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*Chest 2004;125;1081-1102
DOI 10.1378/chest.125.3.1081

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Acute Asthma in Adults*
A Review

Gustavo J. Rodrigo, MD; Carlos Rodrigo, MD; and Jesse B. Hall, MD, FCCP

All patients with asthma are at risk of having exacerbations. Hospitalizations and emergency department (ED) visits account for a large proportion of the health-care cost burden of asthma, and avoidance or proper management of acute asthma (AA) episodes represent an area with the potential for large reductions in health-care costs. The severity of exacerbations may range from mild to life threatening, and mortality is most often associated with failure to appreciate the severity of the exacerbation, resulting in inadequate emergency treatment and delay in referring to hospital. This review describes the epidemiology, costs, pathophysiology, mortality, and management of adult AA in the ED and in the ICU.

Key words: acute asthma; anticholinergics; assessment; β-agonists; corticosteroids; heliox; inhalation therapy; magnesium sulfate; mechanical ventilation; oxygen

Abbreviations: AA = acute asthma; ABG = arterial blood gases; APACHE II = acute physiology and chronic health evaluation; CPAP = continuous positive airway pressure; ED = emergency department; IB = ipratropium bromide; NIPPV = noninvasive positive pressure ventilation; PEEP = positive end-expiratory pressure; PEF R = peak expiratory flow rate; pMDI = pressurized meter dose inhaler; PP = pulsus paradoxus; RR = respiratory rate; SpO₂ = oxygen saturation by pulse oximetry; V̇/Q̇ = ventilation/perfusion; V̇t = tidal volume

Asthma is a chronic inflammatory disorder of the airways associated with hyperresponsiveness, reversible airflow limitation, and respiratory symptoms.1-2 It is the most common chronic lung disease in both the developed and developing worlds. There is evidence that over the last 20 years its prevalence has increased worldwide.3-5 All patients with asthma are at risk of having exacerbations characterized by a progressive increase in shortness of breath, cough, wheezing or chest tightness, and by a decrease in expiratory airflow that can be quantified by simple measures of pulmonary function such as the peak expiratory flow rate (PEFR) and FEV₁. Terms like acute asthma (AA), asthma attack, or status asthmaticus have been used to describe this condition. The severity of exacerbations may range from mild to life threatening. Deterioration usually progresses over hours, days, or weeks; however, a few patients have sudden (over minutes) and unexpected increases in airway obstruction. Epidemic asthma, the simultaneous occurrence in place and time of an unusually high number of asthma attacks, has been reported in at least 12 different locations around the world.6 A number of circumstances may mimic the diagnosis of AA (COPD, congestive heart failure, upper airway obstruction, hyperventilation syndrome, or vocal cord dysfunction). Usually, they can be identified by history and physical examination. Morbidity and mortality are most often associated with failure to appreciate the severity of the exacerbation, resulting in inadequate emergency treatment and delay in referring to hospital.7-10 This review describes the epidemiology, costs, pathophysiology, mortality, and management of adult AA in the emergency department (ED) and in the ICU.

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Manuscript received February 20, 2003; revision accepted June 5, 2003.

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Epidemiology and Costs

AA is a common medical emergency faced by ED and intensive care specialists. In the United States, asthma represents the 11th most frequent ED diagnosis nationwide, and adolescents and young adults are the most likely age groups to visit the ED for treatment.11 Women visit the ED and are hospitalized for AA twice as often as men.12,13 Previous data suggested that 40% of these hospitalizations occur during the premenstrual phase of the cycle.14 Men are less likely than women to report severe asthma symptoms and activity limitations in the presence of airway obstruction.15 Data from Australia, Canada, and Spain reported that AA accounted for 1 to 12% of all adult ED visits.16–18 Of the 1.5 million ED visits by asthma patients in 1995 in United States, 20 to 30% of patients required hospital admission.19,20 Rates of hospital admission for female patients and blacks were consistently higher than for male patients and whites. However, in the past decade there has been a decline in the number of patients with acute severe asthma requiring ICU admission, and a trend toward less advanced presentations with reduced level of respiratory acidosis and decreased ICU length of stay.21 In one large tertiary care hospital, only 4% of asthma admissions required ICU care over a 10-year period.22 In another report, 7% of adult AA patients who presented to 37 EDs in France were transferred to an ICU.10 Probably, most hospitalizations, including those requiring ICU care, are preventable.

Developed economies might expect 1 to 2% of total health-care expenditures to be spent on asthma. The US studies estimated that the total burden of asthma was approximately $6 billion per year.21,24 Direct costs (providing health care to asthmatics) rather than indirect costs (missed work, additional child care, etc.) represented the greater part (almost 90%) of the total societal cost. Together, hospitalizations and ED visits represent the single greatest cost category, accounting for almost 50% of the total cost overall. The average annual cost per patient who had an attack was $600, compared with $170 for those who did not, an increase of > 3.5 times.25 Only approximately 20% of asthmatics have ever been admitted to an ED or hospital, yet these patients account for > 80% of total direct costs (“high-cost patients”). The estimated annual per patient cost for those high-cost patients was $2,500, in contrast with $140 for the rest. These estimates indicate that hospitalization and ED visits account for the largest proportion of costs, and represent the area with the principal potential for savings.

Pathophysiology

Different triggers cause asthma exacerbations by inducing airway inflammation or provoking acute bronchospasm or both. Triggers vary from person to person and from time to time. Exposure to indoor and outdoor allergens, air pollutants, respiratory tract infections (primarily viral), exercise, weather changes, foods, additives, drugs, and extreme emotional expressions are the main triggers identified clinically. Other factors that may cause exacerbations are rhinitis, bacterial sinusitis, polyposis, menstruation, gastroesophageal reflux, and pregnancy. The mechanisms of acute airflow limitation vary according to the stimulus. Allergen-induced bronchoconstriction results from the IgE-dependent release from airway mast cells of mediators, including histamine, prostaglandins, and leukotrienes, that contract the smooth muscle.26 Acute airflow limitation may also occur because airways in asthma are hyperresponsive to a wide variety of stimuli. In this case, the mechanisms for causing bronchoconstriction consist in combinations of release of mediators from inflammatory cells and stimulation of local and central neural reflexes. Finally, airflow limitation results from edematous swelling of the airway wall with or without smooth-muscle contraction. The increase in microvascular permeability and leakage leads to the mucosal thickening and swelling of the airway outside the smooth muscle.

Progressive airway narrowing due to airway inflammation and/or increased bronchiolar smooth-muscle tone is the hallmark of an asthma attack, and leads to increased flow resistance, pulmonary hyperinflation, and ventilation/perfusion (V/Q) mismatching. Without correction of the airway obstruction, respiratory failure is a consequence of increased work of breathing, gas exchange inefficiency, and respiratory muscle exhaustion.

Lung Mechanics and Cardiopulmonary Interactions Associated With Airflow Obstruction

Airflow obstruction is the most important physiologic disturbance in AA. It inhibits airflow during both inspiration and expiration and can be quantitated by simple pulmonary function testing such as the PEFR and FEV1. When expiratory airflow obstruction is sufficiently severe relative to minute ventilation to prevent return of alveolar pressure to atmospheric, dynamic hyperinflation is present. The magnitude of hyperinflation can be assessed by the degree of increase in functional residual capacity and residual volume. This phenomenon may also be apparent when the thorax is imaged, typically as large lung volumes and flattened diaphragms seen on the chest radiograph. If passive expiration is incomplete,
the end-expiratory recoil pressure of the respiratory system results in a positive end-expiratory alveolar pressure. This pressure is termed intrinsic or auto-positive end-expiratory pressure (PEEPi) analogous to positive end-expiratory pressure (PEEP) set by the ventilator-dependent patients. While the level of PEEPi correlates to the magnitude of hyperinflation, it is also influenced by the compliance of the respiratory system and hence can be increased by active expiratory muscle contraction, and increased elastic lung recoil.

