The evaluation and management of acute, severe asthma

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There are 1.8 million emergency department visits, 500,000 hospitalizations, and 5500 deaths yearly in the United States from acute asthma exacerbations. Favorable outcomes in acute, severe asthma can be maximized by using an organized approach to the patient that relies on a focused but thorough clinical assessment, prompt initiation of treatment, and modification of subsequent therapy based on the individual's initial response. A review of recent literature, information obtained from published national and international guidelines [1–6], and the authors' clinical experience form the basis for the following approach to the management of patients with acute, severe asthma. To facilitate presentation, this approach is divided into the following components:

- Clinical evaluation and estimation of asthma severity
- Initial therapy and treatment
- Assessment of initial response to treatment and subsequent therapy
- Indications for noninvasive and mechanical ventilation
Clinical evaluation and estimation of asthma severity

Initial clinical assessment

A brief, focused history and physical examination should be initiated immediately whenever a patient with significant respiratory difficulty is recognized. An initial survey of the patient should focus on identifying features suggestive of a life-threatening attack or the need for emergent assisted ventilation, such as cyanosis, inability to speak without gasping, silent chest or rapid shallow respiratory effort, exhaustion, extreme agitation, or altered consciousness. The subsequent clinical evaluation should provide the physician with enough information to estimate asthma severity and to help guide therapeutic choices.

History

The history should focus on the temporal aspects of the illness including the rapidity of onset and duration of symptoms. The presence of recurrent nocturnal awakening caused by asthma and heavy reliance on bronchodilators in the days leading up to the acute episode suggest progression of airway inflammation in response to infectious, allergic, or persistent irritant triggers. On occasion, ingested foods, food additives, or medications, such as sulfites, nonsteroidal anti-inflammatory drugs, or β-blockers, may also trigger acute bronchospasm. A prior history of severe attacks requiring intensive medical intervention, recent withdrawal from systemic steroids, and comorbid illness are all risk factors for asthma mortality, and underscore a requirement for prompt aggressive management (Fig. 1) [7–11].

Special mention should be made of two recognized patterns of life-threatening asthma delineated by their rate of clinical deterioration and bronchodilator responsiveness: acute severe asthma and sudden asphyxic asthma.

- Past history of sudden severe exacerbations
- Prior intubation for asthma
- Prior admission for asthma to an intensive care unit
- Two or more hospitalizations for asthma in one year
- Three or more emergency care visits for asthma in past year
- Hospitalization or an emergency care visit within past month
- Use of >2 canisters per month of inhaled short-acting beta2-agonist
- Current use of systemic corticosteroids or recent withdrawal from systemic corticosteroids
- Difficulty perceiving airflow obstruction or its severity
- Comorbidity, as from cardiovascular diseases or chronic obstructive pulmonary disease
- Serious psychiatric disease or psychosocial problems
- Low socioeconomic status and urban residence
- Illicit drug use
- Sensitivity to *Alternaria*

Acute severe asthma is the more common pattern (70% of life-threatening asthma cases), occurring predominately in women, and frequently requiring mechanical ventilation [12,13]. There is a gradual, progressive deterioration over several days before presentation and an association with chronic bronchial inflammation, moderate airflow obstruction, and usually a slower response to therapy. Sudden asphyxic asthma, also known as hyperacute asthma, is less common and more often seen in young men. There is usually rapid breathing deterioration over hours and, occasionally over minutes [14], a high level of bronchial hyperreactivity, and often profound hypercapnia [13,15,16]. Because the mechanism of airflow obstruction includes a large component of bronchospasm, these patients may rapidly respond to therapy. Unfortunately, they are more likely to have respiratory arrest before, or shortly after, presentation to a medical facility [17,18].

Physical examination

A focused physical examination to assess respiratory status should allow the physician to categorize the severity of asthma (Table 1). The general appearance of the patient can often lead to near instantaneous recognition of significant respiratory compromise. A patient with severe asthma often maintains an upright sitting position and provides a history using short truncated phrases in a semi-agitated or impatient manner. Rapid, shallow respirations with accessory muscle involvement of the neck, shoulders, and thorax should also alert the examiner that severe airway obstruction is likely. Vital signs also often reflect severe asthma with tachycardia, tachypnea, and pulsus paradoxus as compensatory responses to airway obstruction and hypoxia. The absence of these findings, however, in an obviously dyspneic patient may also suggest imminent respiratory arrest. Auscultation of the chest may reveal wheezing but its absence does not rule out asthma and its absence may also be indicative of impending respiratory failure [19]. The examination should also focus on identifying potential complicating factors, such as sinusitis, nasal polyps, pneumonia, pneumothorax, or pneumomediastinum. A focused repeat examination should be performed after each therapeutic intervention to assess the response to treatment.

