

## Part 10.5: Near-Fatal Asthma

Asthma accounts for >2 million emergency department visits and 5000 to 6000 deaths annually in the United States, many occurring in the prehospital setting.<sup>1</sup> Severe asthma accounts for approximately 2% to 20% of admissions to intensive care units, with up to one third of these patients requiring intubation and mechanical ventilation.<sup>2</sup> This section focuses on the evaluation and treatment of patients with near-fatal asthma.

### Pathophysiology

The pathophysiology of asthma consists of 3 key abnormalities:

- Bronchoconstriction
- Airway inflammation
- Mucous impaction

Complications of severe asthma, such as tension pneumothorax, lobar atelectasis, pneumonia, and pulmonary edema, can contribute to fatalities. Cardiac causes of death are less common.

### Clinical Aspects of Severe Asthma

Wheezing is a common physical finding, but severity does not correlate with the degree of airway obstruction. The absence of wheezing may indicate critical airway obstruction, whereas increased wheezing may indicate a positive response to bronchodilator therapy.

Oxygen saturation ( $SpO_2$ ) levels may not reflect progressive alveolar hypoventilation, particularly if  $O_2$  is being administered. Note that the  $SpO_2$  may initially fall during therapy because  $\beta$ -agonists produce both bronchodilation and vasodilation and may initially increase intrapulmonary shunting.

Other causes of wheezing are pulmonary edema, chronic obstructive pulmonary disease (COPD), pneumonia, anaphylaxis,<sup>3</sup> foreign bodies, pulmonary embolism, bronchiectasis, and subglottic mass.<sup>4</sup>

### Initial Stabilization

Patients with severe life-threatening asthma require urgent and aggressive treatment with simultaneous administration of oxygen, bronchodilators, and steroids. Healthcare providers must monitor these patients closely for deterioration. Although the pathophysiology of life-threatening asthma consists of bronchoconstriction, inflammation, and mucous impaction, only bronchoconstriction and inflammation are amenable to drug treatment. If the patient does not respond to therapy, consultation or transfer to a pulmonologist or intensivist is appropriate.

### Primary Therapy

#### Oxygen

Provide oxygen to all patients with severe asthma, even those with normal oxygenation. Titrate to maintain  $SpO_2 >92\%$ . As noted above, successful treatment with  $\beta$ -agonists may initially cause a decrease in oxygen saturation because the resultant bronchodilation may initially increase the ventilation-perfusion mismatch.

#### Inhaled $\beta_2$ -Agonists

*Albuterol (or salbutamol)* provides rapid, dose-dependent bronchodilation with minimal side effects. Because the administered dose depends on the patient's lung volume and inspiratory flow rates, the same dose can be used in most patients regardless of age or size. Although 6 adult studies<sup>5</sup> and 1 pediatric study<sup>6</sup> showed no difference in the effects of continuous versus intermittent administration of nebulized albuterol, continuous administration was more effective in the subset of patients with severe exacerbations of asthma,<sup>7,8</sup> and it was more cost-effective in a pediatric trial.<sup>6</sup> A Cochrane meta-analysis showed no overall difference between the effects of albuterol delivered by metered dose inhaler (MDI)-spacer or nebulizer,<sup>9</sup> but MDI-spacer administration can be difficult in patients in severe distress. The typical dose of albuterol by nebulizer is 2.5 or 5 mg every 15 to 20 minutes intermittently or continuous nebulization in a dose of 10 to 15 mg/h.

*Levalbuterol* is the R-isomer of albuterol. It has recently become available in the United States for treatment of acute asthma. Some studies have shown equivalent or slight improvement in bronchodilation when compared with albuterol in the emergency department.<sup>10</sup> Further studies are needed before a definitive recommendation can be made.

