at increased risk for near fatal or fatal asthma. These include a history of intubation, hypercapnia, pneumomediastinum or pneumothorax, hospitalization despite chronic oral steroid use, underlying psychiatric illness, and medical noncompliance (11, 12). A history of near fatal asthma requiring mechanical ventilation is the greatest single predictor of subsequent asthma death (13). Kikuchi and colleagues (14) recently reported that patients with a prior history of near fatal asthma, but in remission, have a blunted hypoxic ventilatory response and diminished dyspnea during inspiratory resistive loading as compared with asthmatics without prior severe exacerbations. Accordingly, diminished patient perception of dyspnea or gas exchange abnormalities likely increase the risk of future life-threatening or fatal attacks.

Physical Examination
Features of the current attack that are worrisome include symptoms of long duration, late arrival for care, extreme fatigue, an altered mental state, and sleep deprivation. Deterioration despite optimal treatment, including the concurrent use of oral steroids, identifies high-risk patients who are unlikely to improve quickly. Accelerated use of inhaled beta-agonists also identifies patients at higher risk for fatal asthma (see below). Comorbid conditions such as coronary artery disease place patients at greater risk during SA, and they may predispose to complications of drug treatment.

Vital signs of severe asthma are respiratory rate greater than 30 breaths/min, tachycardia greater than 120 beats/min, and pulse paradoxus greater than 12 mm Hg (17). Pulse paradoxus (PP) is the difference between maximal and minimal systolic arterial blood pressure during the respiratory cycle. In severe airflow obstruction, PP is greater than the normal value of 4 to 10 mm Hg and typically greater than 15 mm Hg. This circulatory consequence of SA is a result of large swings in pleural pressure. During forced expiration, large positive pressure in the thorax diminishes blood return to the right heart. During vigorous inspiratory efforts against obstructed airways, blood flow to the chest is augmented. Right ventricular (RV) filling increases early in inspiration and may shift

the intraventricular septum toward the left ventricle (LV). This confirmational change in the LV may cause diastolic dysfunction and incomplete filling of this chamber. Additionally, large negative pleural pressure may directly impair LV emptying by increasing LV afterload (18, 19). Finally, lung hyperinflation may represent a further afterload on the RV by increasing pulmonary artery pressure (20). The net effect of these cyclical respiratory events is to accentuate the normal inspiratory reduction in stroke volume. Pulsus paradoxus can be a valuable sign indicating asthma severity (21), but it must be emphasized that the PP also falls in the fatiguing asthmatic unable to generate significant changes in pleural pressure, and that the absence of a widened PP does not always ensure a mild attack (16, 17, 22, 23).

Consideration should be given during the physical examination to possible complications of acute asthma (see Table 1). Examination of the head and neck should focus on identifying barotrauma and upper airway obstruction. Tracheal deviation, asymmetric breath sounds, a "mediastinal crunch," and subcutaneous emphysema all suggest pneumomediastinum or pneumothorax and a potentially worse clinical course. Stridor suggests upper airway obstruction (which may mimic acute asthma), although in our experience wheezes from lower airway obstruction are occasionally heard best during auscultation of the anterior neck. The mouth and neck should be inspected for mass lesions or signs of previous surgery such as tracheostomy or thyroidectomy. The lip and tongue should be inspected for signs of angioedema. The classic sign of wheezing correlates poorly with the degree of airflow limitation (24). Severely obstructed patients may have a silent chest if there is insufficient alveolar ventilation and airflow for wheezes to occur. In these patients, the development of wheezes generally indicates improved airflow. Localized wheezing or crackles on chest auscultation may represent mucus plugging or atelectasis, but they should prompt consideration of pneumonia, pneumothorax, endobronchial lesions, or a foreign body.

Most asthmatics are tachycardic on presentation. Successful treatment of airflow obstruction is usually associated with a decrease in heart rate (although some improving patients remain tachycardic because of the chronotropic effects of bronchodilators). Grossman (25) found that in patients hospitalized with SA heart rate decreased from an average of 120 beats/min on admission to 105 beats/min after 24 h of successful therapy. The usual rhythm is sinus tachycardia although supraventricular arrhythmias are not uncommon. Josephson and colleagues (26) found atrial, ventricular, or combined arrhythmias in nine of 44 episodes of SA in 41 patients. Supraventricular arrhythmias were present in seven of the nine patients and ventricular arrhythmias in eight of the nine patients. Patients with arrhythmias were older,

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<th>Complications of Acute Asthma</th>
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<tr>
<td>Pneumothorax</td>
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<td>Myopathy</td>
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<td>Lactic acidosis</td>
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<td>Anoxic brain injury</td>
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TABLE 1
averaging 34 yr of age compared with 26 yr of age in patients without rhythm disturbances.

Clinical signs of right and left heart failure such as a third heart sound, jugular venous distention, and pedal edema suggest primary heart disease. Yet, SA alone can cause exam and electrocardiographic findings of right heart strain, which resolve within hours of response to therapy (25, 27). Transient electrocardiographic findings include right axis deviation, clockwise rotation, and evidence of right ventricular hypertrophy. Jugular venous distention is also seen when dynamic hyperinflation or tension pneumothorax limit venous return to the right heart.

The possibility of myocardial ischemia should be considered in older patients with concomitant coronary artery disease. Patients with SA are at increased risk of myocardial oxygen supply/demand imbalance when large decreases in intrathoracic pressure increase LV afterload and possibly decrease coronary blood flow (28). High doses of beta-agonists, theophylline, and hypoxemia may also adversely affect the balance between oxygen supply and demand.

Measurement of Airflow Obstruction
Objective (though effort-dependent) physiologic measurements of the degree of airflow obstruction can be made by bedside determination of PEFR or FEV₁. Direct measurements are necessary because physician estimates of PEFR are off by more than 20% in greater than 50% of cases—with errors equally distributed between overestimates and underestimates of the actual PEFR (29). In most patients it is easier to measure PEFR than FEV₁, although even this maneuver is difficult for severely dyspneic patients to perform. In these patients, it is wise to defer measurement since deep inhalation may worsen bronchospasm (30) and, in rare cases, precipitate respiratory arrest (31). Still, objective measurement of the severity of airflow obstruction is safe in most patients. In general, PEFR or FEV₁ less than 30 to 50% of predicted or of the patient's personal best (usually corresponding to a PEFR less than 120 L/min and a FEV₁ less than 1 L) indicates severe exacerbation (32). Knowledge of the degree of fixed airflow obstruction and the patient's personal best PEFR or FEV₁ is helpful in interpreting these tests in the acute setting.

Response to Therapy
Several studies have demonstrated that failure of initial therapy to improve expiratory flow predicts a more severe course and need for hospitalization (33–35). Accordingly, measurement of the change in PEFR or FEV₁ over time may be one of the best ways to assess patients acutely and predict need for hospital admission. Rodrigo and Rodrigo (10) studied 194 consecutive patients who presented to the emergency department for treatment of acute asthma. They demonstrated that early response to treatment was the most important predictor of outcome. Patients who were discharged earliest from the hospital were those with the greatest improvement in FEV₁ after 30 min of treatment. Similarly, Stein and Cole (35) found that the change in PEFR after 2 h of bronchodilator treatment predicted the need for hospital admission. In their study of corticosteroid use in the emergency room treatment of acute asthma, 91 emergency room visits resulted in 77 discharges and 14 admissions. Peak expiratory flow rate on entry (which was approximately 250 L/min for the group) did not predict need for admission. On the other hand, after 2 h of treatment patients ultimately discharged from the emergency room had a significantly greater PEFR (about 330 L/min) than did patients requiring admission (in whom PEFR had not changed significantly from entry). The predictive value of changes in PEFR before 30 min of treatment have elapsed may be misleading. Martin and coworkers (36) found that the change in PEFR 20 min after subcutaneous epinephrine did not predict clinical outcome in patients with asthma.

Arterial Blood Gases
Although arterial blood gas determinations have little or no role in the assessment of the patient with mild to moderate asthma, they are of use in the setting of SA. When FEV₁ is less than 1 L or PEFR is less than 120 L/min we recommend arterial blood gas determinations to document the degree of hypoxemia and to determine the patient's acid-base status. Patients in the early stages of SA often exhibit mild hypoxemia and respiratory alkalosis. If respiratory alkalosis is present for hours to days, there may be compensatory renal bicarbonate wasting, which may manifest later as a non-anion-gap metabolic acidosis. As the severity of airflow obstruction increases, Paco₂ generally increases because of patient exhaustion and inadequate alveolar ventilation and/or an increase in physiologic dead space. Hypercapnia usually does not occur unless the FEV₁ is less than 25% of predicted (37). Although its presence indicates severe disease and the possible need for mechanical ventilation, hypercapnia alone is not an indication for intubation. Hypercapnic patients may respond to aggressive drug therapy, and they may have clinical courses similar to those of normocapnic patients (27, 38). Also, the absence of hypercapnia does not exclude the possibility of severe airflow obstruction and impending respiratory arrest (39).

Mountain and colleagues (40) detected metabolic acidosis in 28% of 229 consecutive episodes of acute asthma in 170 patients requiring hospitalization. Metabolic acidosis was more likely to occur in men and in patients with more severe airflow obstruction and hypoxemia. The anion gap in their study patients ranged between 8 and 23 mEq/L (average, 15.8 mEq/L). Although blood lactate was not measured in this study, it is likely that lactic acidosis was the cause of the elevated anion gap (40, 41). The mechanisms of lactic acidosis in SA have yet to be fully described. There is evidence that lactic acidosis arises from the use of parenteral beta-adrenergic agonists and resolves when these drugs are stopped (42). Other possibilities include increased work of breathing resulting in anaerobic metabolism, tissue hypoxia, intracellular alkalosis, or decreased lactate clearance by the liver (which conceivably could develop from passive congestion of the liver in the setting of high intrathoracic pressures). Further studies are clearly needed to understand the pathogenesis of lactic acidosis in acute asthma.