Quantitative measures

Objective measures of ventilation and gas exchange are useful to augment the initial physical examination and serve as a baseline to monitor the response to treatment. Tests that quantify airflow obstruction, such as spirometry or peak expiratory flow rate (PEFR), are especially important in those with severe persistent disease. Many patients adapt to chronic airflow obstruction and may seem less severely ill during exacerbations than objective measures of airflow obstruction indicate. Spirometric measurement of the forced expiratory volume in 1 second (FEV₁) or PEFR help quantify the
### Table 1
Classifying severity of asthma exacerbation

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Respiratory arrest imminent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breathlessness</strong></td>
<td>While walking</td>
<td>While talking (infant: softer, shorter cry; difficulty feeding)</td>
<td>While at rest (infant stops feeding)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can lie down</td>
<td>Prefers sitting</td>
<td>Sits upright</td>
<td></td>
</tr>
<tr>
<td><strong>Talks in</strong></td>
<td>Sentences</td>
<td>Phrases</td>
<td>Words</td>
<td>Drowsy or confused</td>
</tr>
<tr>
<td><strong>Alertness</strong></td>
<td>May be agitated</td>
<td>Usually agitated</td>
<td>Usually agitated</td>
<td></td>
</tr>
<tr>
<td><strong>Signs</strong></td>
<td><strong>Respiratory rate</strong></td>
<td>Increased</td>
<td>Increased</td>
<td>Often &gt;30/min</td>
</tr>
<tr>
<td></td>
<td>Guide to rates of breathing in awake children:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>Normal rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;2 mo</td>
<td>&lt;60/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2–12 mo</td>
<td>&lt;50/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–5 y</td>
<td>&lt;40/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6–8 y</td>
<td>&lt;30/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Use of accessory muscles; suprasternal retractions</strong></td>
<td>Usually not</td>
<td>Commonly</td>
<td>Usually</td>
<td>Paradoxical thoracoabdominal movement</td>
</tr>
<tr>
<td><strong>Wheeze</strong></td>
<td>Moderate, often only end expiratory</td>
<td>Loud; throughout exhalation</td>
<td>Usually loud; throughout inhalation and exhalation</td>
<td>Absence of wheeze</td>
</tr>
<tr>
<td>Pulse per minute</td>
<td>&lt;100</td>
<td>100–120</td>
<td>&gt;120</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>------------------</td>
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<tr>
<td>Guide to normal pulse rates in children:</td>
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</tr>
<tr>
<td>Age</td>
<td>Normal rate</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2–12 mo</td>
<td>&lt;160/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2 y</td>
<td>&lt;120/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–8 y</td>
<td>&lt;110/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulsus paradoxus</td>
<td>Absent &lt;10 mm Hg</td>
<td>May be present 10–25 mm Hg</td>
<td>Often present &gt;25 mm Hg (adult), 20–40 mm Hg (child)</td>
<td>Absence suggests respiratory muscle fatigue</td>
</tr>
</tbody>
</table>

**Functional assessment**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEF % predicted or personal best</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Pao2 (on air)</td>
<td>Normal (test not usually necessary)</td>
</tr>
<tr>
<td>Paco2</td>
<td>&lt;42 mm Hg (test not usually necessary)</td>
</tr>
<tr>
<td>Sao2% (on air) at sea level</td>
<td>&gt;95% (test not usually necessary)</td>
</tr>
</tbody>
</table>

Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents.

The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation. Many of these parameters have not been systematically studied, so they serve only as general guides.

degree of airway obstruction at presentation and subsequently aid in assessment of response to therapy.

Because there is no absolute FEV\textsubscript{1} or PEFR value that accurately predicts the severity of hypoxemia, however, pulse oximetry should be used for this determination in patients presenting with acute asthma [20]. In addition, arterial blood gas analysis may be indicated in patients with an FEV\textsubscript{1} below 1 L or a PEFR below 200 L/min (or approximately 30\% to 40\% of predicted values) because these patients often exhibit an inappropriately normal PCO\textsubscript{2}, hypercarbia, or severe hypoxemia. When the FEV\textsubscript{1} or PEFR is less compromised arterial blood gas analysis should be performed at the physician’s discretion [20].