#### Corticosteroids

Systemic corticosteroids are the only proven treatment for the inflammatory component of asthma, but the onset of their anti-inflammatory effects is 6 to 12 hours after administration. A comprehensive search of the literature by the Cochrane approach (including pediatric and adult patients) determined that the early use of systemic steroids reduced rates of admission to the hospital.<sup>11</sup> Thus, providers should administer steroids as early as possible to all asthma patients but should not expect effects for several hours. Although there is no difference in clinical effects between oral and intravenous (IV) formulations of corticosteroids,<sup>12</sup> the IV route is preferable because patients with near-fatal asthma may vomit or be unable to swallow. A typical initial adult dose of methylprednisolone is 125 mg (dose range: 40 to 250 mg).

Incorporation or substitution of inhaled steroids into this scheme remains controversial. A Cochrane meta-analysis of 7 randomized trials (4 adult and 3 pediatric) of inhaled corticosteroids concluded that steroids significantly reduced the likelihood of admission to the hospital, particularly in patients who were not receiving concomitant systemic steroids. But

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the meta-analysis concluded that there is insufficient evidence that inhaled corticosteroids alone are as effective as systemic steroids.<sup>13</sup>

## Adjunctive Therapies

### *Anticholinergics*

Ipratropium bromide is an anticholinergic bronchodilator that is pharmacologically related to atropine. It can produce a clinically modest improvement in lung function compared with albuterol alone.<sup>14,15</sup> The nebulizer dose is 0.5 mg. It has a slow onset of action (approximately 20 minutes), with peak effectiveness at 60 to 90 minutes and no systemic side effects. It is typically given only once because of its prolonged onset of action, but some studies have shown clinical improvement only with repeated doses.<sup>16</sup> Given the few side effects, ipratropium should be considered an adjunct to albuterol. Tiotropium is a new, longer-acting anticholinergic that is currently undergoing clinical testing for use in acute asthma.<sup>17</sup>

### *Magnesium Sulfate*

IV magnesium sulfate can modestly improve pulmonary function in patients with asthma when combined with nebulized  $\beta$ -adrenergic agents and corticosteroids.<sup>18</sup> Magnesium causes bronchial smooth muscle relaxation independent of the serum magnesium level, with only minor side effects (flushing, lightheadedness). A Cochrane meta-analysis of 7 studies concluded that IV magnesium sulfate improves pulmonary function and reduces hospital admissions, particularly for patients with the most severe exacerbations of asthma.<sup>19</sup> The typical adult dose is 1.2 to 2 g IV given over 20 minutes. When given with a  $\beta_2$ -agonist, nebulized magnesium sulfate also improved pulmonary function during acute asthma but did not reduce rate of hospitalization.<sup>20</sup>

### *Parenteral Epinephrine or Terbutaline*

Epinephrine and terbutaline are adrenergic agents that can be given subcutaneously to patients with acute severe asthma. The dose of subcutaneous epinephrine (concentration of 1:1000) is 0.01 mg/kg divided into 3 doses of approximately 0.3 mg given at 20-minute intervals. The nonselective adrenergic properties of epinephrine may cause an increase in heart rate, myocardial irritability, and increased oxygen demand. But its use (even in patients >35 years of age) is well-tolerated.<sup>21</sup> Terbutaline is given in a dose of 0.25 mg subcutaneously and can be repeated in 30 to 60 minutes. These drugs are more commonly administered to children with acute asthma. Although most studies have shown them to be equally efficacious,<sup>22</sup> one study concluded that terbutaline was superior.<sup>23</sup>

### *Ketamine*

Ketamine is a parenteral dissociative anesthetic that has bronchodilatory properties. Ketamine may also have indirect effects in patients with asthma through its sedative properties. One case series<sup>24</sup> suggested substantial effectiveness, but the single randomized trial published to date<sup>25</sup> showed no benefit of ketamine when compared with standard care. Ketamine will stimulate copious bronchial secretions.

### *Heliox*

Heliox is a mixture of helium and oxygen (usually a 70:30 helium to oxygen ratio mix) that is less viscous than ambient air. Heliox has been shown to improve the delivery and deposition of nebulized albuterol.<sup>26</sup> Although recent meta-analysis of 4 clinical trials did not support the use of heliox in the initial treatment of patients with acute asthma,<sup>27</sup> it may be useful for asthma that is refractory to conventional therapy.<sup>28</sup> The heliox mixture requires at least 70% helium for effect, so if the patient requires >30% oxygen, the heliox mixture cannot be used.