Repeat blood gas sampling is usually not necessary to determine whether a patient is deteriorating or improving. In most cases, valid clinical judgments can be made based on serial physical examinations with attention to patient posture, use of accessory muscles, diaphoresis, estimates of air movement during chest auscultation, and PEFR determinations. Patients who on these grounds are deteriorating to the point of respiratory arrest should be intubated whether or not Paco₂ is rising. Conversely, patients who are more comfortable should continue with pharmacologic therapy despite an elevated Paco₂. In mechanically ventilated patients, however, serial blood gas measurements are helpful to guide ventilatory management (see below).

Radiographic Studies
As for arterial blood gas analysis, chest radiography has little role in the assessment and management of patients with mild to moderate asthma. In addition, a number of studies have demonstrated that the yield of unselected chest radiography is low even in acutely ill asthmatics treated in the emergency department or requiring hospitalization, with findings that influenced treatment revealed...
in only 1 to 5% of studies (43-48). Findley and Sahn (43) reviewed chest radiographs in 90 episodes of acute asthma occurring in 60 patients. Fifty films were interpreted as normal, 33 as demonstrating hyperinflation, and six as showing minimal interstitial markings unchanged from previous radiographs. Only one patient with allergic bronchopulmonary aspergillosis demonstrated an alveolar infiltrate. Zievelink and colleagues (44) found abnormalities on chest radiographs in only 2.2% of 528 films taken in 122 asthmatics seen in the emergency room setting. While and colleagues (47) evaluated initial chest radiographs in 54 adult patients admitted to hospital after failing to respond to a 12-h course of bronchodilator therapy in the emergency department. These investigators noted an incidence of "major radiographic abnormalities" in 20 (34%) cases, which they felt significantly impacted on management. However, the majority of these findings (there were 13 of them) were classified as focal parenchymal opacities or increased interstitial markings, common indicators of focal atelectasis in patients with asthma.

On the basis of these data, chest radiographs are likely indicated only in patients presenting with signs or symptoms of barotrauma (e.g., chest pain, mediastinal crunch, subcutaneous emphysema, cardiovascular instability, or asymmetric breath sounds), clinical findings suggestive of pneumonia (e.g., fever, bronchial breath sounds, or hypoxemia not corrected with low flow supplemental oxygen) (see below), other localizing signs on chest examination (e.g., decreased breath sounds from mucus plugging, foreign body, or atelectasis), or when it is not clear that asthma is the cause of respiratory distress (e.g., measurements of airflow obstruction do not correlate with apparent severity of dyspnea).

Admission Criteria

When repeat assessment demonstrates a good response to initial therapy in the emergency department, discharge home with close follow-up is acceptable. Patients in this group should report significant improvement in shortness of breath, have improved air movement on physical examination, and FEV1 or PEF greater than or equal to 70% of predicted (48). Observation for a minimum of 30 min after the last dose of beta-agonist is recommended to ensure stability prior to discharge. Before discharge, these patients should be provided with written medication instructions as well as a written plan of action to be followed in the event of worsening symptoms. Follow-up appointments should be made prior to discharge whenever possible.

Patients with findings of severe airflow obstruction (use of accessory muscles of respiration, PP > 12 mm Hg, diaphoresis, inability to recline, hypercapnia, or PEFR < 40% of predicted) who demonstrate a poor response to initial therapy (less than 10% increase in PEFR) or who deteriorate despite therapy should be promptly admitted to an intensive care unit. Other indications for immediate admission to an intensive care unit include respiratory arrest, an altered mental status, and cardiac toxicity (tachyarrhythmias, angina, or myocardial infarction). We also recommend intensive care unit admission for patients who present initially with mild or moderate airflow obstruction but who deteriorate in the emergency room despite therapy.

An incomplete response to treatment may be defined as the persistence of wheezing or shortness of breath and a PEFR or fit) at home. Possible explanations for this response include the use of higher or more frequent drug doses and ensuring proper inhaler technique.

Recent data suggest that in nonintubated patients metered-dose inhalers (MDIs) combined with a spacing device are just as
Effective as nebulizers, and they are quicker and cheaper to use (55–57). Even in patients with severe disease, Idris and colleagues (55) showed four puffs of albuterol (0.36 mg) delivered with a spacer to be as effective as 2.5 mg of albuterol by nebulization. Similarly, Turner and coworkers (58) demonstrated equal efficacy between three puffs of metaproterenol delivered via a spacer and 15 mg of metaproterenol by nebulization in the treatment of acute airflow obstruction. Still, many clinicians prefer handheld nebulizers because fewer instructions are needed, less coordination is required, and less supervision is necessary.

Many questions remain regarding optimal delivery of inhaled beta-agonists to intubated, mechanically ventilated patients, including the comparative efficacy of MDIs and nebulizers, optimal ventilator settings to use during drug delivery, ideal site on the ventilator circuit for connection of the nebulizer, and maximal acceptable drug dosages (59). There is a consensus, however, that whether MDIs or nebulizers are used, higher drug dosages are required to achieve a physiologic effect than in nonintubated patients. In mechanically ventilated patients, many machine and host factors (which vary widely) significantly decrease the delivery of inhaled agents to the lower respiratory tract. MacIntyre and colleagues (60) demonstrated that only 2.9% of a radioactive aerosol delivered by a small-volume nebulizer was deposited in the lungs of mechanically ventilated patients. Similar to treatment styles in nonintubated patients, many respiratory therapy staff members have shifted to use of MDIs via an adapter directly attached to the inspiratory limb of the ventilator circuit or via a spacer device on the inspiratory limb for treatment of intubated patients.

This shift in drug delivery technique has been based largely upon demonstration of efficacy in lung models or by radioactive-labeled drug studies in patients such as those in the study of MacIntyre and coworkers (60–69). This practice, however, has been recently questioned. Manthous and colleagues (70) compared the efficacy of albuterol delivered by MDI via a simple inspiratory adapter with nebulized albuterol in mechanically ventilated patients. Using the peak-to-pause pressure gradient at a constant inspiratory flow as a measure of airway resistance, they found no effect (and no side effects) from as many as 100 puffs (9.0 mg) of albuterol delivered by MDI. Albuterol delivered by nebulizer to a total dose of 2.5 mg reduced the inspiratory flow-resistive pressure 18%; nebulized albuterol at cumulative doses of 7.5 mg led to further reductions in this pressure in eight of 10 patients, but it led to toxic side effects in four of the eight. The investigators concluded that nebulized albuterol provided objective physiologic improvement, whereas albuterol administered by MDI through an endotracheal tube adapter had no effect, and that nebulizer treatments can and should be titrated to higher-than-conventional doses using toxic side effects (see text). Manthous and coworkers (60–69). This practice, however, has been recently questioned. Manthous and colleagues (70) compared the efficacy of albuterol delivered by MDI via a simple inspiratory adapter with nebulized albuterol in mechanically ventilated patients. Using the peak-to-pause pressure gradient at a constant inspiratory flow as a measure of airway resistance, they found no effect (and no side effects) from as many as 100 puffs (9.0 mg) of albuterol delivered by MDI. Albuterol delivered by nebulizer to a total dose of 2.5 mg reduced the inspiratory flow-resistive pressure 18%; nebulized albuterol at cumulative doses of 7.5 mg led to further reductions in this pressure in eight of 10 patients, but it led to toxic side effects in four of the eight. The investigators concluded that nebulized albuterol provided objective physiologic improvement, whereas albuterol administered by MDI through an endotracheal tube adapter had no effect, and that nebulizer treatments can and should be titrated to higher-than-conventional doses using toxic side effects and physiologic response to guide therapy. In the accompanying editorial (71), Newhouse and Fuller noted that the "major importance of this study is its potential for raising the awareness of physicians to the need to study aerosol delivery systems as thoroughly as they study the pharmacologic agents themselves, since both are equally important determinants of the therapeutic response." Promising in this regard is the use of MDIs with spacing chambers to deliver bronchodilator during mechanical ventilatory support (72).
Accordingly, it is difficult to make recommendations for fixed dosing of these drugs in intubated patients. Nebulized drug is efficacious in the majority of patients, although MDIs are likely to be effective if used with an appropriate spacing device. Whichever route is used, drug dosages should be titrated to either a beneficial physiologic response as judged by a fall in the airway peak-to-pause gradient under constant inspiratory flow conditions (see Figure 1) (73) or to the development of toxic side effects such as worsening tachyarrhythmias. Our own approach is to prescribe albuterol 2.5 mg by nebulization and measure the change in the airway peak-to-pause pressure. If there is a significant fall in this gradient (i.e., 15% or greater), we continue to deliver this drug dose hourly until there is clear-cut evidence of improving airflow obstruction (see below). At that time fewer doses can be given. If a significant fall in the peak-to-pause gradient is not demonstrated, we deliver additional 2.5-mg doses of albuterol by nebulization until a significant decrease in the peak-to-pause gradient is demonstrated or toxic side effects occur. In this situation, it is particularly important to exclude other causes of high peak airway pressure that are resistant to bronchodilator therapy such as a kinked or plugged endotracheal tube.

In recently extubated patients, MDIs can be used successfully in most patients. Tenholder and coworkers (74) demonstrated a 70% success rate for conversion of recently extubated patients from nebulized therapy to MDIs. Unsuccessful conversions were seen mainly in patients with neuromuscular disease unable to actuate the MDI properly and in patients with dementia or an inability to understand instructions. Failure to convert to MDI use was not related to the degree of airflow obstruction.