Additional laboratory studies may be indicated to identify comorbidities or conditions complicating the treatment of asthma. A complete blood count may be considered in those patients where pneumonia is a diagnostic consideration. A modest rise in leukocytes may be explained by an asthma-induced stressed adrenal response or recent corticosteroid treatment. Patients taking theophylline should also have a theophylline level drawn to ensure therapeutic levels. Serum electrolyte analysis may be wise for patients taking diuretics or to assess a potentially depleted serum potassium, magnesium, or phosphate that may occur in response to frequent β\textsubscript{2}-agonist administration [21].

Chest radiography is not recommended for routine assessment but should be obtained if the physician suspects a pneumothorax, pneumonia, pneumomediastinum, extensive mucous plugging with atelectasis, or congestive heart failure. Baseline electrocardiogram and continuous cardiac monitoring may be appropriate for patients experiencing severe asthma, and particularly for those greater than 50 years of age or known cardiac or pulmonary disease. Right ventricular strain may be seen in some severely obstructed patients, and this finding may resolve with successful therapy.

**Initial therapy and treatment**

Prompt treatment should be initiated as soon as a focused history and rapid assessment of the patient can be accomplished. Laboratory evaluation can be delayed until after treatment is initiated in most circumstances. A summary algorithm for emergency evaluation and treatment is shown in Fig. 2.

**Oxygen administration**

Supplemental oxygen is recommended for most patients by nasal cannulae or mask. The fractional inspired oxygen concentration should be adjusted to maintain oxygen saturation greater than 90\% (>95\% in pregnant women and for patients with coexistent heart disease). Oxygen saturation should be monitored until a clear response to bronchodilator therapy has resulted and normal O\textsubscript{2} saturation (>95\%) can be maintained on room air [5].
Pharmacologic agents

Inhaled short-acting β₂-agonists

Inhaled short-acting β₂-agonists are the cornerstone of therapy for acute asthma. Studies have indicated the most effective means to reverse airway
obstruction is to dose repeatedly (ie, three treatments spaced every 20 to 30 minutes in the first hour) or continuously by nebulization [22–25]. Children and severely obstructed adults are most likely to benefit from continuous nebulization [23–25]. The proposed rationale behind repeat or continuous dosing is that initial bronchodilation allows for more distal deposition of drug particles with subsequent aerosol administration. This results in dilation of smaller airways and further reversal of airway resistance in the entire lung [26]. The short interval between repeat treatments or continuous dosing also prevents deterioration that may occur when longer intervening periods are used.

The most commonly used inhaled short-acting β₂-agonist in the United States is albuterol. The suggested dose for intermittent albuterol nebulization in adults treated in the emergency department or hospital setting is 2.5 to 5 mg every 20 minutes by face mask for three doses. For children, a minimum dose of 2.5 mg is recommended but otherwise 0.15 mg/kg up to 5 mg every 20 minutes for 3 doses by face mask. Albuterol may also be dosed at 10 to 15 mg/h continuously (0.5 mg/kg/h for children) with a face mask at gas flow rates of 6 to 8 L/min [5]. The aerosol should be diluted to a minimum of 4 mL. The heart rate should be monitored with continuous nebulization of inhaled short-acting β₂-agonists with adjustments in rate of delivery at the physician’s discretion because of excessive tachycardia based on patient’s age, comorbidities, and clinical status.

Typically albuterol is administered as a racemic mixture of equal amounts of R and S stereoisomers. Recently it has been recognized that the bronchodilator activity comes from the (R)-albuterol (levalbuterol) with the (S)-albuterol playing no role in bronchodilator activity. Some studies suggest the S-isomer may induce bronchial hyperreactivity [27,28], and because the (S)-albuterol is metabolized more slowly, this isomer has been theorized to contribute to the increased morbidity associated with excessive use of racemic albuterol [29,30]. In initial clinical studies, a nebulized form of the single (R)-stereoisomer (levalbuterol) seemed to have a better therapeutic ratio with equivalent bronchodilation and fewer β-agonist–mediated side effects when compared with racemic albuterol [31–33]. A recent study of severe adult asthmatics presenting to the emergency department demonstrated improved FEV₁ after the third nebulization of 1.25 mg levalbuterol versus 2.5 mg racemic albuterol [34].

This favorable profile for levalbuterol is less clear when studied as a routine rescue medication in chronic asthma. A multicenter trial of chronic mild-to-moderate pediatric asthma patients also found that over a 3-week period, 0.31 mg levalbuterol was equivalent to 2.5 mg of racemic albuterol with fewer β₂-mediated side effects [35]. A study in stable mild-to-moderate adult asthmatics, however, calculated the relative potency of levalbuterol versus racemic albuterol as equivalent with respect to the (R)-isomer activity [36]. This study concluded there was no difference between levalbuterol versus racemic albuterol with respect to the therapeutic ratio, bronchodilation, or β-agonist–mediated side effects in stable adult mild-to-moderate
asthmatics. In summation, at a minimum levalbuterol seems as safe and effective as racemic albuterol, albeit at a greater cost, with further studies needed to elucidate the possible superiority of this drug, especially in acute and severe asthmatics or other subpopulations.