Dynamic hyperinflation, particularly coupled to increased respiratory muscle activity, may profoundly affect cardiovascular performance. Thus, lung hyperinflation increases afterload on the right ventricle by increasing the length of pulmonary vessels and by direct compressive effects. With extreme inspiratory and expiratory muscle effort, typical of the patient with respiratory distress related to AA, large swings in pleural pressure result. During forced expiration, increases in intrathoracic pressure diminish venous return and right ventricular filling. During vigorous inspiratory efforts against obstructed airways, venous return and right ventricular filling increase, and this increase may be so pronounced that the intraventricular septum may shift toward the right ventricle, creating a conformational change of the left ventricle that functionally results in diastolic dysfunction of left ventricular filling. Large negative pleural pressure swings may also impair left ventricular function by increasing afterload. The aggregate effect of these cyclical respiratory events is to accentuate inspiratory increases in stroke volume and expiratory decreases in stroke volume. This can be measured as an increase in the pulsus paradoxus (PP), the difference between the maximal and minimal systolic arterial BP during the respiratory cycle. Finally, if the surrounding pressure of the heart continues to rise with progressive hyperinflation, there can also be mechanical compression of the heart and coronary vessels that can lead to myocardial ischemia and deterioration in cardiac function.

Gas Exchange

Mild-to-moderate hypoxemia, along with hypocapnia and respiratory alkalosis, are common arterial blood gas (ABG) findings in severe AA (Fig 1). If airflow obstruction is severe and unrelied, there may be progression to hypercapnia and metabolic acidosis, the former as a result of muscle fatigue and inability to maintain adequate alveolar ventilation, and the latter a result of lactate production by the respiratory muscles exceeding clearance mechanisms. Analysis of blood gases in three published reports showed that only 13% of patients had PaCO₂ between 45 mm Hg and 60 mm Hg and 4% had values > 60 mm Hg. Studies of patients with respiratory failure secondary to acute severe asthma using multiple inert gas-elimination techniques have shown that bimodality of V/Q distributions with little shunt is a characteristic feature of their gas exchange; these studies demonstrated a substantial fraction of perfusion is associated with areas of lung with low V/Q ratio. Thus, regional V/Q inequality is the most important mechanism of hypoxemia. Carbon dioxide retention during AA also can be associated with V/Q inequality and alveolar hypoventilation due to respiratory muscle weakness and fatigue. Despite the amplitude and severity of V/Q mismatch, intrapulmonary shunt is marginal even in the most severe conditions. This may reflect three pathophysiologic factors: (1) airway occlusion is not complete, (2) collateral ventilation preserves ventilation in distal alveolar units, and (3) hypoxic pulmonary vasoconstriction minimizes the extent of V/Q mismatch and therefore, hypoxemia. These observations carry an important implication for management, since V/Q mismatch is the predominant gas exchange abnormality: patients with even severe asthma can be readily oxygenated with supplemental oxygen at concentrations of 28 to 32%. When patients with AA appear refractory to supplemental oxygen, other abnormalities such as pneumonia should be sought. Multiple mediators are implicated in the V/Q mismatch. Recently, platelet-activating factor has been postulated as a cause that could disturb pulmonary gas exchange.

When patients become asymptomatic, FEV₁ tends to be at least 40 to 50% of predicted; when physical signs disappear, FEV₁ is typically 60 to 70% of predicted or higher. Because pulmonary function
and ABGs assess two different pathophysiologic mechanisms, it is not surprising that correlations between $FEV_1$ and $PaCO_2$ or $PaO_2$ are poor. The observation that signs and symptoms of AA may resolve and spirometric measures may improve significantly while hypoxemia persists is consistent with the notion that bronchodilator therapy achieves early relief of bronchospasm of large central airways, while small airway inflammation persist with associated $V/Q$ mismatching and hypoxemia. Finally, the combination of acute hypercapnia and high intrathoracic pressures in the patient with severe AA can produce a significant rise in intracranial pressure. Thus, there are several published clinical reports of patients who showed neurologic signs such as unilateral or bilateral mydriasis and quadriplegia during an acute episode, and subarachnoid and subconjunctival hemorrhages have been described as well.

**Asthma Attack Evolution**

There are two different pathogenic scenarios involved in the asthma attack progression. When airway inflammation is predominant, patients show a progressive (over many hours, days, or even weeks) clinical and functional deterioration (type 1 or slow-onset acute asthma). Data from different cohort studies showed that the prevalence of this type of asthma progression is between 80% and 90% of adults with AA who presented to an ED (Table 1). Upper respiratory tract infections were frequent triggers, and these patients exhibited a slow therapeutic response. Also, they may have allergic inflammation with eosinophils in the airways. In the less common asthma progression scenario, bronchospasm is predominant and patients presenting with a sudden-onset asthma attack (type 2 or asphyxic or hyperacute asthma) characterized by rapid development of airway obstruction (< 3 to 6 h after the onset of the attack). Respiratory allergens, exercise, and psychosocial stress are the most frequent triggers. Surprisingly, these patients show a more rapid and complete response to treatment. Finally, they have a predominance of neutrophils in their airways.

### Table 1—Main Characteristics of Patients With AA With Sudden or Slow Evolution

<table>
<thead>
<tr>
<th>Slow-onset AA</th>
<th>Sudden-onset, asphyxic, brittle, or hyperacute asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive deterioration: $&gt; 6$ h (usually days or weeks)</td>
<td>Rapid deterioration: $&lt; 6$ h</td>
</tr>
<tr>
<td>50 to 90% patients who presented to an ED</td>
<td>10 to 20% patients who presented to an ED</td>
</tr>
<tr>
<td>Female predominance</td>
<td>Male predominance</td>
</tr>
<tr>
<td>More likely to be triggered by upper respiratory tract infections</td>
<td>More likely to be triggered by respiratory allergens, exercise and psychosocial stress</td>
</tr>
<tr>
<td>Less severe obstruction at presentation</td>
<td>More severe obstruction at presentation</td>
</tr>
<tr>
<td>Slow response to treatment and higher hospital admissions</td>
<td>Rapid response to treatment and lower hospital admissions</td>
</tr>
<tr>
<td>Airflow inflammation mechanism</td>
<td>Bronchospastic mechanism of deterioration</td>
</tr>
</tbody>
</table>

### Fatal Asthma

In many countries, asthma mortality increased from the 1960s to the second half of the 1980s, but reached a plateau and has subsequently declined. This recent downward trend may reflect better management of this condition in primary care. Asthma has a low mortality rate compared with other lung diseases, but mortality does occur, typically in patients with poorly controlled disease whose condition gradually deteriorates over a period of days or even weeks before the fatal attack. Occurrence of this type of asthma progression is between 60% and 90% of adults with AA who have fatal and near-fatal crises. This observation suggests that patients have a window of opportunity for recognition and reversal of this period of deterioration. Infrequently, death occurs suddenly. Accordingly, most deaths are preventable, and a useful practice is to assume that every exacerbation is potentially fatal.

The majority of deaths occur at home, work, or during transport to the hospital. The most specific marker associated with an increased risk of dying from asthma is a history of repeated hospital admissions, particularly if patients required ventilatory assistance. Nevertheless, a history of recurrent admissions is found in only 36% of fatal cases and ventilatory assistance or admission to an ICU in only 6%. Although the presence of such events is extremely important in a given patient, their absence is of no value in assessing risk. It has been reported that a subgroup of patients with near-fatal asthma have blunted perception of dyspnea, and show more ED visits, hospitalizations, near-fatal asthma attacks, and deaths. Additional epidemiologic fatal-asthma markers include psychiatric illness, illicit drug use, and the lack of an asthma self-management plan. Also, anxiety and depression are related to the outcome of ED treatment.