Subcutaneously administered epinephrine or terbutaline sulfate carry no advantage over inhaled beta-agonists unless patients are unable to cooperate (such as those with an impaired sensorium or those in cardiopulmonary arrest) (75-77). Subcutaneous therapy should be considered, however, in patients not responding adequately to inhaled beta-agonists. In 60% of patients not responding to 2 h of inhaled metaproterenol, Appel and colleagues (78) found expiratory flow increased after subcutaneous administration of epinephrine. Subcutaneously administered epinephrine may also be tried in intubated patients not responding adequately to inhaled therapy, although the benefits and risks of this approach have not been well studied. If parenteral beta-agonists are used, care must be taken to avoid hypokalemia, lactic acidosis, and cardiac arrhythmias. In dire circumstances, especially if there is no intravenous access, epinephrine may be delivered effectively down the endotracheal tube.

Known cardiac disease and age greater than 40 yr are relative contraindications to parenteral therapy. Patients older than 40 yr of age have more sinus tachycardia, premature ventricular contractions, and atrial arrhythmias (79). Older patients without a history of recent myocardial infarction or angina, however, tolerate subcutaneously administered epinephrine reasonably well.

There is no advantage to giving the more beta-2-specific agent, terbutaline sulfate, which may in fact result in greater tachycardia for the same degree of bronchodilation than does epinephrine (80). The pregnant patient represents an exception to this tenet. Because epinephrine has been associated with congenital malformations and may decrease uterine blood flow (81), terbutaline is the preferred beta-agonist if one must be given parenterally. Note that terbutaline may inhibit uterine contractility at term.

The available data do not support the routine use of intravenous (IV) infusion of beta-agonists in the treatment of patients with SA. Several studies (82-85) have demonstrated inhaled therapy to be equal to or better than IV therapy in treating airflow obstruction, and less likely to cause cardiac toxicity (mainly tachycardia). Indeed, continuous IV infusion of isoproterenol has resulted in fatal myocardial necrosis (86). Bloomfield and coworkers (84) compared salbutamol given as a 0.5 mg IV injection over 3 min with a 0.5% solution of salbutamol by intermittent positive-pressure breathing for 3 min in a double-blind crossover trial during 22 episodes of asthma. Both treatments significantly improved PEFR, but the inhaled route resulted in greater improvement in pulsus paradoxus and less tachycardia than the IV route. Salmeron and coworkers (85) compared the effects of nebulized albuterol (5 mg administered twice during the first hour of treatment) with intravenously administered albuterol (0.5 mg over 60 min) in 47 patients with severe acute asthma as defined by a PEFR less than 150 L/min. The mean increase in PEFR at 1 h was greater in the group treated with inhaled albuterol (107 L/min versus 42 L/min in the IV group). Inhaled therapy was also associated with a greater fall in PaCO2 and less beta-agonist-induced hypokalemia. On the other hand, Cheong and colleagues (87) found that 4 h of continuous salbutamol (0.72 mg/h) resulted in a greater PEFR than did 5 mg salbutamol nebulized at 30 and 120 min. However, the greater increase in PEFR was modest (25% in the IV group versus 14% in the inhaled group), and this improvement was at the cost of more tachycardia. Also, it could be argued that had higher doses of inhaled salbutamol been given (as is common in clinical practice), there may have been no difference in PEFR response between the two groups.

In our practice, we rarely use intravenously administered beta-agonists in the treatment of SA. On an individual basis, however, intravenously administered beta-agonists may be considered in the treatment of patients (preferably younger than 40 yr of age) who have not responded to inhaled or subcutaneous therapy, and in whom respiratory arrest is imminent or in whom persistent severe airflow obstruction is associated with alarming levels of lung hyperinflation during mechanical ventilation (see below).
A number of recent studies have established a correlation between the long-term use of inhaled beta-agonists and asthma morbidity and mortality (88-90). Patients who use beta-agonists the most are those at greatest risk of asthma death; but whether beta-agonists are the cause of death or a marker of disease severity is yet to be established. In a recent report (89), Suisse and coworkers showed that the "risk of asthma death began to escalate drastically at about 1.4 canisters per month of inhaled beta-agonist" and that the association between beta-agonist use and asthma mortality was confined primarily to the use of these drugs. In response to these concerns, the Executive Committee of the American Academy of Allergy and Immunology recently published their position on the use of inhaled beta-agonists in asthma (92). In their report they concluded that (1) heavy (more than one canister per month) beta-agonist use is a marker for severe asthma, (2) heavy or increased use of beta-agonists warrants additional therapy such as the use of corticosteroids, (3) beta-agonists may make asthma worse, but the available data do not allow for a definitive conclusion regarding this controversy, and (4) patients currently using beta-agonists should slowly withdraw nonessential doses so that medication is used only as needed before exercise or as a rescue medication during "breakthrough" asthma symptoms. It is important to note, however, that concerns regarding the long-term safety of regularly used beta-agonists do not apply to the use of these medications during acute attacks. These drugs continue to be the medications of choice to treat bronchial smooth muscle contraction during attacks—and they should not be withheld or underdosed because of concerns regarding the safety of regular use. Beta-agonists are not, however, sufficient alone to treat patients with acute asthma exacerbations. Patients with slowly progressive disease have significant airway inflammation that needs to be treated specifically with anti-inflammatory agents. Corticosteroids also potentiate the effects of beta-agonists on smooth muscle relaxation, which may be particularly important in patients with sudden asphyxic asthma.

Corticosteroids. Corticosteroids treat airway wall inflammation, potentiate the effects of beta-agonists on smooth muscle relaxation, decrease beta-agonist tachyphylaxis, and decrease mucus production (93-95). Ideally, intensifying a patient's anti-inflammatory regimen should begin whenever the patient's usual medical regimen fails to control symptoms. Unfortunately, many patients (and their physicians) fail to intervene early or aggressively in the course of worsening asthma, and airway wall inflammation is allowed to proceed unchecked. Invariably, whether patients are using corticosteroids or not when they arrive in the emergency room, they have received inadequate doses (see below).

Despite recent controversy about the routine use of steroids in the emergency department (35), most available data support a corticosteroid benefit in this setting, and there is evidence that failure to treat with corticosteroids contributes to asthma deaths (96). Benefits of steroids were recently confirmed by meta-analysis (97) in which more than 700 articles were reviewed to identify 30 randomized, controlled trials suitable for analysis. The investigators concluded that steroids given in the emergency department significantly reduce the rates of admission and the number of future relapses in the first 7 to 10 d. It did not matter whether steroids were given orally or intravenously (although IV therapy is preferred in patients at risk for intubation), as long as a minimum of 30 mg of prednisone (or its equivalent) was given every 6 h. Lower doses were less effective, and there was no obvious benefit to giving higher doses. McFadden (98) recently analyzed the available data on steroids in asthma and recommended 150 to 225 mg/d of prednisone (or its equivalent) to reach maximal therapeutic benefit. He recommended either 40 mg of intravenously administered methylprednisolone every 6 h or prednisone 60 mg given orally every 6 to 8 h for 36 to 48 h depending on the patient's condition. Haskell and coworkers (99) showed that patients receiving 125 mg of solumedrol intravenously every 6 h improved more rapidly than did patients receiving 40 mg of drug, although there was no difference in ultimate improvement. Both the 125-mg and 40-mg doses were superior to 15 mg every 6 h in terms of rate and absolute improvement. Littenberg and Gluck (100) enrolled 97 patients with acute asthma in a double-blind, placebo-controlled, randomized trial of methylprednisolone 125 mg given intravenously on presentation to the emergency room in addition to other standard treatments. Only nine of 48 (19%) of patients treated with methylprednisolone were hospitalized as compared with 23 of 49 patients (47%) in the control group.

Further studies are needed to establish the best dose and dosing frequency of corticosteroids in SA. Currently available data do support the common approach of giving 60 to 125 mg methylprednisolone intravenously every 6 h during the initial 24 h of treatment. We administer the first dose immediately in the emergency department since benefits are not seen clinically for hours (93) (whether or not patients were receiving oral steroids prior to their arrival). Improving patients are switched to prednisone in doses ranging from 60 to 80 mg daily (in single or divided doses), which is then continued until peak flows return to baseline values. Oral steroids are usually required for the next 10 to 14 d as guided by peak expiratory flow readings. Of note, we continue inhaled steroids in patients receiving systemic steroids to avoid confusion about restarting inhaled preparations during oral steroid taper, and because they may be some benefit to treating inflammation from both the luminal and blood sides. Patients with oral candidiasis are excluded from this practice.

Care must be taken during administration of systemic corticosteroids to identify and treat steroid-induced side effects. Problems that may be encountered include hyperglycemia, hypertension, hypokalemia, alterations in mood (including anxiety, insomnia, and frank psychosis), metabolic alkalosis, and peripheral hand or leg edema. When used concurrently with paralytic agents, systemic corticosteroids also appear to play a causative role in the development of myopathy in acute severe asthma (see below section on use of paralytic agents for a more complete discussion).

Oxygen. Obstruction of peripheral airways by airway wall inflammation, mucus, and bronchoconstriction causes ventilation/perfusion mismatch (low V/Q) and hypoxemia. True shunt in acute asthma averages only 1.5% of the pulmonary blood flow (101), so correction of hypoxemia requires only modest enrichment of inspired oxygen (1 to 3 L/min by nasal cannula). McFadden and Lyons (39) found only 5% of patients with acute asthma (all younger than 45 yr of age) had an initial PaO2 of 55 mm Hg or less at low altitude, suggesting that routine administration of supplemental oxygen to this patient population overtreats the majority of patients. There is a rough correlation between the degree of airflow obstruction as measured by the FEV1 or PEFR and hypoxemia (37, 39). However, there is no cut-off value for either measurement that accurately predicts significant hypoxemia. The routine administration of low-flow supplemental oxygen is an entirely safe practice that is recommended if continuous pulse oximetry is not available or comorbid conditions (such as coronary artery disease) exist. When low-flow supplemental oxygen by nasal cannula does not maintain saturation greater than 90% by pulse oximetry, we recommend an arterial blood gas measurement to confirm hypoxemia and to correlate pulse and arterial blood satu-
lations. Refractory hypoxemia is rare and should lead to a search for additional pathologic features such as pneumonia, aspiration, acute lobar atelectasis, and barotrauma. Hypoxemia resulting from peripheral airway obstruction may occur sooner and/or resolve later than airflow rates, which reflect predominantly large airway function (102). Benefits of oxygen therapy include improved oxygen delivery to peripheral tissues (including respiratory muscles), reversal of hypoxic pulmonary vasoconstriction, and airway bronchodilation. Oxygen also protects against the modest fall in PaO₂ often seen after beta-agonist administration resulting from pulmonary vasodilation and increased blood flow to low V̇Q units (103, 104).