The suggested dose of intermittent levalbuterol is 0.63 to 1.25 mg every 20 minutes by face mask for three doses, then every 1 to 4 hours as needed (children same as adults for intermittent dosing, although 0.31 mg may be considered for less severe pediatric patients [35]). Continuous levalbuterol may be dosed at 2.5 to 5 mg/h continuously in adults (children 1.25 to 2.5 mg/h). Similar precautions should be followed with continuous levalbuterol administration as stated previously with continuous albuterol administration.

Several studies demonstrate that equivalent bronchodilation can be achieved with either nebulization or high doses, such as 6 to 12 puffs, from a $\beta_2$-agonist metered dose inhaler (MDI) with spacer or holding chamber under medical supervision [37–39]. Patients unable to coordinating medication inhalation properly from an MDI because of age, agitation, or distress may get more effective bronchodilation with nebulized therapy.

The dose and frequency of $\beta_2$-agonist therapy should be tailored to the patient’s response and indicators of possible toxicity (excessive heart rate, severe electrolyte disturbances, and so forth). Only selective $\beta_2$-agonists (racemic albuterol, levalbuterol, terbutaline, pirbuterol, and bitolterol) should be used in high doses because of the risk of cardiotoxicity with non-selective $\beta_2$-agonists [5]. Fortunately, the onset of action of short-acting $\beta_2$-agonist is within 5 minutes but the duration of bronchodilation in acute, severe asthma is unknown [24].

**Anticholinergics**

Anticholinergics, specifically ipratropium bromide, should be considered for addition to $\beta_2$-agonist treatment in severe asthma exacerbations. Two meta-analyses have demonstrated modest statistical improvement in airflow obstruction in both adult and pediatric populations [40]. In children, combination therapy also improves outcomes by decreasing emergency department treatment time, albuterol requirements before discharge, and hospitalization rates [41–43]. In adults, combination therapy with ipratropium shows trends toward improving albuterol dose requirements while reducing hospitalization rates and subsequent exacerbations [44–47]. Because adding ipratropium to albuterol provides a physiologic benefit without adverse effects, a dosing regimen of four to eight puffs of ipratropium by MDI with spacer or the addition of a unit-dose vial of ipratropium (0.5 mg adults, 0.25 mg children) to albuterol-nebulized treatments is recommended [5].

**Systemic corticosteroids**

Systemic corticosteroids are recommended for most patients presenting with acute asthma. One exception may be the individual with a relatively
mild attack that quickly and completely improves with initial bronchodilator treatment. Clear indications for systemic corticosteroids include patients who historically require prolonged courses of oral steroids; those dependent on moderate-to-high doses of inhaled steroids; previous history of severe asthma that responds poorly to initial bronchodilator therapy; and those with severe bronchospasm (FEV₁ or PEFR < 50% of baseline).

Advantages of administration of systemic corticosteroids include more rapid improvement in acute asthma [48], a decreased risk of relapse in the 2 weeks after emergency department discharge [49], and a decrease in asthma mortality [50]. Although it may take several hours to realize the beneficial effects of systemic corticosteroids, intravenous administration of 125 mg of methylprednisolone in the emergency department has been shown to decrease hospitalization rates [51]. Once hospitalized, systemic corticosteroids also speed resolution of the asthma exacerbation and allow earlier discharge [52,53].

Interestingly, the optimal dosing of systemic corticosteroids has not been established. The authors of the National Asthma Education Program’s Expert Panel Report 2 concluded that there is no clear advantage for exceedingly high doses of systemic corticosteroids [5]. These guidelines include adult dose recommendations of prednisone, methylprednisolone, or prednisolone of 120 to 180 mg/d in three or four divided doses for 48 hours, then 60 to 80 mg/d until the PEFR reaches 70% predicted or personal best. Current children’s dosing of these agents is 1 mg/kg every 6 hours for 48 hours then 1 to 2 mg/kg/d (maximum, 60 mg/d) in two divided doses until PEFR reaches 70% of predicted or personal best. Finally, a subsequent outpatient burst corticosteroid dose of 40 to 60 mg in single or two divided doses for adults (children, 1 to 2 mg/kg/d, maximum 60 mg/d) over 3 to 10 days is recommended. Of note is that there is no apparent advantage of parenteral versus oral therapy provided gastrointestinal transit time or absorption is not impaired [54,55]. Intravenous administration is preferred for patients at risk for intubation, however, to minimize the possibility of aspiration of gastric contents [5].