### *Methylxanthines*

Although previously a mainstay in the treatment of acute asthma, methylxanthines are infrequently used because of erratic pharmacokinetics and known side effects.

### *Leukotriene Antagonists*

Leukotriene antagonists improve lung function and decrease the need for short-acting  $\beta$ -agonists during long-term asthma therapy, but their effectiveness during acute exacerbations of asthma is unproven. One study showed improvement in lung function with the addition of IV montelukast to standard therapy,<sup>29</sup> but further research is needed.

### *Inhaled Anesthetics*

Case reports in adults<sup>30</sup> and children<sup>31</sup> suggest a benefit of inhalation anesthetics for patients with status asthmaticus unresponsive to maximal conventional therapy. These anesthetic agents may work directly as bronchodilators and may have indirect effects by enhancing patient-ventilator synchrony and reducing oxygen demand and carbon dioxide production. This therapy, however, requires an ICU setting, and there have been no randomized studies to evaluate its effectiveness.

## Assisted Ventilation

### **Noninvasive Positive-Pressure Ventilation**

Noninvasive positive-pressure ventilation (NIPPV) may offer short-term support to patients with acute respiratory failure and may delay or eliminate the need for endotracheal intubation.<sup>32,33</sup> This therapy requires an alert patient with adequate spontaneous respiratory effort. Bi-level positive airway pressure (BiPAP), the most common way of delivering NIPPV, allows for separate control of inspiratory and expiratory pressures.

### **Endotracheal Intubation With Mechanical Ventilation**

Endotracheal intubation does not solve the problem of small airway constriction in patients with severe asthma. In addition, intubation and positive-pressure ventilation can trigger further bronchoconstriction and complications such as breath stacking (auto-PEEP [positive end-expiratory pressure]) and barotrauma. Although endotracheal intubation introduces risks, elective intubation should be performed if the asthmatic patient deteriorates despite aggressive management.

Rapid sequence intubation is the technique of choice. The provider should use the largest endotracheal tube available

(usually 8 or 9 mm) to decrease airway resistance. Immediately after intubation, confirm endotracheal tube placement by clinical examination and a device (eg, exhaled CO<sub>2</sub> detector) and obtain a chest radiograph.

### Troubleshooting After Intubation

When severe bronchoconstriction is present, breath stacking (so-called auto-PEEP) can develop during positive-pressure ventilation, leading to complications such as hyperinflation, tension pneumothorax, and hypotension. During manual or mechanical ventilation use a slower respiratory rate (eg, 6 to 10 breaths per minute) with smaller tidal volumes (eg, 6 to 8 mL/kg),<sup>34</sup> shorter inspiratory time (eg, adult inspiratory flow rate 80 to 100 mL/min), and longer expiratory time (eg, inspiratory to expiratory ratio 1:4 or 1:5) than would typically be provided to nonasthmatic patients.

Mild hypoventilation (permissive hypercapnia) reduces the risk of barotrauma. Hypercapnia is typically well tolerated.<sup>35</sup> Sedation is often required to optimize ventilation and minimize barotrauma after intubation. Delivery of inhaled medications may be inadequate before intubation, so continue to administer inhaled albuterol treatments through the endotracheal tube.

Four common causes of acute deterioration in any intubated patient are recalled by the mnemonic DOPE (tube Displacement, tube Obstruction, Pneumothorax, and Equipment failure). This mnemonic still holds in the patient with severe asthma.

If the patient with asthma deteriorates or is difficult to ventilate, verify endotracheal tube position, eliminate tube obstruction (eliminate any mucous plugs and kinks), and rule out (or decompress) a pneumothorax. Only experienced providers should perform needle decompression or insertion of a chest tube for pneumothorax.