Anticholinergics. The available data generally support the use of anticholinergic agents in patients with acute asthma. Still, these drugs should not be thought of as first-line agents. They produce less bronchodilation at peak effect than beta-agonists and achieve a somewhat more variable clinical response, indicating that cholinergic mechanisms play a variable role in patients with acute asthma. Anticholinergics may be particularly useful in patients with bronchospasm induced by beta-blockade (105) or in patients with severe airflow obstruction (FEV₁ < 25% predicted) (106).

Three drugs are currently available in the United States: atropine sulfate, ipratropium bromide, and glycopyrrolate. Atropine sulfate is the least desirable of these drugs, and it is not recommended in the treatment of acute asthma. Although atropine improves airflow in acute asthma (107), it is inferior to metaproterenol as a sole drug and does not produce further improvement in patients who have already received metaproterenol (108). Atropine is well absorbed from the airways because of its tertiary amine structure, and it thus causes unwanted systemic effects. It may also impair mucociliary clearance.

Ipratropium bromide and glycopyrrolate, on the other hand, can both be recommended in the treatment of patients not responding adequately to beta-agonists and steroids. Their quaternary amine structures limit absorption from the airway, minimizing systemic effects, and these drugs are not thought to impair mucociliary clearance. Ipratropium bromide augments the bronchodilating effect of beta-agonists in acute asthma (109-111), an effect that is not explained by inadequate dosing of beta-agonists (112). Bryant and Rogers (111) demonstrated that ipratropium bromide 0.25 mg by nebulizer plus 5 mg of nebulized albuterol resulted in greater improvement in FEV₁ than albuterol alone. In this study, a significant response to ipratropium bromide was detected within 1 min of administration, and the mean time to highest FEV₁ was only 19 min, a much faster time course than is usually seen in patients with chronic stable disease. One in 25 patients in this study had a paradoxical bronchoconstrictive response to ipratropium, which contrasts with prior reports that as much as 20% of patients with acute asthma may demonstrate a bronchoconstrictor response (113). In this patient, administration of a preservative-free solution prevented the paradoxical response. Fitzgerald (114) randomized 324 asthmatics in the emergency department to ipratropium bromide 0.5 mg combined with salbutamol 3.0 mg or salbutamol 3.0 mg alone. Mean FEV₁, at 45 and 90 min trended higher with combined therapy, but values did not reach statistical significance. Fewer patients were admitted to hospital from the combined group.

The optimal dose of ipratropium bromide is not known. Most investigators have used doses between 0.25 and 0.5 mg by nebulization in nonintubated patients who would require more than 10 puffs by MDI (0.018 mg/puff) if delivery to the airways was equivalent. Ipratropium bromide is now available in the United States as a premixed unit-dose inhalation solution for nebulization (0.5 mg diluted with saline). Nebulized glycopyrrolate has not been studied extensively in acute asthma. When compared with nebulized metaproterenol, nebulized glycopyrrolate has been shown to produce the same bronchodilator response with fewer side effects (115).

Available data do not allow for strong recommendations regarding the use of anticholinergics in acute asthma. Our own approach is to use ipratropium bromide or glycopyrrolate as second-line agents in patients not responding adequately to beta-agonists and steroids. We give four to 10 puffs of ipratropium bromide by MDI with a spacing device every 20 min, or 0.5 mg ipratropium bromide inhalation solution by nebulization over 10 to 15 min hourly. Alternatively, ipratropium bromide inhalation solution unit-dose vial (0.5 mg in 2.5 ml) may be used in conjunction with albuterol concentrate (2.5 mg in 0.5 ml). Glycopyrrolate 2 mg in 2.5 ml of normal saline may be administered by an updraft nebulizer over 20 min every 2 h. We generally do not continue inhaled anticholinergics for more than three doses unless there is evidence of a clinical response as determined by subjective improvement in symptoms or by an increase in PEFR.

Theophylline. As monotherapy, theophylline is inferior to beta-agonists in the emergency-room treatment of asthma. Rossing and colleagues (116) randomized 48 patients with acute asthma to treatment with nebulized isoproterenol, subcutaneously administered epinephrine, or theophylline given intravenously (all delivered as monotherapy). The mean improvement in FEV₁ after 60 min of treatment was greater in patients treated with isoproterenol or epinephrine than in patients given theophylline. Additionally, the mean duration of therapy required prior to discharge was significantly longer in the theophylline group. Other studies have demonstrated that the addition of theophylline to beta-agonists in the first few hours of treatment does not confer additional benefit, and that the use of theophylline increases the incidence of tremor, nausea, anxiety, palpitations, and heart rate (117-119). In a recent prospective, double-blind, randomized, and placebo-controlled trial of 44 patients 18 to 45 yr of age, Murphy and coworkers (118) found that when theophylline was added to other standard medications, there was no additional improvement in PEFR over 5 h of therapy, and that patients treated with theophylline had more tremor, nausea or vomiting, and palpitations.

On the other hand, Pierson and colleagues (120) demonstrated that in children treated with theophylline, ventilatory function had improved after 1 and 24 h of treatment without adverse effects. Huang and coworkers (121) conducted a randomized, placebo-controlled, double-blind study of 21 adults treated intravenously with theophylline added to frequent nebulizations of albuterol and intravenously administered steroids. The rate of improvement in FEVi during the first 3 h was faster in patients receiving theophylline than in patients receiving placebo, and this difference persisted over the 48 h of study. Also, in a recent study (122), intravenously administered theophylline was found to confer additional benefit on inhaled beta-agonists and parenteral steroids in the first 4 h of therapy.

Emergency-room administration of theophylline may also result in fewer hospitalizations—even if airflow rates are not different from patients receiving placebo (123). This finding raises the possibility that theophylline benefits patients in ways distinct from bronchodilation (124) such as through anti-inflammatory effects (125, 126) or effects on respiratory muscle function. Kelly and Murphy (127) point out that even when benefit is not detected in the first few hours of therapy, theophylline may improve lung function after 8 to 24 h of therapy. They believe that it is inappropriate to extrapolate data from short-term studies performed in the emer-
ergy room to hospitalized patients with SA in whom administration of theophylline has been demonstrated to be beneficial at 24 h (120, 128). Milgrom (129) also pointed to a possible delayed benefit in the use of theophylline in hospitalized patients with acute asthma.

Taken in sum, the available data do not allow for strong conclusions regarding the use of theophylline in acute asthma. Indeed, Littenberg (130) analyzed 13 trials of theophylline use in the emergency-room treatment of asthma and concluded that there was inadequate evidence to support or reject the use of theophylline in this setting. Further definitive trials are needed to determine the role of theophylline in both the short-term and the long-term management of asthmatics in acute exacerbation. While debate continues (131, 132) and until more data are available, our approach is to add theophylline to patients with a poor or incomplete response to treatment with beta-agonists and corticosteroids. We prefer IV dosing to limit oral intake in patients who may go on to intubation, although there is no difference in efficacy between IV and oral therapy. The loading dose of theophylline is 5 mg/kg (6 mg/kg aminophylline) by peripheral vein over 30 min in patients not receiving theophylline followed by a continuous infusion of 0.4 mg/kg/h (0.5 mg/kg/h aminophylline). In patients receiving theophylline, serum levels should be checked on arrival to the emergency room before additional theophylline is given. If the level is within the therapeutic range, a continuous infusion may be started, or the oral preparation may be continued.

Several investigators (121, 133–135) have demonstrated that theophylline can be used safely if attention is paid to serum drug levels and to factors that increase serum levels. Serum levels should be checked within 6 h of IV loading to avoid toxic levels and to guide further dosing. We aim for levels between 8 and 12 \( \mu g/ml \) to avoid toxicity. Factors that decrease theophylline clearance and thereby increase risk of toxicity include: congestive heart failure, liver failure, and a number of medications, including ciprofloxacin, macrolide antibiotics, and cimetidine.

Unproven Alternative Therapies

**Magnesium sulfate.** Intravenously administered magnesium sulfate has been reported to be a useful adjunctive therapy in patients with acute asthma refractory to treatment with inhaled beta-agonists (136–142). This benefit has been described in patients with normal serum magnesium levels, although hypomagnesemia has been reported in 50% of patients with acute asthma (143). If magnesium is beneficial in acute asthma, the mechanism is unknown. One possibility is that magnesium inhibits calcium channels of airway smooth muscle, thus interfering in calcium-mediated smooth muscle contraction (144). Magnesium also decreases acetylcholine release at the neuromuscular junction, which may interfere with bronchoconstriction from parasympathetic stimulation. Magnesium reduces histamine-induced (145) and methacholine-induced (146) bronchoconstriction in asthmatics, and it also affects respiratory muscle force generation (147).

Studies reporting a magnesium benefit in acute asthma suffer from the small number of patients studied. Many are anecdotal. One patient in acute hypercapnic respiratory failure has been described in whom 1 g magnesium sulfate delivered intravenously over 15 min was associated with dramatic improvement midway through the ventilator circuit (148). Sydow and colleagues (149) gave high doses of magnesium sulfate (10 to 20 g) over 1 h to five mechanically ventilated asthmatics. They demonstrated a significant decrease in peak airway pressure (43 to 32 cm H\(_2\)O) and in inspiratory flow resistance. Despite serum magnesium levels as great as three times normal, the only significant side effect was moderate systemic hypotension in two of the five patients.