**Assessment of initial response to treatment and subsequent therapy**

A repeat evaluation of the patient’s progress following initial treatment is essential to guide subsequent management. The patient should be reassessed approximately 20 minutes following each therapeutic intervention, whereas O₂ saturation should be continually monitored in those patients believed at risk for rapid deterioration.

**Good response**

The patient with a good response usually exhibits marked improvement or absence of breathlessness or subjective chest tightness and has a sustained
response lasting more than 60 minutes after the last treatment. The physical examination may still reveal some wheezing but PEFR or FEV\textsubscript{1} should improve to greater than 70\% of personal best with normal oxygen saturation while breathing room air. Such patients can be considered for discharge to home. Discharge plans should include continued intermittent treatment with inhaled \( \beta \text{-agonists}; \) oral corticosteroids (if initiated); updated treatment plans (including inhaled corticosteroids in most cases) [56]; and short-term medical follow-up.

**Partial response**

In many patients, some improvement is noted after initial treatment, but breathlessness, wheezing, and distress persist to some degree. Chest auscultation usually reveals persistent wheezing with PEFR or FEV\textsubscript{1} typically between 50\% and 70\% of personal best. Supplemental oxygen may still be required to maintain normal O\textsubscript{2} saturation. These patients require continued treatment in the emergency department or acute care setting.

**Poor response**

Some patients do not experience adequate improvement after initial therapy, whereas others may have significant deterioration despite intensive treatment for several hours. The initial group requires further aggressive therapy with extended care in a clinical observation unit or inpatient facility, whereas the latter group of patients likely requires admission to an intensive care unit for close observation for further deterioration despite aggressive intervention. Supplies for emergency assisted ventilation and endotracheal intubation should be kept immediately available. Common signs suggesting impending respiratory arrest and potential need for intubation include a silent chest, drowsiness or confusion, deteriorating PEFR or FEV\textsubscript{1}, and normalized or elevated PCO\textsubscript{2} in the face of persistent hypoxemia.

**Continued therapy for patients with partial or poor response to initial treatment**

**Oxygen and bronchodilator therapy**

Oxygen and bronchodilator therapy should be continued with the frequency of intermittent nebulization or continuous nebulization dose guided by the severity of persistent airway obstruction. Inhaled ipratropium should be considered if not already initiated. Ipratropium may be administered separately but may also be combined in the nebulizer with \( \beta \text{-agonists}. \) Ipratropium is typically dosed as 0.5 mg (0.25 mg for children) every 30 minutes for three doses initially, then every 2 to 4 hours as needed [5]. Alternatively, four to eight puffs of ipratropium by MDI with spacer could also be used in patients who are still capable of using an MDI efficiently.
Corticosteroids

Systemic corticosteroid therapy should be continued as previously discussed.

Intravenous fluids and correction of electrolytes and acidosis

Patients presenting with acute severe asthma, especially if symptoms have progressed over a few days, may have mild-to-moderate dehydration. Dehydration also occurs commonly in children. These patients should receive supplemental fluids and electrolytes to restore normal hydration and electrolyte status. Electrolyte disturbances commonly observed in acute asthma include decreases in potassium, magnesium, and phosphate [21,57]. These abnormalities, if mild, usually correct themselves as the severity of asthma and frequency of therapy decrease.

Extended care considerations

The decision to proceed with plans for extended care (clinical decision unit or hospitalization) can typically be made within several hours of presentation. In one study, two thirds of patients obtained a proposed discharge threshold status (little or no wheeze and PEFR or FEV₁ improving to greater than 70% of personal best) within 1 hour of treatment with high doses of β₂-agonist [58,59]. Early response to treatment as measured by percent increase in FEV₁ or PEFR at 30 minutes over baseline seems to be the best predictor of outcome [10]. Factors to be considered in the decision for extended care include a history of prolonged or near-fatal attacks, ease of access to medical facilities and medications, medication requirements at the time of exacerbation, home social support and conditions, and the coexistence of psychiatric illness [16].

Additional therapeutic considerations for acute asthma

Magnesium sulfate

Intravenous magnesium sulfate (MgSO₄) has failed to show benefit in several large, prospective studies for patients presenting to the emergency department with acute asthma [60–63]. A subgroup analysis, however, indicated that in patients with the most pronounced bronchospasm (FEV₁ less than 25% of predicted), MgSO₄ administration improved airflow and lowered hospitalization rates [64].