Two hypotheses have been postulated for the cause of asthma-related deaths. Cardiac arrhythmias may contribute to some of the observed mortality,
particularly in adults. The risk is theoretically increased by hypokalemia and prolongation of the QTc interval coupled to the use of β-agonists in high doses. However, in a series of patients with near-fatal attacks, few arrhythmias other than sinus tachycardias and bradycardias were found. While some have claimed that this mechanism of death is supported by literature that points to an association between more β-agonist use and mortality, this association could be explained on the basis of more severe asthma requiring more treatment and exhibiting a higher death rate despite treatment, not because of it. A more likely hypothesis is that deaths occur as a result of asphyxia due to severe limitation of airflow and hypoxemia. This hypothesis has received support from the pathologic evidence indicating that patients with fatal asthma almost invariably have extensive airway obstruction, with mucous plugging and dynamic hyperinflation apparent even at autopsy. Data suggest it is very uncommon to die without substantial luminal obstruction. Smooth-muscle contraction and production of inflammatory mucus exudates are important mechanisms for fatal attacks in young and old individuals with asthma.

**ERGENCY DEPARTMENT MANAGEMENT**

**Assessment**

AA is a medical emergency that must be diagnosed and treated urgently. The assessment of an asthma exacerbation constitutes a process with two different dimensions: (1) a static assessment to determine the severity of attack, and (2) a dynamic assessment to evaluate the response to treatment. Overall, it requires an analysis of several factors.

**Medical History:** A brief history pertinent to any exacerbation should be obtained. The objectives are to determine time of onset and severity of symptoms, especially compared with previous exacerbations, all current medications, prior hospitalizations and ED visits, prior episodes of respiratory failure (intubation, mechanical ventilation), and psychiatric or psychological disorder. The existence of such events has been associated with poor outcomes, but their absence does not ensure low risk.

A number of conditions may mimic or complicate the diagnosis of AA. The absence of a history of asthma, particularly in an adult, should alert the ED physician to an alternative diagnosis. Congestive heart failure, particularly predominant left ventricular failure or mitral stenosis, occasionally may present with episodic shortness of breath accompanied by wheezing. Perhaps the most common and most difficult diagnostic problem in asthma is its differentiation from COPD. In subjects > 40 years of age, a distinction between COPD and asthma is often difficult, if not impossible. Laryngeal/tracheal/bronchial obstruction resulting from any of a number of causes may produce shortness of breath, localized wheezing, inspiratory stridor localized over the trachea, or unilateral hyperinflation noted on chest radiography, which often mimics asthma. Recurrent small pulmonary emboli may be manifested by attacks of shortness of breath and, very rarely, wheezing heard on careful auscultation. Finally, recurrent attacks of shortness of breath at rest may be due to the hyperventilation syndrome.

**Physical Examination:** Particular attention should be paid to the patient’s general appearance. Patients with the most severe conditions will be sitting upright. The use of accessory muscles has received attention as an indicator of severe obstruction, and the presence of sternocleidomastoid retractions or suprasternal retraction correlated with impairment in lung function. In consequence, accessory muscle use can be considered a useful sign of severe airflow obstruction.

Respiratory rate (RR) > 30 breaths/min, tachycardia > 120 beats/min, or PP > 12 mm Hg have been described as vital signs of acute severe asthma. However, composite data from large clinical studies demonstrated that > 50% of patients with acute severe asthma have heart rates ranging between 90 beats/min and 120 beats/min, with only 15% exceeding this value. In general, successful treatment of airflow obstruction is associated with a decrease in heart rate, although some improving patients remain tachycardic because of the chronotropic effects of bronchodilators. While distinguishing between asthma-related tachycardia and treatment-related tachycardia can be difficult, patients who note subjectively improved breathing but exhibit a fine tremor are likely receiving excessive β-agonist dosing. Specifically, older patients tend toward treatment-related tachycardia. RR range between 20 breaths/min and 30 breaths/min in > 50% of patients, and are ≥ 30 breaths/min in < 20% of patients. In severe airflow obstruction, PP is greater than the normal value of 10 mm Hg and typically > 15 mm Hg; however, only severe PP (> 25 mm Hg) was a reliable indicator of severe asthma. Additionally, PP is not easy to evaluate. It is also extremely important to emphasize that PP is dependent on patient effort, since it reflects the inspiratory and expiratory excursions of thoracic pressure resulting from active respiratory muscle contraction. When patients fail to improve and have fatigue, with decreasing respiratory effort, PP will
fall. Interpreting the falling PP in this context as improvement in airflow obstruction is a grave error. Finally, wheeze and dyspnea are present in virtually all patients with AA, and they correlated poorly with the degree of airflow limitation.96

Objective Measurement of Airflow Obstruction: The major cause of respiratory failure and fatal asthma is an underestimation of the severity of a given attack. Nevertheless, the severity of airflow obstruction cannot be accurately judged by means of symptoms and physical examination by themselves.82 The measurement of lung function provides a more objective assessment of obstruction, but does depend on good technique and adequate patient effort. On presentation, after the initial treatment, and at subsequent frequent intervals, it constitutes an integral part of the assessment of disease severity (static assessment) and the response to therapy (dynamic assessment) in any patient > 5 years of age.1,2 Measurement of airflow obstruction should be made using one of following techniques: PEFR measured with a peak flowmeter, or FEV1 determined by spirometry. Many studies83,91–96 have found satisfactory correlations between both measures among healthy and stable patients or patients with acute asthma. PEFR values tended to have more variability when pulmonary function was more impaired, and to underestimate the degree of pulmonary impairment. Even though spirometry is the “gold standard,” in most asthma patients, it is easier to measure PEFR than FEV1; PEFR measurement is common in the ED because it is inexpensive, portable, and safe. The typical asthmatic patient who presents for care to an ED will exhibit a broad range of PEFR and FEV1 values.88,97 Approximately 55% of patients will have values < 40% of normal, and one fifth will range between 40% and 60% of normal.

Pulse Oximetry: Measurement of oxygen saturation by pulse oximetry (SpO2) is necessary in all patients with AA to exclude hypoxemia; it allows monitoring of SpO2 on a continuous basis. The measure of SpO2 indicates which patients may be in respiratory failure and therefore in need of more intensive management.98 The goal of treatment should be to maintain SpO2 at ≥ 92%.99,100 However, it does not help to predict which patients can be hospitalized.101

ABGs: ABG determination is rarely necessary before the initiation of treatment. Because of the accuracy and utility of pulse oximetry, only patients whose oxygenation is not restored to > 90% with oxygen therapy require ABG determination. When adequate oxygenation remains a problem despite supplemental oxygen, additional complicating conditions such as pneumonia should be considered. Repeated ABG sampling usually is not needed to determine whether a patient is deteriorating or improving.102 In most cases, valid judgments can be based on serial physical examinations and PEFR determinations. In fact, the decision to proceed with endotracheal intubation and mechanical ventilation is a clinical assessment and should not be overly influenced or await ABG analysis.103

Chest Radiography: Chest radiography plays only a small role in the assessment and management of patients with AA. Many studies104–108 have demonstrated that the incidence of specific abnormalities on chest radiography in adults with uncomplicated AA is low, and have suggested that the information obtained is rarely helpful in ED management. On the basis of these data, chest radiographs are indicated only in patients who present with signs or symptoms of pneumothorax (pleuritic chest pain, mediastinal crunch, subcutaneous emphysema, cardiovascular instability, or asymmetric breath sounds), in patients with clinical findings suggestive of pneumonia, or in an asthmatic patient who after 6 to 12 h of intensive treatment does not respond to therapy.

Cardiac Rhythm Monitoring: ECGs need not be routinely obtained, but continual monitoring is appropriate in older patients,109 and in those with coexisting heart disease.2 The usual rhythm is sinus tachycardia, although supraventricular arrhythmias are not uncommon. Frequent transient ECG findings include right-axis deviation, clockwise rotation, and evidence of right ventricular strain. If due to asthma alone, reversal within hours of response to therapy is to be expected.

Response to Therapy: Measurement of the change in PEFR or FEV1 over time may be one of the best ways to assess patients with acute asthma and predict the need for hospital admission. The response to initial treatment in the ED is a better predictor of the need for hospitalization than is the severity of an exacerbation at presentation.110–114 Early response to treatment (PEFR or FEV1 at 30 min) is the most important predictor of outcome.114,116 PEFR variation over baseline > 50 L/min and PEF > 40% of normal, both measured at 30 min after beginning of treatment, are predictors of good outcome.115–117

In summary, symptoms and signs guide treatment decisions, but repeated measurement of PEFR or FEV1 compared to baseline joined with continuous monitoring of SpO2 is critical to evaluate the severity...
of airway obstruction, the adequacy of gas exchange, and the response to treatment (Table 2).