However, the two largest prospective studies failed to show a benefit from the use of magnesium in acute asthma. One hundred twenty consecutive emergency department patients with acute asthma unresponsive to inhaled albuterol received 2 g magnesium sulfate intravenously if they presented on odd days and no magnesium if they were seen on even days (150). Physicians were not blinded, but respiratory therapists and patients were unaware of the study. There were no differences in hospitalization rates, duration of emergency department treatment, or changes in PEFR between treated and untreated patients. Tiffany and coworkers (151) conducted a randomized, double-blinded, placebo-controlled trial of 48 patients given magnesium or placebo if their initial PEFR was less than 200 L/min and failed to double after two albuterol treatments. Patients were randomized to three groups: 2 g magnesium sulfate given intravenously over 20 min followed by an infusion of 2 g/h for 4 h, 2 g magnesium sulfate given intravenously followed by placebo infusion, or a placebo loading dose and infusion. In this study, magnesium sulfate did not improve FEV\(_1\) or PEFR over approximately 4 h of measurement. The investigators concluded that "IV administered magnesium sulfate does not provide clinically meaningful improvement in pulmonary function test results when used in addition to standard bronchodilator therapy in patients with moderate to severe asthmatic exacerbations." They pointed out, however, that there may be patients in whom their conclusions may not apply such as less severely ill patients not receiving high-dose beta-agonists or more severely ill (i.e., ventilated) patients. They also raised the possibility that the sex of the patient may play a role since estrogen has been reported to augment the bronchodilator effect of magnesium (152). Indeed, there was a trend toward female responsiveness in this study, and in one other study demonstrating a magnesium effect, 25 of 34 patients were women (136).

In general, magnesium sulfate is a safe drug, particularly in doses not greater than 2 g given intravenously over 20 min (150), a dose that increases serum levels to about twice the original level (141). Most studies have not reported major complications of magnesium administration. Still, care must be taken to avoid magnesium intoxication, particularly in patients with impaired renal function. The loss of deep tendon reflexes and hypotension have been reported in magnesium intoxication. Minor complications include flushing and mild sedation.

The available data do not support the routine use of magnesium sulfate in the treatment of SA. Further definitive studies are needed to clarify efficacy and to identify possible subsets of patients for whom this agent may be beneficial. In our practice, we consider magnesium sulfate in patients who have failed treatment with other standard agents because it is generally safe and inexpensive. We give 1 g intravenously over 20 min and repeat 20 min later (unless the patient is hypomagnesemic, in which case normalization of serum levels should be achieved). All patients receiving magnesium should have levels followed and be observed closely for toxic side effects.

**Heliox.** Heliox is a blend of helium and oxygen with a gas density less than that of air. It is generally available in mixtures of 80:20 helium:oxygen, 70:30, and 60:40. It can be delivered through a tight-fitting nonbreathing face mask in nonintubated patients and through the inspiratory limb of the ventilator circuit in mechanically ventilated patients. Because this gas mixture is less dense than air, airway resistance is decreased in bronchi with turbulent flow regimes. This may decrease work of breathing and delay inspiratory muscle fatigue until concurrent definitive bronchodila-
tor/anti-inflammatory therapy becomes effective. Manthous and colleagues (153) observed a significant decrease in pulsus paradoxus and significant increase in peak flow in patients with acute asthma breathing heliox for 15 min as compared with control subjects. To the extent that pulsus paradoxus reflects the inspiratory fall in pleural pressure, and that the inspiratory drop in pleural pressure is related to Inspiratory airway resistance (Raw), the reduction in pulsus paradoxus during heliox administration indicates a substantial reduction in inspiratory Raw. Heliox also resulted in a 35% increase in peak flow, which signals a similar reduction in expiratory Raw. Taken together, these effects of heliox may diminish muscle fatigue and lung hyperinflation. If these favorable results are confirmed, heliox may prove to be a useful bridge to effective bronchodilator/anti-inflammatory therapy.

Gluck and colleagues (154) administered a 60:40 blend of heliox to seven intubated asthmatics. Within minutes, heliox decreased peak airway pressure by a mean of 33 cm H2O and PaCO2 by a mean of 35.7 mm Hg. If heliox is used during mechanical ventilatory support, it is important to recognize that recalibration of gas blenders and flow meters to this low-density gas will be required to obtain accurate measures of oxygen concentration or tidal volume. Although these results are promising, further studies regarding the efficacy of heliox in SA are clearly indicated before this gas can be recommended in the routine management of patients with acute asthma.

Antibiotics. Because respiratory tract infections that trigger asthma are usually viral, there is no role for the routine use of antibiotics. Antibiotics are frequently prescribed for these patients based on an increase in sputum volume and purulence. However, sputum that looks purulent typically contains an abundance of eosinophils and not polymorphonuclear leukocytes, a distinction that can be made only after microscopic inspection of the specimen. Indeed, transtracheal aspirates obtained from adults thought to have acute "infective" asthma demonstrated culture results similar to those from normal control subjects (155). Graham and coworkers (156) conducted a randomized, double-blind study of amoxicillin and placebo in 60 adult patients admitted to hospital with acute exacerbations of asthma. They did not demonstrate differences in improvement between groups for length of hospitalization, patient's self-assessment, or spirometry.

Patients for whom antibiotics are indicated include those with fever and sputum containing polymorphonuclear leukocytes, those with clinical findings of pneumonia, and those with signs and symptoms of acute sinusitis. We also favor the use of antibiotics in patients who, on clinical grounds, have clinical findings suggestive of mycoplasmal or chlamydial infection.

MECHANICAL VENTILATION

For patients who have received pharmacologic treatment in the emergency room or inpatient setting, intubation should be considered if there is clinical deterioration. As previously stated, the general appearance of the patient is the primary determinant of need for ventilatory support. Changes in posture, alertness, speech, extent of accessory muscle use, and respiratory rate can all indicate worsening respiratory failure that does not need blood gas or peak flow confirmation. Fatiguing patients and patients with altered mental status should be intubated whether or not PaCO2 is rising; and patients who are more comfortable, better able to speak, and less attentive to the task of breathing should continue with medical therapy despite an elevated PaCO2. Ultimately, the decision to intubate is made by a clinician's estimate of the ability of a patient to maintain spontaneous respiration until bronchodila-lator/anti-inflammatory therapy takes hold. Immediate intubation is indicated for patients arriving in the emergency room in cardio-pulmonary arrest, near cardiopulmonary arrest (e.g., patients unable to speak and/or gasping for air), coma, or significant obtundation.

Noninvasive Ventilation

Noninvasive face mask mechanical ventilation may be an option for short-term ventilatory support in patients with hypercapnic ventilatory failure who are (1) not responding adequately to pharmacologic intervention and (2) not thought by the physician to be in need of immediate intubation and mechanical ventilation. Patients who are encephalopathic or in need of airway protection to manage secretions should not be considered for this form of ventilatory support. Advantages of noninvasive over invasive ventilatory support may include decreased need for anesthesia, sedation and paralysis, decreased incidence of nosocomial pneumonia, decreased incidence of otitis and sinusitis, and improved patient comfort (157). Potential disadvantages include increased risk of aspiration of gastric contents secondary to gastric insufflation, facial pressure necrosis, and less control of the patients' ventilatory status when compared with invasive ventilation (157). Shivaram and colleagues (158) studied 21 patients in SA with a mean PEFR of 144 L/min. They showed that nasal CPAP of 5 or 7.5 cm H2O significantly decreased respiratory rate and dyspnea compared with placebo (CPAP mask without positive-pressure therapy) perhaps by decreasing the inspiratory work of breathing (159). Only two patients in the study group were withdrawn from the group because of increased dyspnea during CPAP of 5 cm H2O, and there was no evidence that these low levels of CPAP adversely affected expiratory airflow, hemodynamics, or arterial blood gas determinations. Similarly, Mansel and coworkers (160) reported a patient with acute, severe asthma and metabolic acidosis who was able to forgo intubation by face mask CPAP and continuous sodium bicarbonate infusion. Meduri and coworkers (157) evaluated face mask pressure support ventilation in 18 patients with acute hypercapnic respiratory failure, two of whom had SA. Both patients had failed aggressive inpatient treatment for more than 24 h and had developed signs of respiratory muscle fatigue and hypercapnia. Noninvasive ventilation was performed using a Puritan Bennett 7200 ventilator (Puritan Bennett Co., Carlsbad, CA). Initial ventilator settings consisted of CPAP with pressure support (details not provided) titrated to achieve a respiratory rate less than 25 breaths/min and tidal volume greater than or equal to 7 ml/kg. Both patients were ventilated upright using a full face mask with a nasogastric tube on low intermittent suction to prevent gastric insufflation. One patient was ventilated for 18 h, the other for 44 h. Both patients demonstrated a decrease in respiratory rate and PaCO2, and neither patient required subsequent intubation.

Further studies involving larger numbers of patients are needed before strong recommendations can be made regarding the use of noninvasive face mask ventilation in SA. Although the above reports are promising, in our experience this mode of ventilation is often poorly tolerated by severely dyspneic patients who describe mask ventilation as causing claustrophobia. Still, we consider noninvasive ventilation in cooperative patients who are not improving (or who are deteriorating) as long as they are not thought to be in need of immediate intubation, and as long as there are personnel available who are experienced with this form of therapy. By decreasing work of breathing, noninvasive ventilation may lessen inspiratory muscle fatigue, buy time for concurrent pharmacologic therapy to become effective, and thereby avert the need for intubation in some patients.
Intubation

Once the decision has been made to proceed with intubation and mechanical ventilation, the goal is to take rapid and complete control of the patient’s cardiopulmonary status. Intubation should be performed by the most experienced available clinician since manipulation of the upper airway may induce laryngospasm. Oral intubation allows for placement of a large endotracheal tube (8 mm or greater), which is important to suction tenacious mucus plugs mobilized during recovery from SA and to decrease airway resistance. This latter benefit is especially important at high airflows. At a flow of 120 L/min, endotracheal tube airflow resistance is more than twice as much with a 6.0 mm tube than with a 7.0 mm tube in vitro, a difference that may be even greater in vivo (161). Nasal intubation is probably safe in most patients, and it may be the preferred route in an awake, breathless patient anticipated to be difficult to ventilate with a bag-valve-mask (e.g., obese patients with short necks). Fiberoptic guidance is useful to facilitate nasal intubation in these semielective situations. However, there are several problems with the nasal approach, including the need for a smaller endotracheal tube and the high incidence of nasal polyps and sinusitis in this patient population.