Check the ventilator circuit for leaks or malfunction. High end-expiratory pressure can be quickly reduced by separating the patient from the ventilator circuit; this will allow PEEP to dissipate during passive exhalation. To minimize auto-PEEP, decrease inhalation time (this increases exhalation time), decrease the respiratory rate by 2 breaths per minute, and reduce the tidal volume to 3 to 5 mL/kg. Continue treatment with inhaled albuterol.

### Cardiac Arrest in the Asthmatic Patient

When the asthmatic patient experiences a cardiac arrest, the provider may be concerned about modifications to the ACLS guidelines. There is inadequate evidence to recommend for or against the use of heliox during cardiac arrest (Class Indeterminate).<sup>36</sup> There is insufficient evidence to recommend compression of the chest wall to relieve gas trapping if dynamic hyperinflation occurs.<sup>37</sup>

### Summary

When treating patients with severe asthma, providers should closely monitor patients to detect further deterioration or development of complications. When there is no improvement and intubation is required, these patients require the care

of experienced providers in an intensive care setting. Some tertiary centers can offer experimental therapies as a last resort, and transfer should be considered for patients with near-fatal asthma that is refractory to aggressive medical management.

### References

1. Division of Data Services. *New Asthma Estimates: Tracking Prevalence, Health Care, and Mortality*. Hyattsville, Md: National Center for Health Statistics; 2001.
2. McFadden ER Jr. Acute severe asthma. *Am J Respir Crit Care Med*. 2003;168:740–759.
3. Rainbow J, Browne GJ. Fatal asthma or anaphylaxis? *Emerg Med J*. 2002;19:415–417.
4. Kokturk N, Demir N, Kervan F, Dinc E, Koybasiglu A, Turkas H. A subglottic mass mimicking near-fatal asthma: a challenge of diagnosis. *J Emerg Med*. 2004;26:57–60.
5. Rodrigo GJ, Rodrigo C. Continuous vs intermittent beta-agonists in the treatment of acute adult asthma: a systematic review with meta-analysis. *Chest*. 2002;122:160–165.
6. Khine H, Fuchs SM, Saville AL. Continuous vs intermittent nebulized albuterol for emergency management of asthma. *Acad Emerg Med*. 1996;3:1019–1024.
7. Lin RY, Sauter D, Newman T, Sirleaf J, Walters J, Tavakol M. Continuous versus intermittent albuterol nebulization in the treatment of acute asthma. *Ann Emerg Med*. 1993;22:1847–1853.
8. Rudnitsky GS, Eberlein RS, Schoffstall JM, Mazur JE, Spivey WH. Comparison of intermittent and continuously nebulized albuterol for treatment of asthma in an urban emergency department. *Ann Emerg Med*. 1993;22:1842–1846.
9. Newman KB, Milne S, Hamilton C, Hall K. A comparison of albuterol administered by metered-dose inhaler and spacer with albuterol by nebulizer in adults presenting to an urban emergency department with acute asthma. *Chest*. 2002;121:1036–1041.
10. Nowak R. Single-isomer levalbuterol: a review of the acute data. *Curr Allergy Asthma Rep*. 2003;3:172–178.
11. Gibbs MA, Camargo CA Jr, Rowe BH, Silverman RA. State of the art: therapeutic controversies in severe acute asthma. *Acad Emerg Med*. 2000;7:800–815.
12. Ratto D, Alfaro C, Sipsey J, Glovsky MM, Sharma OP. Are intravenous corticosteroids required in status asthmaticus? *JAMA*. 1988;260:527–529.
13. Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev*. 2000;CD002178.
14. Aaron SD. The use of ipratropium bromide for the management of acute asthma exacerbation in adults and children: a systematic review. *J Asthma*. 2001;38:521–530.
15. Rodrigo G, Rodrigo C, Burschtin O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. *Am J Med*. 1999;107:363–370.
16. Plotnick LH, Ducharme FM. Acute asthma in children and adolescents: should inhaled anticholinergics be added to beta(2)-agonists? *Am J Respir Med*. 2003;2:109–115.
17. Keam SJ, Keating GM. Tiotropium bromide. A review of its use as maintenance therapy in patients with COPD. *Treat Respir Med*. 2004;3:247–268.
18. Silverman RA, Osborn H, Runge J, Gallagher EJ, Chiang W, Feldman J, Gaeta T, Freeman K, Levin B, Mancherje N, Scharf S. IV magnesium sulfate in the treatment of acute severe asthma: a multicenter randomized controlled trial. *Chest*. 2002;122:489–497.
19. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo CA Jr. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. *Cochrane Database Syst Rev*. 2000;CD001490.
20. Blitz M, Blitz S, Beasley R, Diner B, Hughes R, Knopp J, Rowe B. Inhaled magnesium sulfate in the treatment of acute asthma. *Cochrane Database Syst Rev*. 2005;CD003898.
21. Cydulka R, Davison R, Grammer L, Parker M, Mathews J IV. The use of epinephrine in the treatment of older adult asthmatics. *Ann Emerg Med*. 1988;17:322–326.
22. Victoria MS, Battista CJ, Nangia BS. Comparison of subcutaneous terbutaline with epinephrine in the treatment of asthma in children. *J Allergy Clin Immunol*. 1977;59:128–135.