**Treatment**

The severity of asthma exacerbations determines the treatment. The goals of treatment may be summarized as maintenance of adequate arterial oxygen saturation with supplemental oxygen, relieve airflow obstruction with repetitive administration of rapid-acting inhaled bronchodilators (β-agonists and anticholinergics), and reduce airway inflammation and to prevent future relapses with early administration of systemic corticosteroids.

**Oxygen:** Because hypoxemia is produced by V/Q mismatch, it is usually fully corrected with modest increases in fraction of inspired oxygen (eg, 1 to 3 L/min by nasal cannula or mask). In spite of this, the use of high-flow oxygen has been assumed to be harmless and recommended to all patients with AA. Uncontrolled oxygen has been postulated to correct the effects of hypoxemia and to compensate any trend for PaO₂ to fall with β-agonist therapy. Nevertheless, there is evidence that hyperoxia may be harmful for some patients. Recently, the first randomized controlled study on the effect of administration of two oxygen concentrations (28% vs 100%) on gas exchange in AA showed that patients receiving 28% oxygen had a fall in PaCO₂; opposite, patients who received 100% oxygen showed an increase in PaCO₂, particularly those patients with PaCO₂ before oxygen treatment > 40 mm Hg (Fig 2). Hyperoxia associated with hypercarbia occurring in asthma exacerbations had been explained by the regional release of hypoxic pulmonary vasoconstriction. These data emphasize that treatment by the regional release of hypoxic pulmonary vasoconstriction in asthma exacerbations had been explained (Fig 2). Hyperoxia associated with hypercarbia occurring in asthma exacerbations had been explained by the regional release of hypoxic pulmonary vasoconstriction. 

**β-Agonists:** Specific short-acting inhaled β₂-agonists are the drugs of choice to treat AA. Their onset of action is rapid, and their side effects are well tolerated. Salbutamol (albuterol in North America), the most frequently used drug in the EDs around the world, has an onset of action of 5 min and a duration of action of 6 h. Other used drugs are metaproterenol, terbutaline, and fenoterol. Long-acting drugs cannot be recommended for emergency treatment. Levalbuterol (R-albuterol) may prove to be more efficacious and less toxic than racemic albuterol. A recent prospective, open-label, ED pilot study about patients with AA demonstrated improved FEV₁ after the third nebulization of 1.25 mg of levalbuterol vs 2.5 mg of racemic albuterol. However, further studies are required to clarify dosing, therapeutic effects, and cost-effectiveness of this drug. Finally, subcutaneous epinephrine has become up to date because of its marked cardiac side effects compared with inhaled agents, and should be reserved only when patients are not benefiting from inhaled medicines.

With regard to β-agonist use, there are four areas of debate: IV vs inhaled therapy, doses and intervals of administration, pressurized metered-dose inhalers (pMDIs) with spacer vs small-volume nebulizers, and continuous vs intermittent nebulization. The inhaled route has a faster onset, fewer adverse

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<td>Spirometry (PEFR or FEV₁)</td>
<td>Sign of severe airflow obstruction</td>
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<td>Dynamic assessment</td>
<td></td>
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<tr>
<td>Serial measurements of lung function</td>
<td>Determination of hypoxemia level (goal of treatment ≥ 92%)</td>
</tr>
<tr>
<td>(PEFR or FEV₁) each 30 min</td>
<td>Response of treatment (treatment guide and outcome prediction)</td>
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<td>Continuously SpO₂ monitoring</td>
<td>Variation from baseline (PEFR &gt; 50 L/min and &gt; 40%, at 30 min, are predictors of good outcome)</td>
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<td></td>
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effects, and is more effective than systemic routes. Although popular in some countries, available evidence does not support the use of IV \( \beta_2 \)-agonists in the treatment of patients with severe AA. Therefore, they should be considered only if the response to the inhaled drug is poor or if the patient is coughing excessively, is moribund, or becomes so despite inhalation therapy.

Doses and dosing intervals should be individualized using objective measures of airflow obstruction as guides. A substantial body of evidence supports the use of high and repeated doses. The aim of treatment is to induce maximal stimulation of \( \beta_2 \) receptors without causing significant side effects. Previous studies have shown two different patterns to inhaled cumulative doses of albuterol. Approximately two thirds of patients will be sensitive to inhaled albuterol, and optimal treatment for this group is 2.4 to 3.6 mg delivered by pMDI and spacer (four puffs each 10 min) or 5 to 7.5 mg delivered by jet nebulizer. For the remainder of patients, albuterol even in high doses has little effect. A single dose of 7.5 mg of nebulized albuterol or sequential doses of 2.5 mg of nebulized albuterol are clinically equivalent in the treatment of patients with moderate-to-severe AA; however, twice as many patients in the single-dose group experienced side effects. These findings argue against the routine use of continuous nebulization in the ED treatment of patients with AA.

More rapid and profound bronchodilatation with fewer side effects and less time in the ED can be achieved when sufficient doses of \( \beta \)-agonists are administered using pMDIs and large-volume spacers (valved spacer device) than when conventional doses are administered with a jet nebulizer. This is true particularly in patients with the most severe obstruction. Each \( \beta_2 \)-agonist treatment with a pMDI and spacer takes 1 to 2 min, as compared with 15 to 20 min for each treatment with a jet nebulizer. In our experience, the pMDI plus spacer constitutes the only way to deliver quickly high doses of bronchodilators to patients with acute severe asthma or life-threatening asthma with reduced level of consciousness.

Continuous nebulization is thought to be more beneficial than intermittent therapy; however, a recently published meta-analysis of randomized controlled trials of adults with AA found no significant differences between the two methods in terms of pulmonary function improvement or hospital admission; nevertheless, continuous nebulization was associated with lower side effects. These findings argue against the routine use of continuous nebulization in the ED treatment of patients with AA.

Finally, side effects are dose dependent and can occur with all routes of administration, but are more pronounced with oral and IV routes than with inhalational delivery methods. For selective \( \beta_2 \)-adrenergic agonists, the principal side effects are mediated via receptors on vascular smooth muscle (tachycardia and tachyarrhythmia), skeletal muscle (tremor, hypokalemia due to potassium entry into muscle cells), and cells involved in lipid and carbohydrate metabolism (increase in blood-free fatty acids, insulin,

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**Figure 2.** PaCO\(_2\) during oxygen administration as a function of PaCO\(_2\) before oxygen treatment. The variables correlated significantly in both groups \( p < 0.01 \). Patients breathing 28% oxygen had a PaCO\(_2\) fall \( \text{left panel} \); on the contrary, patients who received 100% oxygen showed an increase in PaCO\(_2\), particularly those with PaCO\(_2\) before oxygen treatment > 40 mm Hg \( \text{right panel} \). Used with permission from Rodrigo et al.
的数据来源为 Fe3。

146–148。它已被假定为可以刺激c-AMP和c-GMP的增加，从而促进转录因子的活化。

Corticosteroids inducing transcriptional effects commonly develops in patients receiving IV β-agonists. 然而，它也导致了血浆中葡萄糖和乳酸的升高。

Another unexpected effect is an increase in V/Q mismatching, leading to an increased alveolar-arterial oxygen tension difference. 这已被归因于对不同区域血管和支气管扩张的影响。

Available data about the use of high doses of β2-agonists support the concept that treatment of patients with AA with albuterol, 2.4 mg/h (four puffs at 10-min intervals by pMDI and spacer) or 2.5 mg every 20 min by nebulization, produces satisfactory bronchodilation, low serum concentration, and minimal side effects.77,78,138,139,150 在一些患者中，尤其是那些病情严重的患者，可能需要增加剂量到每个20 min每支，每20 个20 min。一个4-mL量的每灌注和6 to 8 L/min氧气流量被建议来确保一个高的气溶胶输出，小的颗粒尺寸，和短的治疗时间。