Sedation

Sedation is invariably required in awake patients to prepare for intubation and to allow for safe and effective mechanical ventilation. Sedation improves patient comfort, helps prevent unwanted respiratory efforts, facilitates procedures, and decreases oxygen consumption and carbon dioxide production. Sedation may also decrease the risk of barotrauma. Despite the frequency with which sedatives are used in the ICU setting, surprisingly little data are available from which to form strong conclusions regarding which agents or combinations of agents are best and how to administer these agents optimally to maximize patient comfort and minimize side effects. The development and validation of sedation and analgesia protocols will help in this regard.

See Table 3 for a summary of agents, doses, and cautions for commonly used sedatives in SA. In preparation for intubation, we give midazolam 1 mg intravenously followed by 1 mg every 2 to 3 min until the patient allows positioning and inspection of the airway. Bolus administration of morphine sulfate is avoided because of its potential to induce systemic hypotension through a combination of direct vasodilation, histamine release, and vagally mediated bradycardia (162). Opioid-induced vomiting is also undesirable in the peri-intubation period. Ketamine, an IV general anesthetic with sedative, analgesic, anesthetic, and bronchodilating properties (163, 164), has been used successfully for the emergency intubation of patients with SA. In four of five patients with SA requiring intubation in the emergency room, ketamine and succinylcholine in the peri-intubation period were associated with decreased wheezing (165). The fifth patient had been intubated and ventilated with a rising PaCO2 after ketamine, wheezing and PaCO2 both decreased. The usual dose of ketamine, 1 to 2 mg/kg given intravenously at a rate of 0.5 mg/kg/min, generally provides 10 to 15 min of general anesthesia (166) without significant respiratory depression. Rapid bolus administration may result in respiratory depression (167). Bronchospasm may improve within minutes after IV administration, but this effect generally does not last for more than 20 to 30 min after bolus administration (165, 168, 169). Potential risks to ketamine use include its ability to increase heart rate and arterial blood pressure because of sympathomimetic effects. It is therefore relatively contraindicated in patients with atherosclerotic vascular disease, hypertension, increased intracranial pressure, and preeclampsia. Another drawback to the use of ketamine is its potential to lower the seizure threshold, alter mood, and occasionally cause delirium, effects that may occur in as much as one third of patients older than 16 yr of age (166, 169, 170). Ketamine increases laryngeal secretions and does not block pharyngeal and laryngeal reflexes (166); thus, particular care must be taken in the peri-intubation period to avoid laryngospasm and aspiration (171). Ketamine is broken down in the liver

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Cautions</th>
</tr>
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<tbody>
<tr>
<td>Midazolam</td>
<td>1 mg intravenously slow push; repeat every 2 to 3 min as needed.</td>
<td>Hypotension, respiratory depression.</td>
</tr>
<tr>
<td>Ketamine</td>
<td>1 to 2 mg/kg intravenously at a rate of 0.5 mg/kg/min.</td>
<td>Sympathomimetic effects, respiratory depression, mood changes, delerium-type reactions.</td>
</tr>
<tr>
<td>Propofol</td>
<td>60 to 80 mg/min intravenous initial infusion up to 2.0 mg/kg followed by an infusion of 5 mg/kg/h as needed.</td>
<td>Respiratory depression.</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1 to 5 mg/h intravenous continuous infusion or bolus as needed.</td>
<td>Drug accumulation.</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>1 to 5 mg/h intravenous continuous infusion; avoid bolus.</td>
<td>Ileus.</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.1 to 0.5 mg/min intravenously.</td>
<td>Sympathomimetic effects, delerium-type reactions.</td>
</tr>
<tr>
<td>Propofol</td>
<td>1 to 4.5 mg/kg/h intravenously.</td>
<td>Seizures, hypertriglyceridemia.</td>
</tr>
</tbody>
</table>
to norketamine, which also has anesthetic properties and a half-life similar to that of midazolam (about 120 min). As such, there is some risk for drug accumulation with continuous infusion (167).

Propofol may prove to be a useful drug in the preintubation period, but as with ketamine, experience is limited in patients with SA. In a recent comparative study (172) of propofol and midazolam as sedatives for asthmatics undergoing fiberoptic bronchoscopy, propofol resulted in more rapid onset and resolution of sedation. There were no significant differences in oxygen desaturation or hemodynamic parameters between the propofol and midazolam groups. Patients in the propofol group received initial IV infusions of 60 to 80 mg/min up to 2.0 mg/kg until adequate sedation was achieved followed by an infusion of 5 to 10 mg/kg/h to maintain the desired level of sedation.

Propofol seemingly meets many of the requirements for an ideal sedating drug in the ICU setting. Its rapid onset of action allows for rapid titration of the level of sedation without significant cardiovascular effects; and since patients can be titrated to anesthetic depth sedation, it may avoid the need for muscle paralysis and its consequences (see below). The risk of drug accumulation is low because of rapid metabolism by hepatic conjugation to inactive metabolites, which are renally excreted (173). In addition, a recent report (174) of the use of propofol in two patients with chronic obstructive pulmonary disease (COPD) who developed bronchospasm after insertion of a prosthetic aortic valve suggests propofol may have bronchodilating properties as well. It should be pointed out, however, that propofol has no analgesic properties.

For ongoing sedation we prefer lorazepam over midazolam mainly because of the prohibitive cost of long-term midazolam infusion. When given by continuous infusion in mechanically ventilated patients, benzodiazepines may accumulate and require extended periods of time to clear and permit return of normal mental status (175). The addition of morphine sulfate 1 to 5 mg/h given intravenously by constant infusion helps relieve pain and achieve unconsciousness for the use of paralytic agents. Slow infusions of opioids minimize hemodynamic effects and histamine release (which can be blocked by pretreatment with antihistamines) (162). However, opioids decrease gut motility, cause nausea and vomiting, and depress ventilatory drive in spontaneously breathing patients. They are also slowly cleared in patients with depressed liver or kidney function.

More extensive clinical trials of ketamine and propofol (including the use of continuous infusions) in patients with SA may prove these agents to be acceptable alternatives to benzodiazepines and opioids for long-term sedation. However, a growing body of evidence suggests prolonged propofol administration may be associated with generalized seizures (176–180). Hypertriglyceridermia and increased CO₂ production have also rarely been reported during propofol infusion since the drug is mixed in a fat-based diluent (176, 181). Until further data are available, we do not recommend the routine use of either propofol or ketamine for long-term sedation in SA.

The optimal level of sedation in mechanically ventilated asthmatics is not known. Many clinicians aim for a state of drowsiness and relaxation in which patients are able to open their eyes on command, demonstrate little spontaneous movement, and breathe in synchrony with the ventilator and at the set ventilator rate. Ideally, sedation alone allows for control of the patient’s cardiopulmonary status, and muscle paralysis is not necessary.

Paralysis

Ultimately, the decision whether or not to use a neuromuscular blocking agent as a part of the overall therapeutic strategy is based on the clinician’s judgment that paralysis is needed to maintain stable respiratory parameters and ensure patient safety. Muscle paralysis is indicated in patients who, in spite of sedation, continue to breathe in a desynchronized manner during mechanical ventilation, placing themselves at greater risk of generating high airway pressures and losing airway access. Paralysis augments the beneficial effects of sedation to reduce oxygen consumption, carbon dioxide production, and lactic acid generation, and it may decrease the risk of barotrauma. Eliminating expiratory effort may also be associated with less airway collapse (162).

The preferred paralytic agents are vecuronium and atracurium. These nondepolarizing agents are virtually free of cardiovascular effects, although large boluses of atracurium may cause hypotension through the release of histamine (183). The current trend in many institutions is to use atracurium because of fewer reports of the development of myopathy (see below). One potential disadvantage of atracurium, however, is its histamine-releasing property, which may worsen bronchospasm. Whether this potential problem is of clinical significance in patients with SA is currently unknown. Vecuronium is largely cleared by the liver, although two metabolites are renally excreted making it a poor choice in patients with failure of either organ system. In such patients, atracurium is the better choice because it is eliminated by esterase degradation and spontaneous breakdown in the serum. Pancuronium, which is metabolized in the liver and excreted by the kidney, is an acceptable alternative to vecuronium in most cases and is less expensive. However, its vagolytic properties are more likely to cause tachycardia and hypotension.

Paralytic drugs may be given intermittently by bolus injection or by continuous IV infusion. If a continuous infusion is used, the drug should be withheld every 4 to 6 h to avoid drug accumulation and prolonged paralysis and to assess the need for ongoing paralysis. In all cases, use of a nerve stimulator to define least drug dosage is advisable. Muscle paralysis should be provided only on an as-needed basis and only to unconscious patients. Ensuring unconsciousness in these patients is a challenge since the commonly used indicator of agitation, tachycardia, may not be reliable in patients receiving high doses of adrenergic agents.