Intravenous MgSO₄ therapy may be considered as an intervention potentially to avert mechanical ventilation for severely obstructed patients not responding to standard therapies, particularly in patients presenting with low serum magnesium levels. MgSO₄ is typically administered at a dose of 2 to 4 g intravenously at a rate of 1 g every 1 to 10 minutes [6]. Side effects include flushing and mild sedation to loss of deep tendon reflexes, respiratory depression, and hypotension. Patients with impaired renal function should be monitored closely for toxic side effects caused by renal clearance of the drug.
MgSO₄ has also been studied as a bronchodilator by nebulization. One randomized double-blind control study with 33 patients presenting to the emergency department found 95 mg of nebulized MgSO₄ comparable with 2.5 mg of salbutamol with a 35% improvement in PEFR with MgSO₄ versus a 42% improvement for salbutamol [65]. Another similar study with 35 patients also demonstrated an additive effect of nebulized MgSO₄ with albuterol [66]. If this effect is confirmed in larger studies consideration of MgSO₄ by nebulization in combination with albuterol may be an option for asthma that is refractory to albuterol alone or in combination with ipratropium. Until further investigations are conducted, however, this form of therapy cannot be recommended.

**Leukotriene antagonists**

The overall role of this relatively new class of asthma medication is still being evaluated and refined. There is evidence to suggest, however, that leukotriene receptor antagonists may be beneficial in the treatment of acute, severe asthma.

Leukotrienes play a pathophysiologic role in acute asthma. Induced sputum cysteinyl leukotriene concentrations are significantly higher in subjects with acute severe asthma compared with mild asthma and normal controls [67]. Furthermore, studies of the addition of oral or intravenous cysteinyl leukotriene receptor antagonists to patients with asthma reveal a rapid improvement in FEV₁ lasting greater than 24 hours following a single treatment. This increase in FEV₁ is noted within 15 minutes (peak onset 30 minutes) when cysteinyl leukotriene antagonists are administered intravenously [68].

Several clinical trials of leukotriene antagonists for acute asthma also have been published. A trial of two doses of oral zafirlukast (20 mg and 160 mg) for acute asthma in the emergency department improved pulmonary function and dyspnea with a trend of decreasing hospital admissions in the 160-mg group [69]. Also, a rapid but modest improvement in FEV₁ with intravenous montelukast versus placebo was seen in acute asthma subjects refractory to initial β₂-agonists and oxygen [70]. Although several anti-leukotriene agents have shown promise as a non-β₂-mediated receptor bronchodilator, further studies are necessary with currently available agents to ascertain their role in acute asthma.

**Inhaled corticosteroids**

Although inhaled corticosteroids are not routinely used in the management of acute, severe asthma, two recent studies suggest a possible role for this therapy. The first of these reports shows that a combination of high-dose inhaled flunisolide and albuterol leads to improved airflow at 90 to 180 minutes compared with albuterol alone [71]. A subset of patients in this study who presented with prolonged symptoms (>24 hours) also had fewer hospitalizations compared with controls. A second study involving children randomized to receive a combination of nebulized budesonide and albuterol
or oral prednisolone and albuterol reported that 2 hours after treatment the 
inhaled budesonide group had significantly better symptom scores and a 
trend toward better PEFRs with fewer hospitalizations [72]. Because it may 
take several hours to realize the effects of oral corticosteroids, the early ben-
etits of inhaled corticosteroids are theorized to be caused by rapid onset of 
local pulmonary effects, such as inhibition of mucosal edema and constric-
tion of the microcirculation [73].

Intravenous, intramuscular, or subcutaneous adrenergic agonists

The Expert Panel Report 2 guidelines do not advocate the use of intra-
venous, subcutaneous, or intramuscular adrenergic agonists because there 
is no proved advantage of systemic therapy over the aerosolized form [5]. 
Several international asthma guidelines, however, suggest consideration 
of intravenous β-agonists for acute, severe refractory asthma [1–4,74]. It 
seems reasonable to consider parenteral adrenergic therapy in the setting 
of a patient not responding to frequent or continuous inhaled β2-agonist 
treatment. Close cardiopulmonary monitoring is necessary with adrenergic 
agonist therapy whether by continuously nebulized, intravenous, subcuta-
neous, or intramuscularly routes because of possible adverse effects including 
excessive tachycardia, hypertension, dysrhythmias, and vasoconstriction. 
The likely risk-benefit implications of adding an intravenous, subcutaneous, 
or intramuscular β2-agonist to high-dose nebulized therapy, however, have 
not been adequately studied. Certainly, use of nonselective β2-agonists, such 
as intravenous isoproterenol, in the treatment of asthma should not be con-
sidered because of the risk of cardiac toxicity [75].