23. Victoria MS, Battista CJ, Nangia BS. Comparison between epinephrine and terbutaline injections in the acute management of asthma. *J Asthma*. 1989;26:287-290.
24. Petrillo TM, Fortenberry JD, Linzer JF, Simon HK. Emergency department use of ketamine in pediatric status asthmaticus. *J Asthma*. 2001;38:657-664.
25. Howton JC, Rose J, Duffy S, Zoltanski T, Levitt MA. Randomized, double-blind, placebo-controlled trial of intravenous ketamine in acute asthma. *Ann Emerg Med*. 1996;27:170-175.
26. Hess DR, Acosta FL, Ritz RH, Kacmarek RM, Camargo CA Jr. The effect of heliox on nebulizer function using a beta-agonist bronchodilator. *Chest*. 1999;115:184-189.
27. Rodrigo GJ, Rodrigo C, Pollack CV, Rowe B. Use of helium-oxygen mixtures in the treatment of acute asthma: a systematic review. *Chest*. 2003;123:891-896.
28. Reuben AD, Harris AR. Heliox for asthma in the emergency department: a review of the literature. *Emerg Med J*. 2004;21:131-135.
29. Camargo CA Jr, Smithline HA, Malice MP, Green SA, Reiss TF. A randomized controlled trial of intravenous montelukast in acute asthma. *Am J Respir Crit Care Med*. 2003;167:528-533.
30. Schultz TE. Sevoflurane administration in status asthmaticus: a case report. *AANA J*. 2005;73:35-36.
31. Wheeler DS, Clapp CR, Ponaman ML, Bsn HM, Poss WB. Isoflurane therapy for status asthmaticus in children: a case series and protocol. *Pediatr Crit Care Med*. 2000;1:55-59.
32. Non-invasive ventilation in acute respiratory failure. *Thorax*. 2002;57:192-211.
33. Soroksky A, Stav D, Shpirer I. A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. *Chest*. 2003;123:1018-1025.
34. Marik PE, Varon J, Fromm R Jr. The management of acute severe asthma. *J Emerg Med*. 2002;23:257-268.
35. Mazzeo AT, Spada A, Pratico C, Lucanto T, Santamaria LB. Hypercapnia: what is the limit in paediatric patients? A case of near-fatal asthma successfully treated by multipharmacological approach. *Paediatr Anaesth*. 2004;14:596-603.
36. Rodrigo G, Pollack C, Rodrigo C, Rowe BH. Heliox for nonintubated acute asthma patients. *Cochrane Database Syst Rev*. 2003;CD002884.
37. Van der Touw T, Mudaliar Y, Nayyar V. Cardiorespiratory effects of manually compressing the rib cage during tidal expiration in mechanically ventilated patients recovering from acute severe asthma. *Crit Care Med*. 1998;26:1361-1367.



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