**Anticholinergics:** The rationale for the use of anticholinergic therapy is the presumption of increased airway vagal tone in patients with AA, but the role of anticholinergics has been less well defined than β-agonists. The use of inhaled ipratropium bromide (IB) as the initial bronchodilator for adults with AA consistently has been reported to be inferior to the use of β2-agonists in improving airflow. However, the simultaneous use of both classes of bronchodilators has produced contradictory results. Nevertheless, a succession of large randomized controlled trials and systematic reviews have recently clarified their utility. Overall, the existing literature suggests that inhaled anticholinergic agents provide an additional benefit to children and adults with AA who are treated with β2-agonist medications in an ED, with minimal side effects. The benefit of IB is most readily demonstrated in trials using multiple-dose protocols (high doses); after 60 to 90 min of treatment, the studies reported an important reduction in hospital admission rates (38% with low dose and 57% with high dose), significant differences in lung function exceeding half an SD in change (PEFR variation approximately 50 L/min), and a substantial reduction in costs.151–154 As a result, the addition of multiple doses of IB to β2-agonists seems indicated as first-line therapy in adult patients with severe exacerbations of asthma. Doses of four puffs (80 μg) every 10 min delivered by pMDI and large volume spacer, or 500 μg per dose every 20 min in nebulized form are quite effective.

Corticosteroids: Systemic corticosteroids should be considered in the management of all but the mildest exacerbations of asthma.1,2 Theses agents are not bronchodilators but are extremely effective in reducing airway inflammation present in virtually all asthmatics. Despite controversy about their efficacy, route of delivery, and dosage, data summarized in two systematic reviews suggest the following: (1) systemic corticosteroids probably require > 6 to 24 h to improve pulmonary function, (2) IV and oral corticosteroids appear to have equivalent effects in most patients with AA, and (3) while precise dose-response relationships are not well described, there is a tendency toward greater and more rapid improvement in pulmonary function with medium and high doses, although these effects likely plateau without additional benefit at very high dosing; 800 mg of hydrocortisone or 160 mg of methylprednisolone in four divided doses per day are generally adequate for most patients. The time delay observed between administration and improvement in lung function is consistent with belief that the beneficial effect of corticosteroids result from gene transcription and new protein synthesis (Table 3). Opposed, there is evidence157 that suggests that inhaled corticosteroids can present early therapeutic effects (< 3 h). This rapid response suggests a topical effect (airway mucosa vasoconstriction).158 Locally applied

### Table 3—Effects of Corticosteroids in Acute Asthma

<table>
<thead>
<tr>
<th>Variables</th>
<th>Systemic Corticosteroids</th>
<th>Inhaled Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect</td>
<td>Anti-inflammatory</td>
<td>Topical</td>
</tr>
<tr>
<td>Time delay</td>
<td>Late improvement in outcomes (&gt; 6 h)</td>
<td>Early improvement in outcomes (&lt; 3 h)</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Corticosteroids induce transcriptional effects → synthesis of new proteins</td>
<td>Corticosteroids up-regulating postsynaptic adrenergic receptors → airway mucosa vasoconstriction → decrease airway mucosal blood flow → mucosal desegestion</td>
</tr>
</tbody>
</table>

*Data taken from Felez et al.19, Acuña et al.20 Rodrigo and Rodrigo,157 McFadden,158 and Kumar et al.179*
corticosteroids act by potentiating the adrenergic physiologic effect by up-regulating postsynaptic receptors. Thus, adjusting the dosing interval between inhaled corticosteroids and β-agonists accordingly may be of clinical significance. A recent meta-analysis concluded that inhaled CCS compared with placebo reduced hospital admission rates in patients with AA, but it is unclear if there is a benefit of inhaled corticosteroids when used in comparison or in addition to systemic corticosteroids. Also, data suggest a therapeutic benefit from addition of flunisolide to albuterol and IB administered in high doses, particularly in patients with most severe asthma.

The benefit of therapy, however, with systemic corticosteroids for reducing the number of relapses in patients following an acute attack is conclusive. Hence, oral corticosteroids in a dose equivalent of 40 to 60 mg prednisone or prednisolone per day during a period of 7 to 14 days is effective, cheap, and safe. However, there is some evidence that high-dose inhaled corticosteroid therapy alone may be as effective as oral corticosteroids when used in patients with mild asthma on ED discharge.

Theophylline: As monotherapy, theophylline is inferior to β2-agonists in the ED treatment of AA, and the addition of IV aminophylline to inhaled β2-agonists does not confer significant benefit but does increase the incidence of complicating tremor, nausea, anxiety, and tachyarrhythmia. These observations have resulted in consensus statements and guidelines that do not recommended the routine use of theophylline in the treatment of AA. The use of teophylline/aminophylline should be reserved only for those patients not responding to standard therapy. In these circumstances, a loading dose of 6 mg/kg over 30 min followed by an infusion of 0.5 mg/kg/h with measured of theophylline blood levels is recommended (8 to 12 μg/mL). In patients already receiving theophylline on presentation to the ED, a serum level should be measured and appropriate dosing continued if deemed necessary.

Magnesium Sulfate: The use of magnesium for the treatment of AA was first reported in 1936 by Uruguayan physicians. One suggested mechanism of action is that by inhibiting smooth-muscle cell calcium channels magnesium blocks muscle contraction. In general, this drug is safe and inexpensive in the usual clinical dose of 1.2 to 2 g IV over 20 min. However, three meta-analysis of trials assessing the magnesium administration for AA do not support routine use. Inhaled magnesium preparations have also been evaluated but show no, or clinically insignificant, effects. Finally, a new and large multicenter study demonstrated that IV magnesium sulfate only improves pulmonary function when administered as an adjunct to standard therapy (nebulized β2-agonists and IV corticosteroids) in a very select subgroup of patients (FEV1 < 20% of predicted). However, the standard therapy used is a critical limitation of this study. Thus, the magnitude of the response to magnesium could differ if additional interventions (eg, inhaled IB) were used.

Heliox: Under most breathing conditions, airflow in humans is largely laminar; at high gas velocities and with severe airway narrowing, increasingly turbulent airflow may occur. Turbulence has two complications in the context of AA: (1) the airway resistance for any given degree of anatomic obstruction will be greater, leading to a greater work of breathing and the potential for more dynamic hyperinflation; and (2) turbulence makes the delivery of aerosolized particles to the lower airways more difficult, since gas streams impacting on airway walls can result in droplet deposition above the intended site of delivery. Turbulent airflow can be reduced by the application of gases with a lower density and higher viscosity than air. Heliox (helium and oxygen) is such a gas mixture and is available for administration to patients with AA. The benefits of heliox are lost when large amounts of supplemental oxygen are introduced into the heliox breathing circuit; concentrations of helium much below 70% are not likely to confer significant benefit. Fortunately, most patients with AA do not require large amounts of supplemental oxygen to maintain adequate SpO2 (≥ 92%). Additionally, research using heliox mixtures has demonstrated a greater percentage of lung particle retention and a large delivery of albuterol from both pMDIs and jet nebulizers. This suggests that one of the beneficial effects of heliox use may include improved deposition of aerosolized bronchodilators.

Studies have shown that heliox administered to patients with severe airflow obstruction can reduce both inspiratory and expiratory airway resistance as judged by a decrease in the PP and increase in the PEFR independent of the action of bronchodilators. One recent study has shown that the effects of β-agonist delivered by jet nebulizer to patients with severe AA in the ED can be enhanced by inhalation through a heliox delivery system guaranteeing a high concentration of helium in the inhaled gas. However, data from a recent meta-analysis suggest that the addition of heliox to standard medical care during the course of AA is not more effective, in terms of pulmonary function, than a comparison delivery with air or oxygen. The analysis from the studies that used heliox to deliver nebulized therapy showed a trend...
toward an increase in pulmonary function, suggesting that heliox could be more effective than oxygen/air in delivering inhaled particles of β-agonists to the distal airways. The authors concluded that, at the present time, there is a lack of evidence to support the role of heliox in the initial treatment of adult patients with AA.