Subcutaneous epinephrine can be administered as 0.2 to 0.5 mL (1:1000 
solution) every 20 to 30 minutes as needed for three doses [76]. If rapid onset 
is necessary when intravenous access is not available, then the epinephrine 
should be given intramuscularly [77]. Terbutaline, a β2-agonist with a rela-
tively long duration of action (4 hours or longer), can be administered at a 
dose of 0.25 mg subcutaneously every 20 minutes for three doses [76].

Several dosing regimens for intravenous infusion of adrenergic agents 
have been described. Albuterol has been administered with a loading dose 
of 4 μg/kg over 2 to 5 minutes followed by an infusion of 0.1 to 0.2 μg/ 
kg/min [6]. Intravenous epinephrine has been dosed as 2 to 10 mL of a 
1:10,000 solution over 5 minutes, repeated if necessary, and infused at 1 to 
20 μg/min if improvement was apparent with the initial infusion [78].

Methylxanthines

Theophylline (orally) and aminophylline (intravenously) have been stud-
ied for their potential benefit in acute asthma. Some studies suggest cau-
tion with the use of aminophylline because of low therapeutic index [79–82]. 
A small number of studies, however, have shown that adding theophylline 
to inhaled bronchodilators improves airflow rates in the first several hours 
of management and decreases hospitalization rates [83–85]. Conservatively,
aminophylline can be considered for patients with acute severe asthma when other therapies have failed. Patients already receiving theophylline should have serum levels evaluated despite any history given [86]. The potential for theophylline toxicity caused by concomitant illness or drug use should always be considered. Common drugs that might increase serum theophylline levels include ciprofloxacin, macrolide antibiotics, cimetidine, allopurinol, propranolol, and influenza vaccine.

Side effects, possibly indicating toxicity, include nervousness, agitation, nausea and vomiting, abdominal pain, headache, dysrhythmias, seizures, confusion, hyperglycemia, hypokalemia, hypophosphatemia, hypomagnesemia, leukocytosis, or respiratory alkalosis. An extra measure of caution is required for patients with decreased theophylline clearance (ie, congestive heart failure, liver disease, and so forth).

**Antibiotics**

Virus, chlamydia, and mycoplasma infection are more commonly associated with asthma exacerbation than bacterial pneumonia [87–94]. Antibiotic administration should be limited to individuals with fever and purulent neutrophilic sputum or radiographic evidence of pneumonia. The use of treatment for suspected mycoplasma or *Chlamydia pneumoniae* in regard to acute asthma remains controversial [95]. Treatment of documented infection does shorten the course of the infection, however, and may also have some short-term benefit for asthma [96].

If bacterial sinusitis is suspected, appropriate antibiotics should be administered because concomitant sinusitis is common in patients with allergic rhinitis and asthma and has been commonly identified as a factor contributing to asthma exacerbations [97].

**Mucolytics, cough syrups, and sedatives**

There is no evidence that adding mucolytics or a cough suppressant is beneficial for the patient with acute, severe asthma. Mucolytics (ie, acetylcysteine or potassium iodide) may actually worsen cough or airflow obstruction [98]. Sedative medications including codeine-containing antitussives may also be counter-productive by contributing to hypoxia by hypoventilation. The use of sedatives becomes mandatory, however, before, during, and after endotracheal intubation.

**Antihistamines**

Theoretically, antihistamines have a potential benefit in acute asthma through inhibition of bronchospasm caused by histamine release in the lung. Although antihistamines have been shown to have an inhibitory effect on the early bronchospastic response to allergen inhalation [99], these agents have not been well studied in acute asthma. A recent report, however, concluded that the combination of an antileukotriene (zafirlukast) with an antihistamine (loratadine) more effectively improves FEV₁ during the early and late
asthmatic reaction to inhaled allergen than either agent alone [100]. Although there are no current general contraindications for the use of the newer non-sedating antihistamines in the treatment of acute, severe asthma, their routine use is not recommended.