There are a number of disadvantages to using paralytic agents, including difficulties assessing mental status, a potentially greater risk of developing deep venous thrombosis, and worsening of disuse muscle atrophy (184). Paralytic agents also appear to play a causative role in the development of myopathy in acute severe asthma. Muscle weakness may be mild and of little clinical significance or severe enough to interfere with successful liberation from mechanical ventilation. Most patients recover completely, although some patients require several weeks of rehabilitation. In a recent study (185) of 25 consecutive, mechanically ventilated asthmatics (22 of whom received vecuronium), 19 demonstrated a significant increase in serum creatine kinase (CK), and nine (36%) had clinically detectable myopathy. Mechanical ventilation was significantly prolonged in patients with an elevated CK whether or not there was clinically detectable myopathy. Fluegel and colleagues (186) reviewed 90 episodes of mechanical ventilation for SA. Profound muscle weakness occurred in 14 cases. Median CK (measured in 10 cases) was 1,000 IU/L. Electromyograms in six cases showed a myopathic pattern. Muscle biopsy in three cases showed myonecrosis. All patients had received a neuromuscular blocking agent (five received vecuronium; four, atracurium; two, pancuronium; and three, a combination of these drugs). No patients receiving corticosteroids alone developed muscle weakness. Indeed, there was no association between the dose of corticosteroid used and the development of myopathy. On the other hand,
patients with myopathy received higher doses of vecuronium for longer periods of time.

The data of Fluegel and colleagues suggest that it is the combination of corticosteroids and neuromuscular blocking agents that increases the risk of myopathy; still, other factors may be involved, including hypokalemia, hypophosphatemia, and high-dose beta-agonists. The concern that the steroid structure of vecuronium and pancuronium increases the risk of myopathy (184, 187, 188) (and therefore that atracurium is safer) is not supported by the data of Fluegel and colleagues.

Until further data are available, we recommend the use of paralytics only in patients who cannot be adequately controlled with sedation alone. When paralytics are necessary, they should be dosed using a peripheral nerve stimulator so that lower dosages can be given. Paralytics should be held intermittently to assess the need for ongoing paralysis, serum CK levels should be followed, and blood electrolyte and mineral concentrations should be maintained within normal ranges (187). Although, Fluegel and colleagues (186) found no correlation between the dose of corticosteroids and the development of myopathy, this finding needs to be validated in future trials. For now, we recommend that excessive doses of corticosteroids (which we define as greater than 125 mg methylprednisolone or its equivalent given intravenously every 6 h) should be avoided.

Lung Hyperinflation and Barotrauma

Postintubation hypotension is common. Causative factors are lung hyperinflation, hypovolemia, and sedation. Lung hyperinflation occurs when expiratory airflow obstruction prevents complete alveolar gas emptying. It is directly proportional to minute ventilation (Ve) (189, 190). In the postintubation period, dangerous levels of lung hyperinflation can develop if patients are ventilated excessively in a misguided attempt to stabilize or resuscitate. With severe airflow obstruction, even delivery of a normal or reduced Ve may cause substantial gas trapping and hemodynamic compromise. Clinically, inspired breaths are difficult to deliver (because of both airway obstruction and hyperinflation), breath sounds are diminished, and neck veins are distended. Systemic blood pressure and pulse pressure fall and pulse rate rises. In the same patients, hypovolemia from increased insensible water losses and/or decreased oral fluid intake, sedation, and muscle relaxation all act to decrease mean systemic vascular pressure, further decreasing venous return to the heart. This pathophysiology can be demonstrated by slowly ventilating (2 to 3 breaths/min) the patient while delivering 100% oxygen to avoid hypoxemia. Mean intrathoracic pressure will fall, and within 30 to 60 s, blood pressure will rise, pulse pressure will widen, and pulse rate will fall. Vigorous volume challenge should follow in hypovolemic patients, along with strategies to minimize lung hyperinflation (see below).

Note that the clinical features of lung hyperinflation mimic tension pneumothorax. Indeed, if hypoventilation does not quickly achieve cardiopulmonary stability, consideration should be given to the immediate placement of bilateral chest tubes. But just as important, chest tubes should not be inserted in unstable patients (unless clear-cut evidence of tension pneumothorax exists) until there has been a trial of hyperventilation.

Once the patient has been adequately fluid-resuscitated, ventilator settings should be chosen that avoid excessive lung inflation. Such a strategy decreases the risk of systemic hypotension and pneumothorax, both of which correlate directly with the degree of lung hyperinflation (190). Lung hyperinflation is minimized by allowing an adequate time for exhalation (TE) and by ongoing treatment of expiratory airflow obstruction. Expiratory time can be prolonged by decreasing Ve by either lowering respiratory rate (RR) or tidal volume (VT) or by minimizing inspiratory time (TI) (see Figure 2). Inspiratory time is reduced by increasing inspiratory flow rate and using a square flow wave form. The use of ventilator circuit with a low compressible volume (i.e., low-compliance tubing) decreases the portion of VT wasted in expanding the ventilator tubing, and thereby allows the physician to set a smaller VT to achieve the same effective VT in the patient (191). Thus, a smaller Ve can be set, allowing for longer Te.

Minute ventilation is usually a more important determinant of expiratory time than is Ti. To illustrate this point, consider the consequences of the following ventilator settings (192): VT, 1,000 ml; RR, 15 breaths/min, and inspiratory flow rate, 60 L/min. These settings result in a Ti of 1 s and a Te of 3 s (I:E ratio of 1:3). Decreasing RR to 12 breaths/min prolongs Te to 4 s (I:E of 1:4), whereas doubling of inspiratory flow prolongs Te to only 3.5 s (I:E of 1:7). Decreasing RR in this example results in less lung hyperinflation than increasing flow because there is more time to exhale the 1-L breath. Note how the I:E ratio can be misleading. In general a low I:E ratio is desirable because it suggests a ventilator strategy is in place that prolongs Te. In the above example, however, the strategy that achieved a higher I:E resulted in longer Te.

For an average-sized adult an initial Ve between 8 and 10 L/min
The volume, termed V_el, is the volume of gas at end-inspiration above FRC and is the sum of the tidal volume (VT) and volume at end-exhalation above FRC (VEE). V_el above a threshold value of 20 ml/kg (1.4 L in an average-sized adult) has been shown to predict complications of hypotension and barotrauma. (From reference 193, with permission.)

Auto-PEEP is another measure of lung hyperinflation. When expiratory airflow obstruction prevents complete emptying of alveolar gas, end-expiratory alveolar pressure remains positive. This pressure is not reflected at the airway opening if the expiratory port of the ventilator is open (which allows airway opening pressure to approach atmospheric pressure or the level of ventilator-applied PEEP). If the expiratory port of the ventilator is occluded at end-expiration, however, central airway pressure equilibrates auto-PEEP measurements are accurate only in relaxed patients since expiratory muscle contraction elevates auto-PEEP without adding to dynamic hyperinflation. Auto-PEEP has not been shown to correlate with complications (193); there are recent data from Leatherman and colleagues (194) demonstrating that auto-PEEP may significantly underestimate the degree of lung hyperinflation in some patients—again suggesting the presence of noncommunicating gas resulting from airway closure.

Ventilator-applied PEEP should be avoided in mechanically ventilated patients with SA because it has the potential to increase lung volume and intrathoracic pressure in sedated and paralyzed patients (195). We also avoid applied PEEP in hyperinflated patients who are actively breathing (even though this strategy may decrease inspiratory work of breathing) because the degree of auto-PEEP is difficult to assess in spontaneously breathing patients, and applying PEEP above the level of auto-PEEP may add to lung hyperinflation.

The use of high inspiratory flow rates minimizes lung hyperinflation, but this choice is not without possible risk. High inspiratory flows increase Ppk (see Figure 2), a pressure several investigators have suggested is associated with risk of barotrauma (193, 196). Recent data, however, fail to show a relationship between Ppk and complications of mechanical ventilation (193). The reason may be that Ppk does not predict alveolar pressure or the degree of lung hyperinflation because of the pressure gradient between the large robust airways and the alveoli. High inspiratory flow rates may also increase annular flow of mucus toward alveoli (197) and preferentially fill (and hyperinflate) more normal lung units with faster time constants. The clinical significance of these last two possibilities is unknown.

In the most severely obstructed patients, a V_el of 8 to 10 L/min may result in unacceptable lung hyperinflation as judged by V_el, Pplat, or auto-PEEP. In this circumstance, V_el should be progressively decreased, even if hypercapnia ensues. However, decreasing V_el may not increase PACO2 if decreasing lung hyperinflation.
Figure 5. Measurement of auto-PEEP. Under normal conditions, alveolar pressure (Pαv) closely tracks the pressure at the airway opening (Pao), which is reported on the ventilator manometer. At end-expiration, Pαv falls to atmospheric pressure (0 cm H2O) and is accurately reflected by Pao. In severe airflow obstruction, Pαv may increase because of gas trapping, and at end-expiration Pαv has not fallen to atmospheric pressure and does not equal Pao. If an expiratory hold maneuver is performed, Pao will rise, reflecting the degree of gas trapping. (From reference 22, with permission.)

decreases the dead space to tidal volume ratio (VD/VT) by improving perfusion to ventilated lung units. It is the product of VE and (1-VD/VT) that sets alveolar ventilation; so that if alveolar ventilation increases with a drop in VE, PaCO2 may actually fall assuming constant CO2 production.

Purposeful hypoventilation is not without potential risk. Hypercapnic acidosis may cause cerebral vasodilation, cerebral edema, decreased myocardial contractility, vasodilation with a hyperdynamic circulation, and pulmonary vasoconstriction (198). Accordingly, purposeful hypoventilation is a strategy best avoided in patients with raised intracranial pressure (as might occur in the setting of anoxic brain injury from cardiopulmonary arrest) and in patients with severely depressed myocardial function. Still, purposeful hypoventilation is well tolerated by many patients as long as PaCO2 does not exceed 90 mm Hg (199) and acute increases in PaCO2 are avoided. Low values of arterial pH also appear to be well tolerated by most patients—which raises the question as to whether low values of arterial pH need to be treated with buffer therapy. To date, the efficacy of increasing serum pH in the setting of purposeful hypoventilation is unknown, and there is a clear need for additional studies addressing this issue. Our approach is to treat patients with an arterial pH less than 7.20 with sodium bicarbonate (200) unless there is room to increase VE as guided by Pplat, or Pplat is greater than 30 cm H2O, we decrease RR until this goal is achieved.