**Leukotriene Antagonists:** There is some evidence\(^{184,185}\) to suggest that leukotriene modifiers, often used in the management of chronic asthma, may have a role in the treatment of AA as well. A study\(^{186}\) of two doses of oral zafirlukast (20 mg and 160 mg) in the ED demonstrated an improved in pulmonary function and dyspnea score. Also, a rapid but small improvement in FEV\(_1\) with IV montelukast derived from routine therapy.\(^{188}\) However, additional studies are necessary to determine if these agents offer a significant benefit over and above that derived from routine therapy.\(^{188}\)

**Other Therapies:** It is well established that viral respiratory infections can exacerbate asthma.\(^{159,190}\) Common cold viruses such rhinoviruses are the principal triggers of wheezing in older children and adults.\(^{191}\) They may exacerbate asthma through various mechanisms. Viral infections may cause epithelial damage and airway inflammation, and they may be responsible to the formation and release of allergic mediators from lung cells. Also, evidence demonstrates associations between bacterial infections, particularly with *Chlamydia pneumoniae*, and exacerbations of asthma.\(^{192}\) Therefore, in the majority of cases antibiotics are not required.\(^{193–196}\) However, antibiotics are often prescribed in AA because of an increase in sputum volume or purulence. Sputum that looks purulent may contain an abundance of eosinophils and not polymorphonuclear leukocytes, and thus reflect the type of airway inflammation typical of AA in the absence of infection. Antibiotics are indicated for patients with fever and sputum containing polymorphonuclear leukocytes, clinical findings of pneumonia, or acute sinusitis.

Other agents have been suggested to be of benefit for AA therapy, including inhaled general anesthetics,\(^{197,198}\) lidocaine,\(^{199}\) and inhaled furosemide\(^{200,201}\); however, there are inadequate data to support these therapies as anything other than experimental. Inhaled mucolytic drugs have not been shown to benefit treatment of exacerbations, and they may worsen cough or airway obstruction.\(^{202}\) Finally, sedation should be strictly avoided during AA because of the respiratory depressant effect of these drugs. Studies\(^{203,204}\) have shown an association between their use and avoidable asthma deaths.

In summary, initial ED treatment of patients with AA should be titrated to the severity of presentation and the response to initial treatment (Table 4). Supplemental oxygen is recommended for the majority of patients. The goal of treatment should be to maintain SpO\(_2\) at \(\geq 92\%\). Inhaled β\(_2\)-agonists and corticosteroids are the core treatments for almost all patients. The addition of IB to β\(_2\)-agonists seems indicated as first-line therapy in adult patients with severe exacerbations; pMDIs with large-volume valved spacers are preferred to jet nebulizers, particularly in patients with the most severe obstruction. Inhaled corticosteroids could produce early therapeutic effects in patients with prolonged duration of symptoms before ED presentation.

**Discharge or Hospitalization**

Spirometry and clinical assessment are used to establish disposition decisions. “The patient should be hospitalized if, despite 2 to 3 hours of intensive treatment in the ED he or she still has significant wheezing, accessory muscle use, permanent requirement for oxygen to maintain SpO\(_2\) \(\geq 92\%\), and a persistent reduction in lung function (FEV\(_1\) or PEF \(\leq 40\%\) of predicted), in much the same way that the presence of factors indicating high risk of asthma-related death (inadequate access to medical care and medications, difficult home conditions, and difficult-to-obtain transport to hospital in the event of further deterioration) would lead to a decision to hospitalize

Table 4—Recommendations for Initial 1 = h ED Treatment for AA

<table>
<thead>
<tr>
<th>FEV(_1) or PEFR &gt; 50%</th>
<th>FEV(_1) or PEFR &lt; 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low flow (1 to 3 L/min) O(_2) through nasal catheter or low concentration mask to achieve SpO(_2) (\geq 92%)</td>
<td>Low-flow (1 to 3 L/min) O(_2) through nasal catheter or low concentration mask to achieve SpO(_2) (\geq 92%)</td>
</tr>
<tr>
<td>Inhaled β(_2)-agonists: albuterol four puffs (400 μg) every 10 min via pMDI and spacer or 2.5 mg in 4 mL saline solution nebulized with O(_2) (6 to 8 L/min) each 20 min</td>
<td>Inhaled β(_2)-agonists + anticholinergics; albuterol + ipratropium bromide four puffs (400 μg and 80 μg) every 10 min via pMDI and spacer</td>
</tr>
<tr>
<td>Anticholinergics for patients with poor initial response</td>
<td>High doses of inhaled corticosteroids?</td>
</tr>
<tr>
<td>Systemic corticosteroids if no immediate response to bronchodilators</td>
<td>Systemic corticosteroids: IV hydrocortisone 200 mg or methylprednisolone 40 mg q6h</td>
</tr>
</tbody>
</table>

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CHEST / 125 / 3 / MARCH, 2004

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the patient. However, if a patient is free of symptoms, and has lung functions (FEV₁ or PEFR) ≥ 60 of predicted, the patient can be discharged unless other mitigating circumstances exist. Finally, patients with posttreatment lung function between these two extremes (40 to 60% of normal) require continued treatment. These patients can potentially be discharged, assuming adequate follow-up is available and compliance ensured. In general, 3 to 4 h in the ED is adequate time to determine if patients with AA can improve for safe discharge from the ED. Accordingly, a recent study demonstrated that after discharge, short-term relapse is uncommon among patients with asthma, suggesting that strict pulmonary function cutoffs may be unnecessary if risk factors are considered. In all cases, observation for a minimum of 30 min after the last dose of a β-agonist is recommended to ensure stability before discharge. Under most circumstance, a decision concerning final disposition of the patient can be made in 3 to 4 h, avoiding excessive time in the ED. Most patients discharged to home should be placed on at least a 7- to 14-day course of prednisone while contact is made with the next tier of care providers. β-agonist use should be able to be decreased over this time; if increasing use of “rescue” β-agonist use is undertaken, the patient should return immediately to the ED or to primary care provider. Patients receiving long-term corticosteroid treatment should resume corticosteroids upon discharge from the ED.

Admission to the ICU

Patients with findings of severe airflow obstruction who improve minimally or deteriorate despite therapy should be admitted to an ICU. Clinical markers for this include respiratory distress, high PP or a falling pulsus in a patient with fatigue, or the patient’s subjective sense of impending respiratory failure. Other indications for ICU admission include respiratory arrest, altered mental status, Spo₂ < 90% despite supplemental oxygen, and a rising PaCO₂ coupled to clinical evidence of nonresolution. While noninvasive positive pressure ventilation (NIPPV) has revolutionized the management of patients with diverse forms of respiratory failure, the published experience with patients with AA is not large. In one study of feasibility, continuous positive airway pressure (CPAP) at a level of approximately 12 cm H₂O was administered to asthmatic subjects in whom bronchospasm was induced by aerosolized histamine. Under these controlled circumstances, CPAP was demonstrated to raise residual decrease intrathoracic pressure swings associated with tidal breathing and diminish the inspiratory work. This potentially beneficial effect of positive pressure in spontaneously breathing asthmatics was thought to result from a reduction in the increased work of breathing associated with initiation of inspiratory flow under conditions of dynamic hyperinflation, eg, a reduction in inspiratory threshold load.