Helium and oxygen mixtures (heliox)

Heliox is a blend of helium and oxygen in concentrations ranging from 60% to 80% helium and 20% to 40% oxygen. Helium is an inert gas with no known side effects or any direct therapeutic effect. Because the helium-oxygen blend is less dense than room air or oxygen alone, however, this low-density formulation given by non-rebreather mask [101] reduces a patient’s work of breathing and may improve oxygenation by decreasing airway turbulence and resistance, pulsus paradoxus, and alveolar-to-arterial gradient while increasing peak expiratory flow [101,102]. There are no large prospective trials evaluating heliox as adjunctive treatment for preventing intubation, improving outcome, or shortening hospital stay. One small prospective, randomized, controlled study with 23 spontaneously breathing patients reported a more rapid improvement in peak flow in patients who breathed heliox [103]. Other smaller studies in nonintubated patients, however, suggest little benefit of heliox in acute asthma [104,105]. Nonetheless, heliox can be considered in patients at risk for ICU admission or intubation in which conventional treatments are failing. It should also be mentioned that heliox can affect nebulizer function, peak flow meter, and pulmonary function measurements unless they are adjusted for the mixture [106]. For instance, nebulizer flow rates should be increased by about 50% to ensure adequate output from the nebulizer [106].

The usual commercially available 20% oxygen and 80% helium mixture can be mixed with pure oxygen to provide the desired helium concentration and fraction of inspired oxygen. Additionally, if the desired fraction of inspired oxygen concentration is above 40%, the limited quantity of helium likely does not provide therapeutic benefit and limits the use of heliox in severely hypoxic patients [106]. Pulse oximetry is essential during heliox therapy to ensure adequate oxygen is being provided.

Other agents

Although an initial publication suggested benefit for inhaled furosemide in asthma [107], this benefit could not be reproduced in acute asthma [108]. Anesthetic agents have also been studied for possible use in acute asthma. In one study, ketamine in low doses did not improve pulmonary function or admission rates [109]. Additionally, halothane and isoflurane have been anecdotally reported as beneficial in status asthmaticus but no clinical trials are available [110,111]. The proposed mechanisms by which inhaled anesthetic agents are believed potentially to be beneficial include bronchial smooth muscle relaxation, inhibition of vagal tone, and synergistic bronchodilatory effect with catecholamines.
Indications for noninvasive and mechanical ventilation

The technical aspects of noninvasive ventilatory support and mechanical ventilation are outside the scope of this article. Some discussion, however, regarding the indications for these two modes of treatment for acute, severe asthma is appropriate.

Noninvasive ventilatory support

Good candidates for noninvasive positive pressure ventilation (NPPV) include patients who are alert and cooperative, are hemodynamically stable, and have no need for endotracheal intubation to protect their airway or to remove excessive secretions. In addition, no facial trauma should be present to allow application of a properly fitted mask [112]. NPPV decreases work of breathing, alleviates muscle fatigue, helps re-expand atelectasis, and allows spontaneous ventilation [112–114]. A recent consensus conference on NPPV concluded that nonrandomized studies with concurrent cohort comparison provided supportive evidence that NPPV may avert endotracheal intubation in status asthmaticus [115]. This mode of treatment may not be appropriate for many including children because of the tight-fitting mask causing discomfort and anxiety, leading to a lack of cooperation [116].

Indications for mechanical ventilation

Intubation and subsequent mechanical ventilation ultimately control a person’s airway and reduce the work of breathing. Patients who are severely distressed, becoming obtunded, or who are hemodynamically unstable because of respiratory efforts are candidates for immediate intubation. Additionally, patients who seem exhausted or are exhibiting deterioration in respiratory rate, level of awareness, or ability to cooperate also require intubation and ventilation [12].

Certainly, a controlled elective intubation is desirable in comparison to an uncontrolled emergent intubation. A patient’s verbalized self-assessment of near exhaustion or collapse should be taken as seriously as should deteriorating objective values, such as PEFR or FEV₁, respiratory rate, or rising PaCO₂ despite treatment [117]. Deterioration in overall clinical presentation, however, is often the best guide to a physician’s decision for intubation rather than any set numeric value or standard.

Summary

This article provides a systematic approach to the patient with acute, severe asthma. After a brief, focused evaluation prompt treatment with inhaled β₂-agonists and systemic corticosteroids remains the cornerstone of treatment. Ipratropium bromide is now recognized as a useful addition...
for both adult and pediatric populations, whereas consideration of intravenous MgSO4 and theophylline is warranted for refractory patients. Ongoing evaluation of antileukotriene agents offers a possibility of these agents as alternative bronchodilators. Further research with a number of potential acute asthma agents will further expand treatment options for rapid symptomatic airway improvement and prevention of progressing airway obstruction, hospitalization, and potential respiratory failure.

References

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