Figure 6. Recommended initial ventilator settings and an algorithmic approach to mechanical ventilation in patients with status asthmatics.

SA. We recommend initial ventilator settings of: VT, 8 to 10 ml/kg; RR, 11 to 14 breaths/min; PEEP, 0 cm H2O; inspiratory flow rate, 100 L/min with a square flow wave form. FIO2 should be 1.0 (humidified) in the peri-intubation period, but it should be decreased to a nontoxic level once the patient is stable. Ventilator mode is irrelevant in the sedated and paralyzed patient since assist-control and intermittent mandatory ventilation both provide controlled ventilation in this setting. There are no data that one ventilator mode is better than another in patients with respiratory efforts, and the clinician should choose the mode with which he or she is most familiar (182). One caution is that the use of volume-cycled assist control ventilation in the initial treatment of awake asthmatics may be associated with increased risk of hyperinflation (202). Similar to Tuxen and colleagues (189) and Leatherman and coworkers (192), we accept the above settings if they achieve a Pplat less than 30 cm H2O and an arterial pH greater than 7.20. If Pplat is greater than 30 cm H2O, we decrease RR until this goal is achieved. If purposeful hypoventilation results in an arterial pH less than 7.20 and there is no room to increase VE as guided by Pplat, we consider adding sodium bicarbonate to the maintenance infusion while continuing to lower CO2 production with sedation and paralysis.

Although the available data justify the use of a ventilator strategy that limits lung hyperinflation and tolerates hypercapnia, this approach needs validation in larger clinical trials. Whether using such a strategy will decrease the mortality of ventilated asthmatics as well as morbidity remains unknown. Tuxen’s group (193) has reported zero asthma mortality (albeit in a small number of patients), but so have other groups caring for ventilated asthmatics during the last 15 yr. Braman and Kaemmerlen (196) reported no deaths during 24 episodes of mechanical ventilation for SA between 1978 and 1987. These investigators did not provide details regarding ventilatory strategy or arterial blood gas measurements during ventilation, but in all cases the ventilator was preset to limit Ppk to less than 50 cm H2O, and initial PaCO2 averaged 89 mm Hg. Darioli and Perret (199) similarly reported zero mortality during 34 episodes of mechanical ventilation for SA when Ppk was limited to 50 cm H2O and hypercapnia was tolerated. Bellomo and coworkers (203) also accepting of high levels of PaCO2, reported one death (which was attributed to brain death prior to ventilation) during 35 consecutive cases of SA requiring mechanical ven-
Inhalational Anesthetics

Rarely, the above strategies do not allow for adequate ventilation at a safe level of lung inflation, and consideration should be given to the use of inhalational anesthesia. Both halothane and enflurane are bronchodilators that can acutely reduce Ppk and Paco₂ (207, 208), but effects do not last after drugs are stopped. Inhalational anesthetics have considerable cardiovascular effects, including myocardial depression, arterial vasodilation, and arrhythmias, but hemodynamic stability can usually be maintained during administration by skilled anesthesiologists. As mentioned previously, a blend of 60% helium and 40% oxygen has been studied in seven intubated asthmatics (154). Within minutes helium decreased peak airway pressure by a mean of 33 cm H₂O and Paco₂ by a mean of 35.7 mm Hg; one patient who responded quickly to heliox had previously failed a trial of halothane. There has been recent interest in the use of nitric oxide (NO) to induce bronchial relaxation, but there has been limited experience in patients with SA. Hogman and colleagues (209) recently reported their experience with NO in healthy volunteers, adults with airway hyperreactivity during methacholine challenge, patients with stable asthma, and patients with COPD. They concluded that NO inhaled at 80 ppm exerted a weak bronchodilatory effect in asthmatics but not in patients with COPD.

Bronchoalveolar Lavage

One of the most striking findings noted in patients dying of SA is the degree of mucus impaction of both large and small airways (210). In refractory patients, retained secretions, not yet mobilized by bronchodilators and corticosteroids, contribute to airflow limitation and lung hyperinflation. Unfortunately, other strategies to mobilize mucus such as chest physiotherapy or treatment with mucolytics or expectorants have not proved efficacious in controlled trials (211, 212). BAL, on the other hand, using either saline or acetylcysteine, may be useful to remove mucus plugs in some patients with refractory SA (213–217). Lang and colleagues (214) recently demonstrated that BAL improved airflow obstruction in nonintubated patients with stable but refractory acute asthma. There were no major complications. Minor complications included three episodes of transient hypoxemia and four episodes of worsening bronchospasm, which resolved after treatment with subcutaneous or inhaled beta-agonists.

In intubated asthmatics, however, this procedure is more risky. The presence of the bronchoscope within the lumen of the endotracheal tube and large airways increases expiratory airway resistance and may lead to dangerous levels of lung hyperinflation. Temporarily decreasing Ve may minimize this complication, but it is likely to result in further increases in Paco₂. Despite these risks, some physicians advocate a quick inspection of the airways to remedy possible diffuse mucus impaction in patients who are not improving after several days of mechanical ventilation. This practice may prove to be beneficial for rare patients, but convincing data demonstrating benefit and safety of BAL in this setting are needed before this practice can be validated. For now, BAL should not be considered a part of the routine management of ventilated asthmatics.

Extubation

Once airway resistance starts to fall and Paco₂ normalizes, paralytic agents and sedatives should be withheld in anticipation of extubation. If signs of worsening bronchospasm are not present, we favor a quick return to spontaneous breathing through a T-piece or by decreasing the respiratory rate on SIMV. The use of 5 to 8 cm H₂O of pressure support helps overcome endotracheal tube resistance. If patients tolerate a trial of spontaneous breathing, we move quickly toward extubation. This tempo minimizes endotracheal-tube-induced bronchospasm and other risks of prolonged intubation and mechanical ventilation. Close observation in the ICU is recommended for an additional 24 h postextubation during which time clinicians can focus on safe transfer to the general medical ward.

PREVENTING FUTURE EPISODES OF STATUS ASTHMATICUS

After the patient has arrived on the general medical ward, the treating team should address the prevention and treatment of subsequent asthma attacks. This process starts with extensive patient education regarding the definition of asthma, the signs and symptoms of asthma, how to control or eliminate triggers, and how to identify and treat attacks appropriately. Patients should be provided with written medication instructions as well as a written plan of action to be followed in the event of worsening symptoms. A peak flow meter should be given to all patients to help them recognize and treat symptoms. Time should be taken to address psychosocial and financial issues that may interfere with medication compliance, and follow-up appointments should also be made prior to discharge whenever possible.

A common goal is to treat airway wall inflammation by controlling the patient's environment and by the religious use of anti-inflammatory medications. When inhaled corticosteroids are prescribed, patients must be told not to expect immediate relief of respiratory symptoms, as these medications are not bronchodilators. The regular use of anti-inflammatory therapy must be stressed, and patients should demonstrate their ability to administer inhaled drugs effectively. Corticosteroid side effects should be discussed with patients, who are often quite concerned about the use of these drugs even for short periods of time, and strategies should be provided that minimize the risk of these side effects occurring. Patients inhaling corticosteroids should use a spacing device and be counseled to rinse and spit after usage to decrease systemic absorption and the risk of oral candidiasis. For patients using oral preparations, exercise and nutritional guidance should be provided to minimize weight gain and the risk of...
hyperglycemia and hypertension. Attention should also be paid to the prevention of steroid-induced osteopenia.

Patients should be taught how to recognize early warning signs so that they may initiate proper treatment. In general, warning signs of worsening airflow obstruction include a 20% drop in PEFR below predicted or personal best, and an increase in cough, shortness of breath, chest tightness, or wheeze (48). Although mild asthma episodes (PEFR between 70 and 90% of baseline) may be treated by a temporary increase in bronchodilator therapy, bronchodilators alone are not sufficient to treat more severe attacks (48). Indeed, beta-agonists may even confer a false sense of security and delay the administration of anti-inflammatory therapy. Accelerated use of beta-agonists should be a warning sign that airway wall inflammation has worsened and that corticosteroid therapy should begin. Should such a strategy be followed, many emergency room visits could be avoided. Patients with a history of sudden asphyxial asthma should also be given an epinephrine kit for the immediate subcutaneous use of this drug during a crisis.

SUMMARY

Despite advancing knowledge of the pathophysiology and treatment of asthma, asthma morbidity and mortality are on the rise. To help avert this trend, clinicians and patients must focus their attention on the early identification and treatment of asthma exacerbations. As in the words of Dr. Thomas Petty: "...the best treatment of status asthmaticus is to treat it three days before it occurs." (7) Still, there will be asthmatics with life-threatening attacks that require careful assessment and aggressive management. Inhaled beta-agonists, systemic corticosteroids, and oxygen remain the drugs of choice in SA. Anticholinergics play a lesser role in the treatment of acute asthma, and debate continues regarding the efficacy of theophylline in this setting. Available data do not support the routine use of magnesium sulfate or antibiotics in patients with SA.

Patients failing drug therapy should be considered early for intubation and mechanical ventilation. A strategy of mechanical ventilation that prolongs TEEP by limiting VE and decreasing inspiratory time, and that tolerates hypercapnia, avoids excessive lung hyperinflation and barotrauma and should improve the outcome of these most critically ill asthmatics. Intubated and mechanically ventilated patients should be aggressively sedated. Paralytic agents should be used only if adequate control of the cardiopulmonary status is achieved by sedation alone. Minimizing the use of paralytic agents may decrease risk of myopathy and other adverse consequences of muscle paralysis. Finally, after successful treatment of a life-threatening episode of asthma, the treatment team should address prevention of future episodes of SA prior to discharge.

References