NIPPV has been used in patients with AA, and small series have been published describing this approach. Meduri and colleagues reported 17 episodes of NIPPV use in asthma. NIPPV was associated with a reduction in PaCO₂ and improvement in dyspnea over the early hours of use. Two patients required intubation, and no complications related to NIPPV were noted. In a retrospective analysis of their experience with AA, Fernandez and colleagues offered a view of the role of NIPPV vis-à-vis other therapies. Of 58 patients with AA admitted to their ICU over a 7-year period, 38% were placed on NIPPV. Three of the patients placed on NIPPV ultimately required intubation. Again, patients treated successfully with NIPPV demonstrated significant reductions in PaCO₂ early in their course. Soroksky et al. in a prospective, randomized, placebo-controlled study, compared 15 patients with AA who received NIPPV plus conventional therapy vs conventional therapy alone. The use of NIPPV significantly improved lung function and decreased hospitalization rate. A course of NIPPV seems warranted in patients at
risk for evolution of respiratory failure or as an alternative to intubation. Based on experience with this modality of treatment for other forms of respiratory failure, early use when the patient is first identified as at high risk, including the ED, is appropriate. Successful use of NIPPV depends on patient education and coordination with the breathing circuit, things that are more easily achieved when the patient is not in extremis. Uncooperative and obtunded patients can rarely if ever be stabilized with NIPPV and are at risk for complications such as aspiration. Patients should be given a well-fitting mask and initially instructed to hold it to their face before securing it with straps to provide for brief accommodation. Initial ventilator settings should be an expiratory positive airway pressure, CPAP, or PEEP of approximately 5 cm H2O and inspiratory pressure (or pressure support) of approximately 8 cm H2O. If the patient has difficulty during inspiration triggering breaths, expiratory positive airway pressure can be gradually increased. If tidal volumes (Vt) are shallow (< 7 mL/kg), inspiratory pressure can be increased. Rarely will patients tolerate total pressures > 15 to 20 cm H2O without mask leaks or a sense of claustrophobia or mask discomfort. When improvement is dramatic and has persisted for hours, episodic removal of the mask or reduction in support pressures can be attempted. If patients do not clearly improve or appear to be of marginal status with NIPPV, it should be appreciated that removal of NIPPV may precipitate rapid deterioration and all means for intubation should be readily available and personnel available to proceed to this next level of treatment. Noninvasive ventilation merits further study in patients with AA, and some consensus panels have suggested that its widespread application in patients with asthma awaits such trials.211

Intubation and Postintubation Stabilization

When patients deteriorate despite pharmacologic intervention with or without NIPPV, intubation should be performed electively. Intubation may be performed awake or with rapid induction. In general, nasal intubation should be avoided because of the higher incidence of sinusitis in asthmatics and the possible presence of nasal polyps. Intubation should be accomplished with the largest possible endotracheal tube for two reasons. Since the tube represents a resistance in series with the obstructed airways, dynamic hyperinflation tends to worsen after intubation and this can be avoided to some extent by selecting a larger tube. Also, it is common for patients intubated for AA to mobilize large mucous plugs during recovery, which has a greater potential for causing acute obstruction in small endotracheal tubes.

Mechanical ventilation follows cardiorespiratory collapse in approximately 20% of episodes.103 Causative factors are pulmonary hyperinflation, hypovolemia, and sedation. In the postintubation period, dangerous levels of pulmonary hyperinflation can develop if patients are “bagged” excessively in a misguided attempt to stabilize or resuscitate. With severe airflow obstruction, even delivery of a normal minute ventilation may cause substantial gas trapping that reduces venous return and hence cardiac output. In the same patients, hypovolemia related to previous dehydration, sedation, and muscle relaxation all act to decrease mean systemic vascular pressure, further decreasing venous return to the heart.212 This pathophysiology can be demonstrated by slowly bagging (2 to 3 breaths/min) the patient while delivering 100% oxygen to avoid hypoxemia. If hypotension is thought to be present during mechanical ventilation, a brief (60 to 90 s) discontinuation from the ventilator (apnea test) is useful.213 Vigorous volume challenge should follow in patients hypovolemic from increased insensible water losses and decreased oral intake, along with strategies to minimize lung hyperinflation. If the patient does not improve with slow manual bagging, consideration should be given to a possible tension pneumothorax, and chest radiography should be performed immediately if time permits. If the more common hyperinflation is the cause of hypotension, the patient should be slowly bagged, intravascular volume administered (1 to 2 L or more is often required) and sedatives given to synchronize of the patient with the ventilator.

Use of Sedatives and Neuromuscular Blockers

The use of sedatives will be discussed in advance of ventilator settings, since the need for settings to achieve hypoventilation tend not to be tolerated by the awake and alert patient. Because of the complications associated with paralytics in patients with asthma undergoing mechanical ventilation, the clinician should at all times attempt to maintain the patient with sedatives alone (Table 5).

In the peri-intubation period, sedative agents with rapid onset are recommended to allow an early transition from postintubation hand ventilation to the ventilator. Midazolam is the preferred benzodiazepine, with an onset of action within a minute or two that permits repeated dosing as required. Ketamine, like the benzodiazepines and propofol, can be used for intubation and then administered longer term by infusion for ongoing sedation of the asth-
matic patient receiving mechanical ventilation. Because ketamine increases heart rate and BP and frequently causes delirium in adults, its use is greater in the management of asthma in children. Propofol is an excellent choice for sedation, but in an asthmatic may require concurrent administration of other drugs to achieve adequate sedation. Since even intubation alone, absent other invasive procedures, is painful, virtually all patients will require concurrent administration of an opiate such as morphine sulfate or fentanyl. Fentanyl is to be preferred when near-immediate effect is desired.

Paralytics were often administered to facilitate synchronization of the asthmatic with the mechanical ventilator, to avoid excessive hyperinflation, to facilitate permissive hypercapnea, and to decrease respiratory muscle activity. However, numerous studies have indicated an unacceptable incidence of post-paralytic myopathy in patients with asthma who have respiratory failure. In most cases, the myopathy is reversible but may take weeks to resolve. It is likely that the combination of high-dose corticosteroids and paralytics employed in these patients interact to cause muscle weakness, but the relative contributions of each class of drugs is not clear. For these reasons, we strongly advocate avoidance of neuromuscular blockers in patients with asthma. Often, these agents can be avoided if multiple sedatives and analgesics are administered. When large doses of sedatives are used, a protocol mandating daily cessation of the continuous infusion of drugs has been associated with avoidance of drug accumulation and decreased duration of mechanical ventilation. The preferred paralytic depolarizing agents are pancuronium, vecuronium, and cis-athracurium. In patients with AA, cis-athracurium is the better choice because it is eliminated by esterase degradation and spontaneous breakdown in the serum. Paralytic drugs may be administered intermittently by bolus injection or by continuous IV infusion. If a continuous infusion is used, a bedside nerve stimulator should be available or the drug should be withheld every 4 to 6 h to avoid drug accumulation and prolonged paralysis. Muscle paralysis should be provided only on an as-needed basis and only to unconscious patients.

Management of the Intubated Patient Receiving Mechanical Ventilation

The aim of mechanical ventilation is to maintain adequate oxygenation and prevent respiratory arrest without circulatory compromise or lung injury until response to bronchodilators permit ventilatory assistance to be withdrawn. A strategy of mechanical ventilation that aims to reduce dynamic hyperinflation will result in the best outcomes. Lung hyperinflation is minimized by allowing an adequate time to exhale alveolar gas and by ongoing treatment of expiratory airflow obstruction. Expiratory time can be prolonged by decreasing minute ventilation (by either changes in RR or V\textsubscript{T}) or by decreasing inspiratory time (by increasing inspiratory flow rate and using a square flow waveform). In clinical practice, both strategies are used, but it should be pointed out that minute ventilation is usually a more important determinant of expiratory time than is inspiratory time, and that the benefits from increasing inspiratory flow decrease as minute ventilation decreases. In general, a low inspiratory/expiratory ratio is desirable because it suggests a ventilator strategy is in place that prolongs exhalation time.

The details of lung mechanics encountered during mechanical ventilation of adults with severe AA were reported in studies performed more than a decade ago. These investigators demonstrated that for an average-sized adult, an initial minute ventilation between 6 L/min to 8 L/min (achieved by a V\textsubscript{T} between 5 mL/kg and 7 mL/kg, and a RR between 11 breaths/min and 14 breaths/min), combined with

| Table 5—Sedatives Used in Status Asthmaticus |
|---|---|---|
| Agents | Dose | Cautions |
| **Peri-intubation period** | | |
| Midazolam | 1 mg IV slow push, repeat every 2 to 3 min as needed | Hypotension |
| Ketamine | 1 to 2 mg/kg IV at a rate of 0.5 mg/kg/min | Respiratory depression |
| Propofol | 60 to 80 mg/min up to 2.0 mg/kg | Sympathomimetic effects |
| **Sedation for protracted mechanical ventilation** | | |
| Lorazepam | 1 to 5 mg/h IV continuous infusion or IV bolus as needed | Drug accumulation |
| Morphine sulfate | 1 to 5 mg/h IV continuous infusion; avoid bolus | Ileus |
| Ketamine | 3 μg/kg/min IV to start | Sympathomimetic effects |
| Propofol | 1.5 μg/kg/h IV to start titrate to desired level of sedation | Delirium type reactions |
| | | Lactic acidosis |
| | | Hypertriglyceridemia |
an inspiratory flow rate of 70 to 100 L/min is unlikely to result in a dangerous degree of lung hyperinflation. However, some measure of lung hyperinflation is needed to ensure that these settings are indeed safe. Williams and colleagues demonstrated that the volume of gas released during a period of prolonged apnea (lung volume at end-inspiration above functional residual capacity) is the best discriminator for the occurrence of dynamic hyperinflation. However, this measure is technically complex, and it is not widely used. Reasonable surrogates are the level of PEEPi and the end-inspiratory plateau airway pressure. These pressures may not correlate well to gas-trapped volume because of varying mechanical properties of the chest wall or because of lung regions that do not communicate with the central airways. Nonetheless, a reasonable bedside target would be to maintain end-inspiratory pressures \(< 35 \text{ cm H}_2\text{O and PEEPi } < 15 \text{ cm H}_2\text{O}.\)

As RRs and Vt's are reduced to achieve target levels of lung volume at end-inspiration above functional residual capacity, PEEPi, or plateau pressure, hypoventilation with hypercapnea may occur. It is worth noting, however, that decreasing minute ventilation does not always increase PaCO\(_2\) since decreasing hyperinflation may decrease the dead space/VT ratio by improving perfusion to ventilated lung units. It is the product of minute ventilation and \((1 – \text{dead space/VT ratio})\) that sets alveolar ventilation; so that if alveolar ventilation increases with a drop in minute ventilation, PaCO\(_2\) may actually fall assuming constant CO\(_2\) production. Yet, in many patients, hypoventilation will be required to achieve the targets of minimal hyperinflation. This appears to be well tolerated in patients with AA as long as PaCO\(_2\) does not exceed 90 mm Hg and acute increases in PaCO\(_2\) are avoided. Low values of arterial pH also appear to be well tolerated by most patients. Acute hypercapnea should be avoided if possible in pregnancy and in patients with elevated intracranial pressure, since it may reduce uterine blood flow and precipitate fetal distress and may increase cerebral blood flow and further elevate intracranial pressure.

When the PEEPi and plateau airway pressure goals cited above are achieved, peak airway pressure is largely irrelevant and is often well above the usual set alarm limits. The mode selected during ventilator support is not extremely important since the goal is to control RR, kept at a low rate by the use of generous sedation. Assist-control ventilation is perhaps least useful for these patients, since there may be a greater tendency for a greater degree of hyperinflation. External PEEP applied through the ventilator circuit should not be used, since it may result in further hyperinflation. Ventilator mode is irrelevant during this early phase of mechanical ventilation of the asthmatic with respiratory failure, since the goal is controlled ventilation with low RRs.

**Adjunctive Therapies During Mechanical Ventilation**

Rarely, the above strategies do not allow for adequate ventilation at a safe level of dynamic hyperinflation, and consideration should be given to the use of other therapies. Inhaled general anesthetics have been used for many years in the treatment of the asthmatic receiving mechanical ventilation, but require expertise in their administration and have never been subjected to careful controlled study for this application. Both halothane and enflurane are bronchodilators that can acutely reduce peak inspiratory pressure and PaCO\(_2\), but effects do not last after drugs are stopped. Heliox may be administered during mechanical ventilatory support. Heliox can be used even in severe asthma requiring supplemental oxygen since the alveolar-arterial gradient improves during heliox administration, likely related to improved V/Q matching. This is important since the benefits of low-density gas inhalation are lost rapidly when the concentration of helium is \(< 70 \text{ to } 80\%\). Many practical problems arise with the use of heliox during mechanical ventilatory support. The flow meters on the ventilator that measure Vt are gas-density dependent and will underestimate Vt during heliox administration unless recalibrated. Other strategies to mobilize mucus such as chest physiotherapy or treatment with mucolytics or expectorants have not proved efficacious in controlled trials. BAL has been recommended by some but has not been well studied, carries theoretical risks, and should be reserved for extraordinary circumstances of mucous impaction.

**Continuation of Pharmacotherapy and Liberation From Mechanical Ventilation**

As the patient is stabilized on the ventilator, it is essential that the pharmacologic agents described above be continued to treat the underlying disease. All patients should receive parenteral corticosteroids, unless a contraindication exists, high doses of \(\beta\)-agonists, and IB. Delivery of aerosols to patients receiving mechanical ventilation involve consideration to several variables, including the type of nebulizer used, actuation of a pMDI into an in-line chamber spacer, timing of actuation, ventilator mode, Vt, circuit humidification, and duty cycle. Administration of aerosols is particularly challenging, since some of the gas delivery parameters that would maximize aerosol delivery—slow
inspiratory flow and large Vt—would have adverse effects on hyperinflation. One compromise is to deliver aerosols continuously by a nebulizer placed close to the endotracheal tube, accepting that only a very small fraction of drug will be delivered to the site of action in these challenging patients. In these patients, pMDI offer several advantages over nebulizers for routine bronchodilator therapy. Close observation in the ICU is recommended for an additional 24-h after extubation, during which time clinicians can focus on safe transfer to the general medical ward and on maximizing outpatient management.

Outcomes From Asthma Complicated by Respiratory Failure

Mortality in ICU patients with AA has been reported from 0 to 22%, depending of age and duration of follow-up. Only recently have series detailing more of the ICU outcomes for patients with asthma appeared in the medical literature. Afessa and colleagues analyzed 89 patients admitted to an urban hospital ICU over a 3-year period. Invasive mechanical ventilation was required in 36% of patients, and noninvasive ventilation initiated in 20% of patients. Eleven patients died, giving a mortality of 8.3% for all patients but a striking 21% mortality for patients undergoing mechanical ventilation. Positively associated with mortality were lower initial pH, higher initial PaCO₂, higher acute physiology and chronic health evaluation (APACHE) II score, and the development of organ failures. Four patients had pre-ICU cardiopulmonary arrest, and three of these patients died. Gehlbach and colleagues studied the first ICU admission for 78 patients with status asthmaticus treated with positive pressure ventilation. Fifty-six patients underwent endotracheal intubation at some point in the ICU course, while 22 patients were treated with NIPPV alone. Three patients died, for a mortality rate of 3.8%. The median hospital length of stay was 5.5 days. Female gender, endotracheal intubation, administration of neuromuscular blockers for > 24 h, increasing APACHE II score, and inhaled corticosteroid use prior to ICU admission were independently associated with increased length of hospital stay.

Summary

AA is a common medical emergency faced by ED and intensive care physicians. Properly managed, there should be a very low mortality rate; but death does occur, typically in patients with poorly controlled disease whose condition gradually deteriorates over a period of days or even weeks before the fatal event. This observation suggests many patients have a window of opportunity for recognition and reversal of this period of deterioration. The assessment of an asthma exacerbation constitutes a process with two different dimensions: to determine the severity of attack, and to gauge the response to treatment. The goals of treatment may be summarized as maintenance of adequate arterial oxygen saturation with supplemental oxygen, relief of airflow obstruction with repetitive administration of rapid-acting inhaled bronchodilators (β-agonists and anticholinergics), and treatment of airway inflammation with systemic corticosteroids to prevent future relapses. Many patients admitted to the ICU with AA simply require additional time for the therapies instituted in the ED to be continued and for respiratory function to improve. A few patients will require positive pressure ventilatory support because of progression to respiratory failure in advance of response to treatment or prior to treatment, and these challenging patients require specific ventilator strategies to be employed to optimize outcome.

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